Excerpts from

The NEURONS and NEURAL SYSTEM:
a 21st CENTURY PARADIGM

This material is excerpted from the full β-version of the text. The final printed version will be more concise due to further editing and economical constraints.

A Table of Contents and an index are located at the end of this paper.

A few citations have yet to be defined and are indicated by "xxx."

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Neural Concepts

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August 1, 2016

3 Chemical and electrical support to the Neurons [1]

3.1 Introduction

As developed in **Chapter 2**, the operation of a neuron involves a wide variety of individual processes. Those processes designed to support, but not participate in, the signaling functions of the neuron can be divided into two major groups. The first group, shared with all biological cells, provides the carbohydrate metabolism used to build and fuel the cell. The second group is only used minimally by other cells and is designed to provide the electrical power to the signaling circuits of the neuron. It will be defined here as electrolytic metabolism and includes the unique electrostenolytic process (an electrolytic process occurring on the surface of a cell lemma) that converts stored chemical energy into (free) electrical energy.

The bulk of this chapter is divided into four parts;
- **Section 3.2** develops the primary electrostenolytic source of power for all neurons and cardiocytes.
- **Section 3.3** develops the source of the glutamic acid used as the primary chemical fuel source for this electrical power.
- **Section 3.4** develops the secondary electrostenolytic power source only documented in cardiocytes.
- **Section 3.5** suggests a framework for discussing the wide range of neuro-affectors used in the neural and hormonal system. It also introduces the subject of exogenic chemicals, primarily known as pharmaceuticals, and their impact on neural operations.
    - **Section 3.5.4** pauses to provide a critical framework for the discussion of neurotransmitters and neuro-affectors in their various forms.

This material is supported by sensory modality specific discussions in Chapter 8 of the author's book on vision[2] and Chapter 3 of his book on hearing[3].

Figure 3.1.1-1 annotates the major processes associated with neural operation in greater detail than in **Chapter 2**. As developed there, a lanyard (dashed line) can be tightened to separate the portions of the cell involved in carbohydrate metabolism and the nucleus from the electrolytic metabolism associated with neural signaling. When the lanyard is loose, this cell would be described as a bipolar neuron using historical morphology labels. When the lanyard is tightened, the same neuron would be described morphologically as a monopolar neuron. The change to accommodate efficient packaging in a crowded organism demonstrates the archaic nature of the historical labels based on morphology.

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[1]Released: August 1, 2016

[2]Fulton, J. (2005) Processes in Biological Vision: A 21st Century Tutorial www.neuronresearch.net/vision

[3]Fulton, J. (2008) Processes in Biological Hearing: A 21st Century Paradigm. www.neuronresearch.net/hearing

The figure shows two distinct inputs from the external neuron matrix. As will be developed in more detail below, the electrolytic metabolism and signaling functions of the neuron operate anaerobically while the conventional carbohydrate metabolism shared with other non-neural cells operates aerobically. This difference has been highlighted recently in MRI studies designed to track oxygen consumption within the brain. These studies do not consistently show an increase in oxygen consumption with presumed neural activity. The electrolytic metabolism of the neuron obtains all of its fuel from glutamate, previously prepared from glucose, and not from the immediately available oxygen of the cardiovascular system. As the frame rate of fMRI techniques increase, this difference will become more apparent. It is desirable to develop alternate fMRI techniques that track the anaerobic fuel consumption in real time.

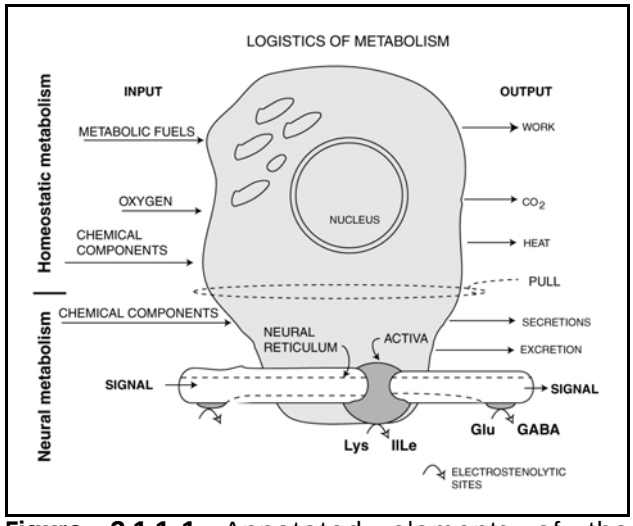

Figure 3.1.1-1 Annotated elements of the metabolic processes in a neuron. Note the lanyard (dashed oval) that can be pulled to isolate the neuron specific functions of the cell from the functions shared with other cells. The metabolism within a neuron will be subdivided into two forms to accentuate its aerobic and anaerobic portions.

It will also be shown that the signaling function does not generate significant heat although energy is consumed in a series of chemical changes. These changes result in a distinct and significant change in entropy that is hidden in the change of state associated with the reaction products.

The electrostenolytic processes associated with signaling appear to occur primarily on the exterior surfaces of the neuron. This condition allows the process to rely upon a broader range of chemical sources. It also allows it to dispose of waste products into the inter neural matrix more efficiently.

The requirement to supply electrical energy to the neurons has highlighted a unique, and specific, role for the limited set of polar amino acids. Among the aliphatic amino acids, there are only two negatively charged amino acids, and only three positively charged amino acids, at biological pH values. It will be shown that the two negatively charged amino acids, glutamic acid and aspartic acid are the primary and backup sources of negative potential within all cells (but specifically neurons). The positively charged lysine is the principle source of the positive potential found within the podaplasm chamber of cardiocytes (cells of the heart).

A second positively charged aliphatic amino acid, arginine plays a critical role as a precursor to a pericrine hormone released widely by neurons operating in conjunction with the cardiovascular system.

The one remaining positively charged amino acid is an aromatic structure, histidine. No specific role has been discovered for this amino acid within the neural system. However, its importance in medicine is undisputed.

The important role of neuro-secretion by the generic neuron will be addressed in **Chapter 5** with additional details provided in **Chapter 8.**.

3.1.1 Early efforts to quantify the energy consumption in the neural system

The recent explosion in interest in MRI techniques, based on the presence of oxygen level in the local blood supply, has heightened the interest in the rate and method of energy consumption in the neural system. Laughlin has provided a comprehensive report on the

energy consumption based on a series of assumptions but little detail as to the operation of the neural system, although she does recognize the dual "analog-digital" processing[4]. The processing is more properly described as analog-phasic or tonic-phasic since the signaling does employ pulse signaling but does not employ digital coding.

Laughlin's results are all based on the conventional chemical theory of the neuron and do not recognize that 95 per cent or more of the neurons in the system are operating in the analog domain. She takes an average firing rate for a phasic neuron as four Hertz. This number is below the background firing rate for most phasic neurons. The results are at best suggestive of the energy consumption of the neural system. While concerned about the energy consumption on the assumption that all neurons are phasic, she overlooks the above percentage of analog neurons that do not generate action potentials.

While Laughlin mentions a role for glutamate, she does not recognize its pre-eminent role in the electrostenolytic process powering the individual neurons.

Laughlin's paper can not be relied upon until it is revised.

3.1.2 Bringing more electro-chemistry into neuroscience

The electrostenolytic process is critical to the operation of each conduit and Activa of the neural signaling system. The typical chemical reaction involves the conversion of glutamic acid (glutamate) into gamma amino-butyric acid (GABA) with the release of CO_2 and an electron. This electron appears on the inner surface of the neurolemma. There, it generates a potential in conjunction with the capacitance of the lemma. The electrostenolytic process is detailed in this chapter.

The electrostenolytic process is well recognized in the studies of metabolism. However, it is normally described using a different terminology specific to that field. Berry, honoring the 80th birthday of the patriarch of that field, Sir Hans Krebs, has provided an extensive article that includes most of the elements of electrostenolytics found associated with the neural system[5]. In that context, they describe the redox reactions on a membrane surface as causing the transfer of electrons across the membrane. The transfer occurs in opposition to a previously present electrostatic potential. They describe this process as "reverse electron transfer" and treat it as a unique situation instead of recognizing that it is the normal situation in any electromotive source (**Section 3.1.2.3**).

3.1.2.1 Distant charge transport

In 2005, the Proceedings of the National Academy of Science, *USA*, presented a special feature on distant charge transport consisting of seven papers. The subject has been most closely studied with respect to photosynthesis in bacteria because of the simplicity of the system.

In the first paper of that set, Gray & Winkler note the ability of charges to travel at least 25 Angstrom through organic materials that they describe as glasses (probably liquid-crystals). Their limit was based on luminescent decay rates. Goldsmith et al. suggested longer distances are achievable in complex bridge molecules exhibiting "wire-like properties," but they were not dealing with membranes.

Elbehti et al did demonstrate the transfer of charge through bacterial plasma membranes.

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[4]Laughlin, S. (2004) The implications of metabolic energy requirements for the representation of information in neurons *In* Gazzaniga, M. *ed*. (2004) The Cognitive Neurosciences, 3rd Ed. Cambridge, MA: MIT Press Chap 14

[5]Berry, M. (1980) The function of energy-dependent redox reactions in cell metabolism. FEBS Letters, vol. 117, supplement, pp. K106-K119

and an electrostenolytic process involving Fe^{2+}–>Fe^{3+}. They described this effect as occurring at oxidoreductase complexes but did not invoke the term enzyme (except when addressing potential alternative processes)..

3.1.2.2 The role of the amino acids in neuron operations

The role of the amino acids in powering the neurons has been absent from the neuroscience literature. No papers could be found that suggested how the quiescent potential of –154 mV was supplied to the typical Node of Ranvier or other pulse generating neurons. Reviewing the bioscience literature from an alternate perspective is enlightening. While the free energy of chemical reactions is usually discussed using units of thermodynamics, kcal/mole, they can just as easily be discussed using electrodynamics, electron-volts. One electron-volt equals 23,060 kcal/mole. As an example, 3,551 kcal/mole equals 154 electron-volts (ev). A reaction releasing 3,551 kcal/mole can force an electron up an electrical potential gradient of 154 ev. Stated more simply, such a reaction can be considered a battery with a maximum potential of 154 ev.

Finkelstein & Ptitsyn presented a very valuable lecture series in 2002[6]. They have described "the 20 'standard' (i.e., DNA-encoded) amino acid residues" of interest here, including the change in free energy involved in going from a water to alcohol solvent (page 118). They have also described on page 120, several properties of the amino acids of major interest in this work, the only two that. release CO_2 and the only one that releases NH_2 <=> NH_3^+. On page, they provide a useful graphic of the side chains of the residues of all of these amino acids remaining after assembly into a peptide chain.

The list of 20 most common amino acids found in proteins is enlightening. A majority are electrically neutral at biological pH values. However, only 2 are electronegative (or acidic) under such conditions. Furthermore, these two are known as di-amino acids, a very unique property.. Only three are electropositive (or basic) under such conditions. It will be shown that the two electronegative amino acids, glutamic (amino) acid and aspartic (amino) acid, are the primary sources of negative potential powering the individual neurons of the neural system. One of the three positive amino acids, lysine (amino) acid, appears to play the principle role in providing a positive potential to the few types of neurons requiring such a potential as a secondary electrical source. Lysine is the only positive amino acid with a single terminal amino group (NH_3^+). Arginine has a similar, but more complex amine group, called guanidinium. The NH_3^+ is typically part of a primary amine (RNH_2) that has hydrogen-bonded with a hydrogen of a water molecule or other source.

The electrostenolytic role of glutamic and aspartic acid, and of lysine will be developed in detail in sections 3.2 and 3.3 respectively.

3.1.2.2.1 Gibb's (free) Energy of selected reactions

In most chemical reactions, a certain amount of energy is released (or absorbed). In the case of the release of energy, some is available for a second essentially simultaneous reaction and some is lost as heat. The energy available for a second reaction is known as the Gibb's (free) Energy. Gibb's Energy is defined by;

$G(p,t) = H - TS_{int}$ or $G = H - TS_{int}$ under standard temperature and pressure

where G = Gibb's Energy (SI unit joule/mole (convertible to kcal/mole or electron-volts)
H = enthalpy (SI unit: joule)
T = temperature (SI unit: kelvin)
S = entropy (SI unit: joule per kelvin)

under standard temperature and pressure;

$\Delta G = -T\Delta S$

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[6]Finkelstein, A. & Ptitsyn, O. (2002) Protein Physics. NY: Academic Press

6 Neurons & the Nervous System

When ΔG is a positive value, ΔS must have a negative value.

For practical purposes, the units of G are usually given in kJ/mole or kcal/mole

As of 2011, Texas A & M University has provided a set of worked out reactions with their change in Gibb's Energy[7].

Reactions can be classified according to the change in enthalpy (heat):

Endothermic - absorbs heat, $H^o > 0$
Exothermic - releases heat, $H^o < 0$

Reactions can also be classified according to the change in the free energy of the reaction:

Endergonic - NON-SPONTANEOUS, $G^o > 0$
Exergonic - SPONTANEOUS, $G^o < 0$

where the superscript ^{o} also refers to standard state conditions;

- The partial pressures of any gases involved in the reaction is 0.1 MPa.
- The concentrations of all aqueous solutions are 1 M.
- Tabulated standard-state thermodynamic data are generally for a temperature of 25C (298 K)

Some author's use the asterisk instead of the superscript ^{o}. To simplify the above and account for normal laboratory conditions;

$\Delta_f G^* = \Delta G$ at their standard states (the most stable form of the element at 25 degrees Celsius and 100 kilopascals).

Figure 3.1.2-1 provides nominal values of interest here.

[7] www.chem.tamu.edu/class/majors/tutorialnotefiles/gibbs.htm

Substance	State	$\Delta_f H^o$ kJ	ΔS^o J/K	$\Delta_f G^*$ kJ/mol	$\Delta_f G^*$ electron volts
H_2O	aqueous			–237.17	
N_2O	gas			+104.18	
NH_3	gas			–3.976	0.172
NH_4^+	aq.	–132.51	113.4	–79.37	
NO_3^-	aq.	–205.0	146.4		
NH_4NO_3	solid	–365.56	151.08		
CO_2	gas			–94.26	4.087
Acetate				–369.4?	
Glucose				–917.22?	
CH_4	gas			–12.14	
CH_3OH				–38.69	
CH_3COOH	aq.			–93.8	
HCOOH	aq.			–82.7	
C_2H_5OH	aq.			–41.7	

Figure 3.1.2-1 Free energy of formation for selected chemicals. A few values are of questionable accuracy and are so marked. One electron volt equals 23.060 kJ/mole in all cases.

The standard-state free energy of reaction can be calculated from the standard-state free energies of formation as well. It is the sum of the free energies of formation of the products minus the sum of the free energies of formation of the reactants:

$$\Delta_f G^* = \sum \Delta_f G^*_{products} - \sum \Delta_f G^*_{reactants}$$

As an example, Texas A & M provided the following;

The reaction: $NH_4NO_{3(s)} \xrightarrow{H_2O} NH_4^+{}_{(aq)} + NO_3^-{}_{(aq)}$

The initial setup:

8 Neurons & the Nervous System

$$\Delta H^\circ = \sum nH^\circ_{f\,products} - \sum mH^\circ_{f\,reactants}$$

$$\Delta H^\circ = \left[\left(1\ \text{mol}\ \cancel{NH_4^+}\ \text{x}\ \frac{-132.51\ \text{kJ}}{\cancel{\text{mol}}}\right) + \left(1\ \text{mol}\ \cancel{NO_3^+}\ \text{x}\ \frac{-205.0\ \text{kJ}}{\cancel{\text{mol}}}\right)\right] - \left(1\ \text{mol}\ \cancel{NH_4NO_3}\ \text{x}\ \frac{-365.56\ \text{kJ}}{\cancel{\text{mol}}}\right)$$

$$\Delta H^\circ = -337.51 + 365.56$$

$$\boxed{\Delta H^\circ = 28.05\ \text{kJ}}$$

The conversion to the free energy of reaction;

$$T_K = 25^\circ C + 273.15 = 298.15\ K$$

$$\Delta S^\circ = 108.7\ \cancel{J}/K \times \frac{1\ kJ}{1000\ \cancel{J}} = 0.1087\ kJ/K$$

$$\Delta H^\circ = 28.05\ kJ$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \qquad \text{Plug in } \Delta H^\circ, \Delta S^\circ, \text{ and T}$$

$$\Delta G^\circ = 28.05\ kJ - (298.15\ \cancel{K})(0.1087\ kJ/\cancel{K})$$

$$\Delta G^\circ = 28.05\ kJ - 32.41\ kJ$$

$$\boxed{\Delta G^\circ = -4.4\ kJ}$$

The free energy of this reaction is equal to 190 mev (milli electron volts)

Ben-Naim has described the secondary processes related to describing actual energy calculations related to biological materials in some form of solution (frequently highly concentrated or liquid crystalline situations)[8]. He notes the Gibb's Energy defined above actually consists of multiple terms at the detailed level with a quantity, δG, representing all of the solvation related contributions to the Gibb's Energy change. Using the equation,

$$\Delta G^{\ell} = \Delta G^{g} + \delta G$$

to describe the Gibb's Energy in the liquid condition, he notes, "Each of the two quantities, ΔG^{g} (the vacuum level energy) and δG is too complicated to be calculated exactly for any biochemical process."

He defines solvation process as the process of transferring of a solute α, being at a specific conformation, from a fixed position in vacuum to a fixed position in the liquid, the process being carried out at a given temperature *T*, pressure *P* and solvent composition." Even this definition does not address the subject of the Helmholtz boundary layer associated with the native neuron lemma

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Clearly, care is needed to maintain consistent units in this area of science. Furthermore, the conditions as they exist in solution are of most interest here (not necessarily their most stable form and certainly not as gases). In addition, stereochemistry is also involved in the specific reactions of interest. In some cases, hydrogen bonds may also be involved.

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[8]Ben-Naim, A. (1993) Solvation thermodynamics of biopolymers *In* Westhof, E. *ed*. Water and Biological Macromolecules. NY: CRC Press Chap 14

The calculation of free energy for a specific molecule is frightfully complicated as discussed by Kondo et al[9].

Staneva & Wallin have provided an article discussing peptides where the C-terminal is believed/assumed to be the significant stereochemical binding site[10]. Unfortunately, they define but do not address their class III short peptide as Asp/Glu-X-Φ-COOH, respectively, where Φ is any hydrophobic amino acid, X is any amino acid, and COOH is the C-terminal.

3.1.2.3 Reverse electron transfer–an inadequate model

As noted above, several parts of the biological community have focused on the concept of reverse electron transfer as a new phenomenon. The fact is that the metabolites are acting as the electrolyte in a battery in generating the electrostatic potential from the flow of electrons. They also note the reversibility of the reaction by discussing redox cycles. The reversibility in the case of neurons is limited by the tendency of the GABA and CO_2 to diffuse away from the site.

Berry offered an important statement during the 1980's in a convoluted context: "It is concluded that energy-dependent reverse(d) electron transfer is a fundamental feature of the living state. It provides a mechanism for the reversal of thermodynamically unfavorable redox reactions by energy coupled steps, distinct from the forward reactions." Paraphrasing, he continues, these redox reactions maintain the cell in a state removed from chemical equilibrium and helps support a balance between degradative and synthetic processes. Finally, "It would appear that living systems can conserve energy derived from degradation of foodstuffs, not only by synthesizing new chemical bonds, but also by storing separated charge. The energy conserved in the electric field so created can be used to drive . . . reverse electron transfer . . . This interaction of chemical and electrical energy within the cell makes living systems highly efficient units operating close to equilibrium." Berry introduces the term "static head" from hydraulics to describe the electrical potential across the cell membrane. Why he did not settle on conventional electrical terminology and the concept of recharging a battery using an electrical potential greater than the battery itself is unclear.

Ohki has said; "Until recently the possibility of electron conduction in living systems was not seriously considered, with perhaps a few notable exceptions to be mentioned below. Traditionally, the origin of electrical potentials observed in living systems has been attributed almost exclusively to ionic permeability." He goes on to discuss the electron transfer now assumed in photosynthesis[11].

Beginning in the 1990's, the study of "reverse electron transfer" blossomed into its own specialty within the family of electron transfer processes. It has been intensively studied within the mitochondria of animal cells. It has been studied most intensively in the plasma membrane of light sensitive bacteria. These studies have developed the "electron hole[12]" as a significant feature of DNA processes. It has also described the transport distance as at

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[9]Kondo, H. Okimoto, N. Morimoto, G.& Taiji, M. (2011) Free-energy landscapes of protein domain movements upon ligand binding *J. Phys. Chem. B* vol 115(23), pp 7629–7636

[10]Staneva, I. & Wallin, S. (2011) Binding free energy landscape of domain-peptide interactions *PLoS*, Aug issue www.ploscompbiol.org/article/info%3Adoi%2F10.1371%2Fjournal.pcbi.1002131

[11]Ohki, S. (1985) The origin of electrical potential in biological systems *in* Srinivasan, S. et. al. Comprehensive Treatise of Electrochemistry, vol. 10, Bioelectrochemistry. NY: Plenum Press pg 83+

[12]Bongiorno, A. (2008) Energy landscape of an electron hole in hydrated DNA *J Phys Chem* B vol 112(44), pg 13945- 13950

least 25 Angstrom[13] and suggested it may occur by "tunneling" or by hydrogen bonding. Tunneling remains largely conceptual within the biological sciences.

Friedrich & Schink have described reverse electron transport across the membrane of bacteria using similar symbology to that used here for electrostenolytics[14]. Elbehti et al. have described what they call uphill electron transfer as used on an industrial scale in copper and uranium extraction from ores[15]. They did not diagram their discussion but did note the common occurrence of reverse electron transfer under anaerobic conditions in bacteria.

They have described reverse electron transport across the membrane of bacteria based on very sophisticated chemical analysis but little discussion of the physical chemistry involved. Their reaction actually provides the electromotive potential required to push the electrons through the diode formed by type 2 lemma. The reaction appears like a battery with its positive terminal connected to the surrounding fluid and the negative terminal connected to the type 2 lemma.

> ***The actual concept of a reverse electron transport is very old. It is the concept of an electrical charging circuit where the applied potential is opposite to and exhibits a higher potential than the circuit being charged so that the net potential is in the direction to push electrons around the circuit in the opposite direction to current flow in the absence of the charging potential. No new concept is required.***

3.1.3 Broadening the concept of metabolism in neuroscience

The advent of PET, MRI and fMRI procedures has introduced a new era in imaging of the brain, and other parts of the body. These studies have demonstrated the critical role that glutamate plays in the operation of the neural system through its relative abundance in neural tissue. As noted briefly in **Section 3.1**, it is becoming important to expand the concept of metabolism to separate the anaerobic electrostenolytic fueling of the neural portion of the neuron from the more conventional aerobic fueling of the non-neural portion that is shared with other cells This separation will continue to rise in importance as higher resolution (in both space and time) fMRI techniques and equipment become available.

The imaging community has recently uncovered, but not resolved, the highly unexpected fact that the relative consumption of oxygen by the brain does not rise in proportion to the relative consumption of glycogen during short-term neural activity. While glycogen consumption may rise by 40-50%, the rise in oxygen consumption rises by 5% or less. This finding highlights the fact the neurons of the brain do not rely upon oxidative metabolism based on hemoglobin during their short term operation. The primary role of oxygen from hemoglobin is in restoring the reactants used in the electrostenolytic process over a longer interval.

Until 1986, the conventional wisdom was that the brain operated on a metabolism related directly to oxygen from hemoglobin in its operation. In that year, Fox & Raichle demonstrated a significant decoupling between the rate of cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen consumption ($CMRO_2$)[16]. They hypothesized that the

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[13]Goldsmith, R. Sinks, L. Kelley, R. et al. (2005) Wire-like charge transport at near constant bridge energy through fluorene oligomers *Proc Nat Acad Sci USA* vol 102, pp 3540-3545

[14]Friedrich, M. & Schink, B. (1993) Hydrogen formation from glycolate driven by reversed electron transport in membrane vesicles of a syntrophic glycolate-oxidizing bacterium *Eur J Biochem* vol 2(7), pp 233-240

[15]Elbehti, A. Brasseur, G. & Lemesle-Meunier, D. (2000) First Evidence for Existence of an Uphill Electron Transfer through the bc1 and NADH-Q Oxidoreductase Complexes of the Acidophilic Obligate Chemolithotrophic Ferrous Ion-Oxidizing Bacterium, *Thiobacillus ferrooxidans*. *J Bacteriology* vol.182(12), pp 3602-3606

[16]Fox, P. & Raichle, M. (1986) focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci USA* vol. 83, pp 1140-1144

CBF was controlled by a mechanism independent of the cerebral metabolic rate of oxygen. Subsequent studies confirmed this startling decoupling[17]. Both Fujita and Vafee[18] have provided some transient data on oxygen consumption both during and following neural activation. Confirmation of these results has led to a variety of explanations attempting to rationalize this coupling relationship between the CBF and $CMRO_2$. To date, these studies have not recognized the role of glutamate in providing power to the neurons independent of the rate of oxidative metabolism.

Until the advent of PET and MRI techniques, nearly all studies of brain activity were based on global calculations, frequently influenced by the restrictions introduced by the blood-brain-barrier. Since then, the studies have been much more local in nature. They are currently limited largely by the resolution of the PET and MRI techniques. This resolution is described in terms of the voxel (the volumetric pixel).

The complexity of measuring the CBF and $CMRO_2$ should not be underestimated. As will be shown below, indirect means are used followed by complex calculations. The investigators should be given great credit for achieving the precision illustrated in their data.

Buxton has provided a readable, but complex description of the methods required to determine the CBF and $CMRO_2$[19]. His presentation is limited to the conventional wisdom concerning neural system operation. The following sections will deviate from his presentation in order to provide a broader context. This context will explain the decoupling found experimentally and suggest additional experimental activity.

The PET and MRI techniques rely upon the interactions of various constituents of organic tissue with crossed magnetic and radio frequency fields. These constituents incorporate a molecule that exhibits distinctive magnetic characteristics that can be recognized easily. The techniques used, and the associated mathematical processing, have advanced rapidly since the early 1990's. As with sonography in medicine, PET and MRI currently employ most of the techniques found in modern radar and sonar equipments. This level of sophistication makes it difficult to describe all of the optimization techniques used in PET and MRI. Buxton has provided an introduction to many of these specialized techniques as well. The signal sensed by the simplest equipments is in what is generally called the spatial frequency domain. The more advanced machines sense signals in the spatial frequency domain under transient temporal conditions. Converting these signals into a spatial position domain is necessary prior to interpretation. This requires the use of the two-dimensional Fourier Transform. This in turn requires considerable computational capability only available with the largest available computers. To conserve on computational power, or computational time until an answer is available, the Fourier Transform process is frequently truncated. This results in the Gibbs phenomenon familiar to all electrical circuit designers. Edges are emphasized in the imagery in spite of the underlying data.

Because of the four-dimensional nature of the most desirable signals, presentation of the resulting data is frequently a problem. The most common presentations present the desired transient data overlaid on a static presentation to provide visual reference to the voxels of interest. Frequently, the overlay is in a contrasting color for clarity.

In summary, the neural system employs two distinctly different processes to provide energy. The first involves metabolism at the cellular level for *slow* homeostasis and generally involving

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[17]Fujita, H. Hiroto, K. Reutens, D. & Gjedde, A. (1999) Oxygen consumption of cerebral cortex fails to increase during continued vibrotactile stimulation *J. Cereb Blood Flow Metab* vol. 19(3) pp 266-271

[18]MVafee, M. Meyer, E. Marrett, S. Paus, T. Evans, A & Gjedde, A. (1999) Frequency-dependent changes in cerebral metabolic rate of oxygen during activation of human visual cortex. *J Cereb Blood Flow Metab* vol 19(3) pp 272-277

[19]Buxton, R. (2002) Introduction to Functional Magnetic Resonance Imaging. Cambridge: Cambridge University Press

the oxidation of glucose, by oxygen, supplied by the hemoglobin of blood, to provide energy to the cell. The second is a totally independent separate process involving the oxidation of glutamic acid (glutamate) to GABA, in the electrostenolytic process without the direct participation of oxygen from hemoglobin in support of *fast* signaling.

3.1.3.1 Nomenclature

The nomenclature used in PET and MRI revolves around the notion of the voxel, the volumetric pixel of organic tissue. It is the metabolism of the tissue enclosed within an individual voxel that is of interest. To study this subject, the flow of nutrients into and out of the voxel must be quantified. The complexity of the tissue involved within an arbitrary voxel makes this process quite difficult. Some volume of the voxel is occupied by blood vessels transporting bulk blood. Some volume is occupied by the capillary bed providing blood components to the neural tissue. Finally, some volume is occupied by neural and other types of cellular material.

The general approach involves two steps. The first step is to describe the local cerebral blood flow, "lCBF," into and out of the voxel. The second step is to describe the specific components of interest in the blood both entering and leaving the voxel. To date, the additional specific components have been primarily related to the flow of glycogen and oxygen into and out of the voxel. As a result, the two most prominent measurements have been of the cerebral metabolic rate of glycogen introduction, CMRGlc, and the cerebral metabolic rate of oxygen consumption, $CMRO_2$. Both of these are typically expressed on a local basis. This analysis will show that two other components are critical to the understanding of the local metabolism of the brain. The first is the cerebral metabolic rate of glutamate consumption, CMRGlu. Glutamic acid (or glutamate) is the fuel most directly involved in neural operation. The second is the cerebral metabolic rate of GABA consumption, CMRGABA. The term GABA consumption is a misnomer, GABA is actually the primary waste product of neural operation. However, it is quickly regenerated into glutamate as discussed below. These two materials participate in an electrostenolytic process on the surface of every lemma associated with every neuron.

3.1.3.2 Parameters involved in the Fourier transforms of MRI

Although not of great importance here, being aware of certain parameters used in optimizing MRI images is useful. The white matter (primarily myelinated stage 3 neurons), the grey matter (primarily unmyelinated stage 2 neurons and the necessary capillary beds) and the bulk cerebral fluids (frequently described as the cerebral spinal fluids, CSF) exhibit different time constants when relaxing after excitation by a radio frequency, RF, field. The nominal values for these factors are given in **TABLE 3.1.3-1.**

TABLE 3.1.3-1
TYPICAL MAGNETIC PARAMETERS FOR COMPONENTS OF THE BRAIN

Material	M_0 (arb. units)	T_1 (ms)	T_2 (ms)
Gray matter	85	950	95
White matter	80	700	80
CSF	100	2500	250

M_0 is defined as the equilibrium magnetization of the material. T_1 is defined as the longitudinal relaxation time associated with the dominant magnetic species within the material. T_2 is defined as the transverse relaxation time associated with the dominant magnetic species.

Also important are certain factors associated with the MRI apparatus and the transform calculations. One is the time between repetitions of the scanning operation, TR. The second

is the echo time, TE. The relationship between these factors is presented in Edelman, et. al[20]. They are basically used in optimizing the power of the machine and in "weighting" the Fourier Transform calculations described above. The result is higher contrast in the reconstructed images for the features of interest. These weightings are frequently related to the following **Figure 3.1.3-1**.

3.1.3.3 Metabolic mechanisms and additional nomenclature

Workers in the field of developing PET and MRI techniques have used a simplistic view of the metabolic processes of the body. The initial assumption that complete oxidation of glycogen was to be expected within the brain does not recognize the multitude of serial steps involved in metabolism, or the multitude of alternate paths supporting that metabolism. A more complete illumination of the steps in metabolism and the results of this work highlighting the role of glutamate in neural operation leads to a different interpretation of metabolism in the neural system.

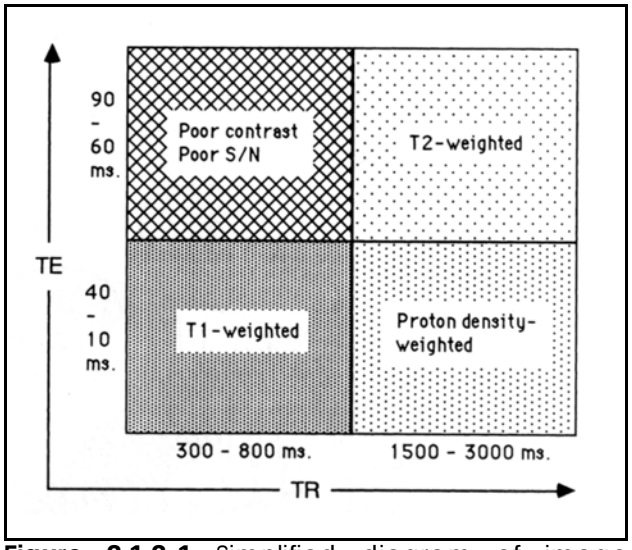

Figure 3.1.3-1 Simplified diagram of image contrast as a function of TR & TE. From Edelman, et. al. 1996.

The overall concept of the utilization of food and oxygen in the support of life is generally defined as metabolism. Our understanding of metabolism, although remarkable, remains at a primitive level. The complexity is recognized in the nomenclature of Lehninger[21]. His chapter 14 begins with a discussion of "Intermediate metabolism." By this term, he means metabolism as the sum total of an immense variety of intermediate steps and residues leading to metabolism. He does not mean some intermediate stage of metabolism *per se*.

Metabolism has historically been defined as the sum total of the enzymatic reactions occurring in the cell. These have been divided into four categories.

1. Extract chemical energy from the environment (food or sunlight).

2. Convert exogenous nutrients into building blocks of macromolecular components of cells.

3. Assemble the macromolecules into proteins, nucleic acids, lipids and other components.

4. Form and degrade those biomolecules required in specialized functions of cells.

The last category is very important in the neural system. One of those degradation processes is used to power each individual neuron. It is the process of electrostenolysis occurring on the surface of every neuron and involving the conversion of glutamic acid into GABA.

Within metabolism, the processes can also be broken down into functional categories. The two most common are:

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[20]Edelman, R. Hesselink, J. & Zlatkin, M. (1996) Clinical Magnetic Resonance Imaging, 2nd Ed. vol. 1. London: W. B. Saunders. Chapter 1

[21]Lehninger, A. (1972) Op. Cit

1. Catabolism– An enzymatic degradation, largely by oxidative reactions of relatively large molecules. Process releases free energy as ATP.

2. Anabolism– An enzymatic synthesis of larger molecular components of cells from similar precursors. Requires energy in the form of ATP.

A third form of metabolism will be discussed below.

Fermentation is a major function within metabolism. It takes on a number of forms that are generally associated with catabolism. However, it includes both aerobic and anaerobic variants. In general, fermentation involves oxidation-reduction reactions that do not involve oxygen. No net oxidation of the fuel and residue of these reactions occurs. These reactions involve primarily rearrangement accompanied by the release of hydrogen, water or carbon dioxide. They frequently involve amination. The changes in energy level of the constituents are frequently small.

Glycolysis is a major activity within the fermentation function. It involves a myriad of individual steps that are difficult to annotate in a single figure. Glycolysis involves two major chemical sequences terminating in the generation of pyruvate or lactate (depending on the personal interests of the investigator). Lactate is particularly important in muscular activity because of its creation in an anaerobic environment and its ability to pass easily through cell walls. The interest here is focused more on pyruvate. Glycolysis can be explained if the processes involved are divided into three types.

1. Degradation of glucose to lactate (the carbon pathway).

2. Introduction of phosphate group (the phosphate pathway).

3. Oxidation-reduction (the electron pathway).

The participation chemical energy, ATP, NAD, etc., supporting the conversions associated with the steps in the above pathways must also be considered in a complete analysis.

Following glycolysis, the chemistry of metabolism broadens immeasurably in complexity. The framework for this broadening was first defined by Krebs. He proposed the citric acid cycle as the basic element of the framework. This cycle begins with the creation of citric acid from pyruvate via an incredibly complex enzymatic molecule known to this day as "coenzyme A." The cycle includes a variety of side loops, shunts and other frequently obscure processes. One of particular interest here is the glutamate shunt discussed below. The general nature of the process of metabolism centered on the citric acid cycle of Krebs, also known as the Tri-Carboxylic-Acid (TCA) cycle, and glutamate is illustrated in **Figure 3.1.3-2**. The number of carbon atoms, followed by the number of oxygen atoms, in each molecule is given in parentheses. Noting that the cycle involves multiple decarboxylations along the right hand side is important. The reconstitution of the six carbon citrate from the four carbon succinates and oxaloacetate is more complex than generally addressed in discussions of the cycle.

The steps leading to the formation of pyruvate occur within individual cells. The tri-carboxylic-acid cycle occurs within the mitochondria. The glutamate-to-GABA transformation occurs on the surface of the membranes of the neuron as part of the electrostenolytic mechanism.

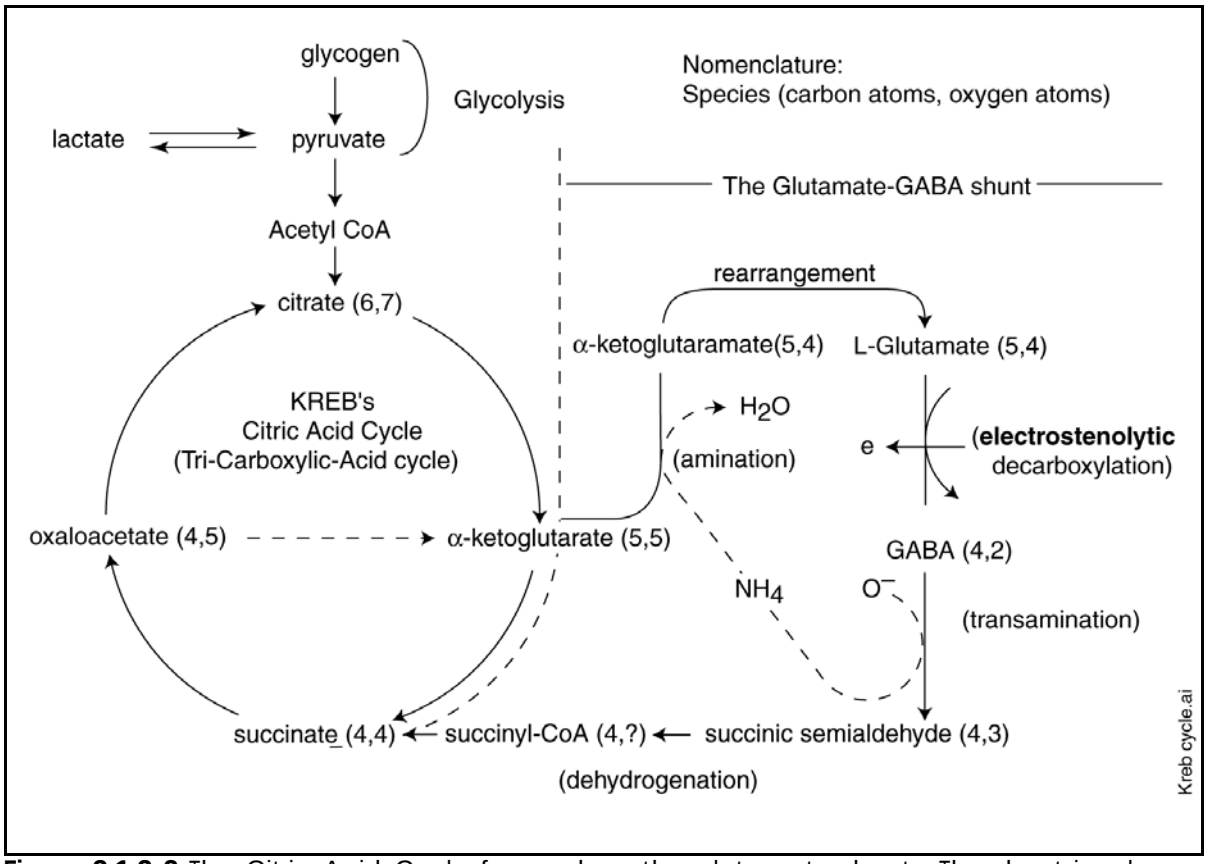

Figure 3.1.3-2 The Citric Acid Cycle focused on the glutamate shunt. The shunt involves o decarboxylation but no involvement of oxygen. The decarboxylation is part of the electrostenolytic process powering the neurons. This process generates a free electron. The reported close coupling between the amination of α-ketoglutarate to α-ketoglutarmate and the transamination of GABA is shown by the dashed line. The symbol and word "electrostenolytic" has been added to the figure. From McGeer, Eccles & McGeer, 1987.

The glutamate shunt begins with an amination of α-ketoglutarate to α-ketoglutaramate. This process is followed by a rearrangement. The resulting molecule is L-(+)-glutamic acid, more commonly known as glutamate among the metabolic and nutrition communities. The next step in this shunt is unique in that it does not involve an enzyme in the molecular sense. It involves the decarboxylation of the glutamate on a special area of a cell membrane acting as a substrate. Whether this process requires the presence of pyridoxal phosphate as a coenzyme is unknown. However, lack of this material generally inhibits neural activity (and presumably other reactions associated with glycolysis or the TCA cycle) within the brain.

The nomenclature is correct as of 1987. The more recent IUPAC nomenclature is slightly different and is summarized below. The RSC numbers are used in a new Jmol library being maintained by the Royal Society of Chemistry. The library supports the three-dimensional visualization of these and other molecules.;

α-Ketoglutarate (C5H4O5) a.k.a. IUPAC 2-Ketogluramic acid is RSC molecule #144236.
α-Ketoglutaramate (C5H7NO4) a.k.a. IUPAC 2-Ketoglutaramic acid RSC #47
L-glutamate (C5H9NO4) a.k.a. IUPAC L-(+)-glutamic acid is RSC # 30572

The individual layers of the two walls of the bilayer lemma forming the wall of a neuron are

asymmetrical at specific locations at the molecular level. As a result, the membrane acts as an electrical diode. The electrostenolytic decarboxylation process occurring on this membrane generates a free electron on one side of the membrane. This electrostenolytic process is the power source for each electrical conduit within a neuron. It is the physical analog of the putative ion-pump proposed by Hodgkin & Huxley (1952).

Glutamate participates in a wide variety of enzymatic reactions within the organism. These reactions and the glutamate shunt are well documented[22]. Its support in powering the neurons has not been previously reported. According to Harper, the shunt is particularly important in the gray matter of the brain. The glutamate shunt includes a sub-loop of interest. The sub-loop involves the removal of ammonia from GABA by a pyridoxal-dependent enzyme. This ammonia can participate in a transamination of α-ketoglutarate to glutamate. This sub-loop is shown by the dashed line in the figure.

Estimates appear in the literature suggesting as much as 80% of the glucose delivered to the brain is used in neuronal activity. The high utilization of glutamate within a neuron suggests the processes of glycolysis and glutamate formation may tax the capability of a single cell. Both Frahm, et. al[23]. and Magistreeti & Pellerin[24] have suggested that a major role for astrocytes within the brain (and their familial neuroglia, Schwann cells in the peripheral neural system) is to aid the neurons by providing additional lactate. The solubility of lactate in intercellular space would allow easy movement of lactate from the astrocytes to the neurons. Although the views of these authors are conventional, their conclusions are compatible with the Activa and neuron of this work. Particularly in stage 3 projection neurons, there is a need for glutamate at locations quite distant from the soma of the neuron itself.

Figure 3.1.3-3 provides a more detailed description of the events related to the glutamate shunt variant of the tri-carboxylic-acid cycle. It is divided into four major sections. The shaded area on the left describes the chemical activity on the surface of a neuron upon excitation. The basic event is the (reversible) conversion of a small part of a pool of glutamate into GABA with the release of an electron into the plasma of the neuron and the release of CO_2. The steps related to the tri-carboxylic-acid (TCA or Krebs) cycle required to remove the GABA and restore the glutamate supply are enclosed in the large dashed box. These steps normally occur within the mitochondria of the cell. The extraction of glucose from the bloodstream and the formation of pyruvate are shown at upper right. These steps normally occur within the larger volume of the cell. The extraction of oxygen from the bloodstream is shown at the lower right.

Synaptic excitation of any neuron results in a change in the potential of at least one of the signaling related plasmas within the neuron. If the activity leads to a reduction of the negative potential in any of the plasmas, the electrostenolytic power source for that plasma will attempt to restore the nominal potential by injecting additional electrons into the plasma. This process converts glutamate to GABA. If the potential has risen, the electrostenolytic process has the theoretical capability of extracting electrons from the plasma and causing GABA to be converted back to glutamate (as discussed below).

The TCA box contains two distinctly different paths. The top row describes the replacement of glutamate through the extraction of glucose from the bloodstream. This is the path usually considered when discussing BOLD signal generation in the fMRI technique. However, it should be noted that a second path exists as shown in the second row. This path reconstitutes the glutamate from GABA without using any new material derived from glucose. Here, no BOLD signal, related to direct extraction of glucose from the blood stream

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[22]Harper, H. (1975) Review of Physiological Chemistry, 15th Ed. Los Altos, CA: Lange Medical Publ. pg 378

[23]Frahm, J. Kruger, G. et. al. (1996) Dynamic uncoupling and recoupling of perfusion and oxidative metabolism during focal brain activation in man *Magn Resonance Med* vol. 35, pp 143-148

[24]Magistretti, P. & Pellerin, L. (1999) Astrocytes couple synaptic activity to glucose utilization in the brain *New Physiol Sci* vol. 14, pp 177-182

and its conversion into glutamate, is found.

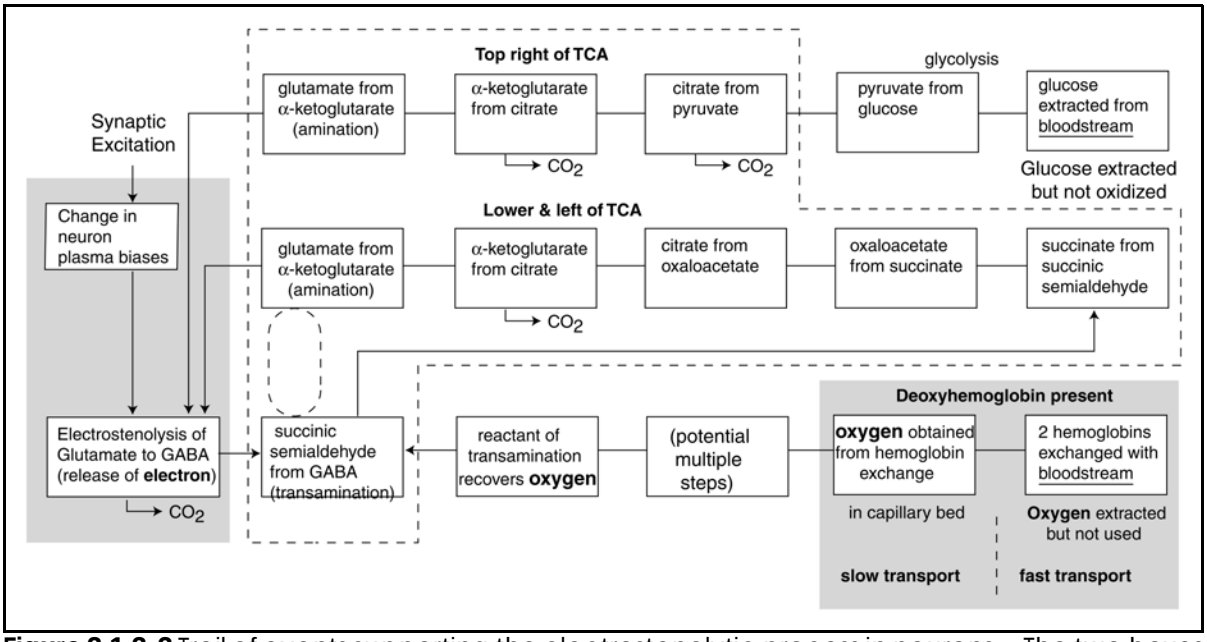

Figure 3.1.3-3 Trail of events supporting the electrostenolytic process in neurons. The two boxes at lower right support the BOLD Effect in fMRI experiments. The dashed subloop shows how ammonia can be removed from GABA and used immediately in the amination process forming glutamate.

Note that the extraction of glucose from the bloodstream and its conversion into glutamate does not involve oxidation involving oxygen. It merely involves a series of oxidative-reductions (which actually releases oxygen in the form of CO_2).

The glutamate to GABA reaction releases CO_2. The replacement of the glutamate in the pool necessarily involves the replacement of the lost CO_2. However, the top path in the figure shows that the glutamate can be replaced using glucose from the bloodstream without any involvement of oxygen from the bloodstream. In this case, no $CMRO_2$ signal associated with the BOLD signal is seen.

Alternately, the glutamate can be regenerated without the participation of new glucose using the middle and lower paths of the figure. This method does require the acquisition of oxygen from some source. The lower row of the figure shows the potential source of oxygen via the bloodstream. The process involves the reconstitution of the reactant used in the transamination mechanism shown. This path has not been documented. However, it involves the removal of oxygen from hemoglobin within the capillary bed supporting the neuron.

3.1.3.4 Energy calculations related to metabolism

The normal tendency in PET and MRI studies is to expect the complete metabolism of glucose. This involves the consumption of considerable oxygen in the creation of 38 units of ATP, an energy carrier.

Glucose + $6O_2$ —> 6CO2 + $6H_2O$ (+38 ATP)

Each unit of ATP in the above calculations contain 7500 calories.

The various phases of metabolism involved in supporting neuronal activity are quite different situations. They do not involve the complete reduction of glucose. The goal of glycolysis is the production of pyruvate or lactate (a more easily stored form) that can be used within the tri-carboxylic-acid cycle (TCA).

Glucose —> 2 Lactate

Similarly, each cycle of the Krebs TCA cycle consumes no oxygen.

$CH_3COOH + H_20$ —>$2CO_2 + 8H$

These reactions only involve small changes in energy compared with that involved in complete oxidation.

3.2 The primary electrostenolytic process powering the neurons

Sections 2.1 and 2.2 discussed the functional neuron from an operational perspective. This section will address the molecular and electrostenolytic mechanisms supporting the operation of such cells. These are the mechanisms that provide the electrical power required to operate the electrolytic circuits of the neurons. This discussion builds on the previous detailed discussion of the biological bilayer membranes (BLM's) of the neuron on a region by region basis.

The electrostenolytic process introduces a new area of metabolism not covered in the current literature. Previous discussions of metabolism related to the neural system has focused on the metabolism associated with cell development and cell homeostasis, not neural signaling. Conventional metabolism has focused on the utilization of various chemical forms, lipids, carbohydrates, proteins etc. Recent studies have delved deeper into the metabolism associated with the tricarboxylic acid cycle (TCA)[25,26]. Some of these studies have differentiated between the neuronal and astrocyte variations of these cycles. Bachelard (1997, pg 32-33) addressed the intracellular compartmentation of metabolism within a cell. It is the stereo-specific *in-vivo* metabolism occurring on the surface of the neuron and associated with the glutamate shunt that is defined here as electrostenolytic metabolism.

The powering of the neural system through electrostenolytic metabolism is dependent on many features of the vascular system for resources. In this sense, the power supply of the neural system operates in parallel with the metabolic systems supporting cell growth and homeostasis. Only the critical aspects of the vascular system will be discussed in this section.

As earlier, it is proposed that the passage of large particles through the type 3 plasma membrane for purposes of genesis and growth are outside of the scope of this work. In addition, the type 1 membrane is not only impervious to ions and molecules, it is a near perfect electrical insulator. The passive nature of the type 1 membrane prevents it from participating in the electrostenolytic process powering the neurons. The subject of this section will be the passage of fundamental charges through type 2 regions of the BLM and the inducement for such passage by the electrostenolytic processes. As noted in **Section 1.1.3.2.3**, it is the high mobility of holes in the semi-metallic water lattice forming the base of each Activa that defines the electrical requirements of the neuron. For analog circuit operation, the collector must be biased negatively with respect to the base region. When this requirement is met, the injection of holes (extraction of electrons) from the emitter (due to a positive change in emitter to base potential) will cause a proportional number of electrons to pass from the collector to the base region of the Activa. This loss of charge on the capacitance associated with the collector causes the collector voltage to become more positive.

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[25]Bachelard, H. (1997) Magnetic Resonance Spectroscopy and Imaging in Neurochemistry. NY: Plenum Press

[26]Ross, B. Lin, A. et. al. (2003) Clinical experience with ^{13}C MRS in vivo *NMR Biomed* vol. 16, pp 358-369

As a result of this method of operation, it is necessary to provide a set of biases to the terminals of the Activa that will sustain the above operation. These biases are established by an electrostenolytic process associated with regions of type 2 BLM dedicated to this task.

This section will address the operation of the neural system without regard to its homoeostatic and growth functions. The emphasis is on the unique requirements of the neurons to achieve different electrical potentials within the different electrical conduits of the neuron. These conduits are usually described as the lemmas of the cell. The dendrolemma, podalemma and axolemma are physically distinct from each other.

McIlwain & Bachelard have provided a comprehensive description of the Biochemistry of the Central Nervous System[27]. However, it is interesting to note they do not discuss the stereochemistry or electrostenolytic chemistry so crucial to the provision of power to the neurons. Otherwise, their coverage of the biochemistry of the CNS is very broad.

Ruscak & Ruscakova have provided very valuable data on the presence of glutamic acid and GABA in the brains of mice under a very broad range of experimental conditions[28]. Although addressed from a different perspective, it is proposed that their findings are in total agreement with the expected results based on the theory presented below. Ross, Lin, et. al., and the recent work edited by Blanchard, have extended their work considerably. These works have begun to consider improper operation of the TCA within astrocytes, as potentially related to Alzheimer's Disease (which they associate with a mitochondrial disorder). Ross, Lin, et. al. propose that "Alzheimer's may represent a failure of glutamine-glutamate cycling and glutamate neurotransmission". However, they did not address the glutamate shunt per se, and the consequences of a malfunction of the electrostenolytic metabolism associated with this shunt. Their discussions did not include the role of GABA. This work would suggest the problem focuses on the availability of glutamate and its electrostenolytic conversion to GABA while powering the neurons.

3.2.1 Electrical power requirements of the neural system

It is the hydraulic and nutritional properties of the eye and optic nerve that support the operation of, and control the adaptation characteristics of, the visual system. This section will illustrate the role played by these portions of the overall biological system in supporting the neural system, especially regarding vision.

3.2.1.1 The power requirements presented symbolically

The hydraulic and metabolic systems play a very important role in determining the state of adaptation of the visual system. Because of this fact, a description of this role is illustrative of the general requirement. **Figure 3.2.1-1** illustrates the relevant elements of the system. The amplifiers shown in symbolic form are the adaptation amplifiers of the individual photoreceptor cells. They receive excitation from their respective spectrally selective Outer Segments. They deliver their output to their respective distribution amplifiers also contained within the photoreceptor cells. The amplifiers normally employ internal negative feedback. However, they are drawn as if they used negative external feedback to highlight this function. The capacitances, C_A, are shunted across the nodes shown by the black dots and no external path back to the input of the amplifiers exists.

The crosshatched blocks are the electrostenolytic supplies to each amplifier. These supplies are connected in parallel to the vascular system as shown at the top of the figure. The vascular system is shown by an electrical analog where the capacitors represent hydraulic

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[27]McIlwain, H. & Bachelard, H. (1985) Biochemistry and the Central Nervous System. NY: Churchill & Livingstone.

[28]Ruscak, M. & Ruscakova, D. (1971) Metabolism of the nerve tissue in relation to ion movements in vitro and in situ Baltimore, MD: University Park Press pp 85-98

reservoirs and the resistances represent the impedances of the vascular channels. The symbols, V_x, represent the energy potential of the vascular system at a given point. The relative values of these elements are not currently known. However, the multistage character of this network is the source of the dark adaptation characteristic of the visual system. The differential equation describing this situation is third order. Its solution results in the exponential sinewave that is characteristic of the dark adaptation function. See **Section 12.5.3** and **17.6.1**.

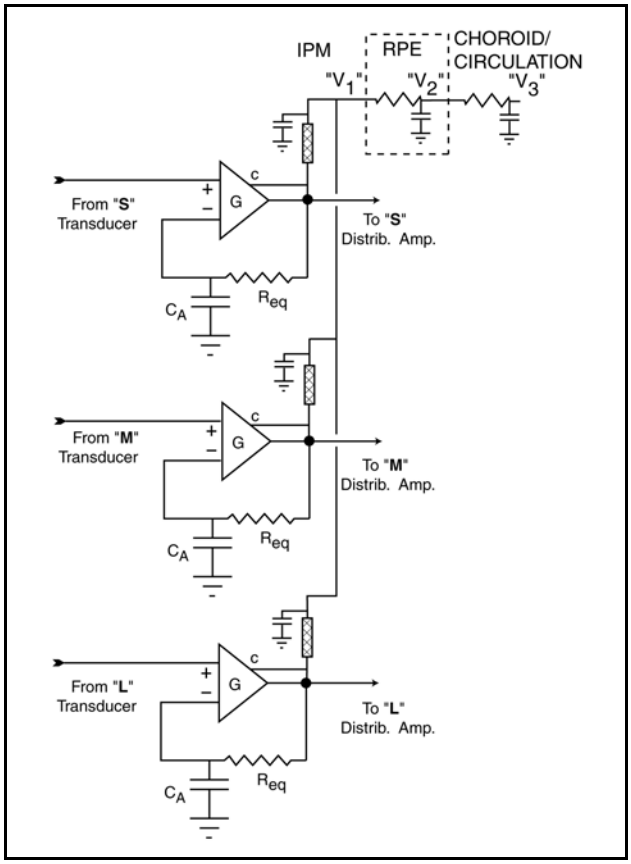

Figure 3.2.1-1 The adaptation amplifiers share a common power supply. The adaptation amplifiers are shown symbolically to highlight what is normally an internal feedback mechanism (C_A & R_{eq}). The gain of each amplifier is controlled by the voltage applied to the collector terminal, c.

The supply of electrostenolytic materials to the neurons of the visual system is a responsibility of the vascular system. The adequacy of the vascular system in meeting this requirement is represented most clearly by the variation in sensitivity of the photoreceptors as a function of their position in the retina. Although addressing the subject from a different perspective, Spillmann & Fuld[29] and Wooten, et. al[30]. have provided valuable information in this area. They test a concept that attempts to account for the variation in sensitivity with position in the retina by a single function that can be described as an equivalent illumination (a dark light?). Their results showed that each location followed its own time course. The process was obviously more complex than they suspected. However, their data is good. It allows one to determine the relative impedance and time constant of the vascular supply system serving each photoreceptor (or each zone) of the retina. This is particularly useful in calculating the adaptation characteristic as a function of position in the retina. It also provides a method of specifying the magnitude of the Halo Effect seen in conjunction with high contrast edges in the field of view.

3.2.1.2 The power requirements presented at the circuit level

The above paragraph establishes the need for a power source of about -150 to -154 mV. As discussed in **Chapters 8 & 9**, the Activas of any neural circuit must normally be biased such that the emitter terminal (the dendroplasm) is negative with respect to the base terminal (the podaplasm). To satisfy the variety of bias requirements required in different circuit configurations, a potential source of -25 to -30 mV is needed. While such a potential can be derived from the higher potential, it would be more efficient if a lower electrostenolytic voltage source were available.

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[29]Spillmann, L, & Fuld, K. (1979) The equivalent background and retinal eccentricity. Vision Res. vol. 19, pp. 117-122

[30]Wooten, B. Fuld, K. & Spillmann, L. (1975) Photopic spectral sensitivity of the peripheral retina. J. O. S. A. vol. 65, pp. 334-342

3.2.2 Use of Glutamic acid in neural metabolism, i.e., electrostenolysis

There is a dichotomy in the biological literature. Two amino acids have gained the distinction of being labeled "nonessential amino acids," aspartic and glutamic acids. This label is a bit misleading, at least in the case of glutamic acid. It does not imply these amino acids are not essential to the organism; they are critical to all animals. It was meant to imply that the animal need not ingest them since it can readily manufacture them from other materials. They are the only two amino acids with two carboxyl acid groups. This makes them polar and negatively charged (acidic)[31]. Tyrosine, while acidic, does not have two carboxyl groups (a critical factor in the stereochemistry of electrostenolysis). These unique features are critically important to neural cells and the operation of the neural system of an organism. The neural literature is well aware of the importance of glutamic acid (generally glutamate in pharmacology) in the operation of the neural system and vision. Unfortunately, their precise role in the neural process has not been recognized.

Donnerer & Lembeck[32] have made an interesting observation by quoting Kmjevic in 1970, "During the 1960's (the 'Dark Ages') excitatory amino acids and GABA were regarded as pharmacological curiosities. In the 1970's (the Renaissance') glycine was established as an inhibitory transmitter in spinal cord interneurons. In the following 'Baroque Era', the physiological role of glutamate was established, an advance mainly based on the discovery of specific antagonists." The metaphors and the terminology suggest the exploratory character of this early work. It did not place the role of glutamate and GABA in the larger context they deserve. In an earlier paragraph on the same page, they did place these materials in a better position. "Other important arguments against amino acids as transmitters were that they produced prompt, powerful, and readily reversible but redundant effects on every neuron tested; the dicarboxylic amino acids glutamate and aspartate produce excitation, and the monocarboxylic ω-amino acids GABA and glycine produce a qualitatively similar inhibition." This latter quotation (with slightly updated terminology and an expansion to include BAPA, the monocarboxylic residue of aspartate decarboxylation) is much closer to the current beliefs and actual operation of these materials developed in this work. Their discussion of receptor sites is also largely the work of exploratory research and not the development of a comprehensive theory.

Young & Ajami have provided a Keynote presentation (a significant review) of glutamate from a nutritional perspective as part of a special supplement to the Journal of Nutrition[33]. The paper is extensive, authoritative and important. However, its keywords and text do not include any discussion of neural physiology, electrostenolytics or even the role of glutamate in taste (gustation). This is in spite of a discussion of the Citrus Cycle that is broad and even includes a listing of enzymes affecting each of a dozen process paths. It does not however include any discussion of the glutamate shunt, or the role of GABA in this shunt. Neither does it discuss whether this shunt involves an enzyme or an electrostenolytic mechanism independent of any enzyme.

Young and Ajami introduce glutamate, aspartate and a third material aminoadipate acid (AAA) as homologs. However, aminoadipate acid, containing two additional backbone carbons, has not been reported to exist in mammals. They focus on the interatomic distances between two "proximate" oxygen atoms, one in each of the carboxylic acid groups. Although of major interest in nutrition, this relationship is not critical to the electrostenolytics of the neural system. While discussing the broad presence of glutamate in the physiological system, they did not address the close association between glutamate and the individual neural pathways. Neither did they address the dipole moment or dipole

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[31]Pethig, R. (1979) Dielectric and electronic properties of biological materials. NY: Wiley pp 36-39

[32]Donnerer, J. & Lembeck, J. (2006) The Chemical Languages of the Nervous System. NY: Karger pg 170

[33]Young, V. & Ajami, A. (2000) Glutamate: An amino acid of particular distinction *J Nutri* Suppl.vol 130, pp 892S-900S

potential of these homologs.

Glutamic acid (glutamate) has been given the label neurotransmitter based primarily on the fact that its presence enhances neural activity. On the other hand, the presence of GABA appears to depress neural activity. It was therefore labeled a neurotransmitter blocker. McGeer said in 1987 "Nevertheless, it must be recognized that truly definitive markers that can be applied at the cellular level do not exist for glutamate and aspartate as they do for several other neurotransmitters. Therefore, evidence for neuronal identification and for pathways involving these amino acids must in all cases be considered as tentative."[34] More recently, N-acetyl aspartate has been identified as a marker for aspartate[35]. NMDA, N-methyl-D-aspartate is a frequently mentioned variant of glutamate/apartate used in experiments. This work holds that glutamate is a neuro-facilitator, and GABA is a neuro-inhibitor due to their roles in the electrostenolytic process providing electrical power to the neurons. Neither material plays any direct role in signal transmission across a gap junction. Fuster has asserted that, "Glutamate is the most abundant excitatory neurotransmitter in the central nervous system[36]." He also asserted, "Gamma amino butyric acid (GABA) is the most abundant inhibitory neurotransmitter in the cortex, especially in synaptic terminals of non-pyramidal interneurons."

The broader role of all neuro-facilitators will be introduced in **Section. 3.5.4**.

The more recent work of Ross and others may have changed the situation with respect to markers[37]. They report N-acetyl aspartate is a marker for neurons, axons and dendrites (presumably all neurites).

The roles of glutamate as a neuro-facilitator and GABA as a neuro-inhibitor have gained attention recently due to a recently uncovered anachronism in fMRI investigations. While the use of glycogen in ultimately fueling the neural system is easily measured, the lack of an equivalent absorption of oxygen from the blood during a similar time period has come as a surprise. This subject is introduced in **Section 3.1.1**.

Glutamic acid is present in abundance in the CNS. It is used in protein and peptide formation, fatty acid synthesis, control of ammonia levels and many other functions. ***This paragraph will concentrate on the role of glutamate as the principal reactant in the mechanism providing power to the neural system***. As in nearly all biological systems, alternate manufacturing paths are provided to satisfying a requirement that is critical to the organism. Here, aspartic acid can play such a backup role. Other backup materials may also exist.

With respect to neurology, the vascular system is primarily involved in the transport of the reaction products supporting the electrostenolytic process common to the power supplies of all neurons. This is the metabolic reaction of the glutamates at the various surfaces of individual neurons. The glutamates participate in a "glutamate cycle" but not a glutamate cascade. The vascular system must bring the appropriate materials to each site and carry away the waste products. It must also support the storage of the reaction materials near the reaction sites in sufficient quantity to meet the variable demand under operational conditions. Fortunately, because of the location of the adaptation amplifiers at the very front of the electrical signal chain in the visual system, the variation in the consumption of electrostenolytics is small. Unfortunately, this has made it difficult to explain the ubiquitous presence of the glutamate cycle materials near neurons. Their consumption does not correspond to areas of high signal activity (as discovered by Wong-Riley).

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[34]McGeer, P. Eccles, Sir John. & McGeer, E. (1987) Op. Cit. pg 176

[35]Ross, B. Lin, A. et. al. (2003) Clinical experience with ^{13}C MRS *in vivo, NMR Biomed* vol. 16, pp 358-369

[36]Fuster, J. (2003) Cortex and Mind: Unifying Cognition Cambridge, Eng: Oxford Univ Press pg 48

[37]Ross, B. Lin, A. et. al. (2003) Op. Cit.

24 Neurons & the Nervous System

An important aspect of glutamate utilization is its limited ability to cross the blood-brain-barrier[38]. This requires that the vast majority of the glutamate used within the brain be created from glycogen within the brain enclosure.

Many references to the concentration of materials related to glutamate cycle along the neurons of the body appear in the literature. Lolley, et. al[39]., referencing Blanks & Johnson[40], say that the individual photoreceptor cells are "coated with a mixture of glycoproteins and glycolipids which may play important roles in maintaining the unique structural and/or functional organization of the cell." They did not further define the chemical nature of these materials. Korschen, et. al. have provided a more detailed mapping of materials in intimate contact with the photoreceptors[41]. Similar statements appear concerning other types of neurons. Whereas, glutamate is frequently present as ligands in short glycolipids, the properties of these lipids are not of significance here.

Berman has presented considerable information on the metabolism employed by the visual system. However, She did not explore any electrostenolytic systems[42]. She shows two versions of the tricarboxylic acid cycle including a variety of associated cycles (fig. 7.2 & 7.20). Her notation uses that of the nutritionist, glutamic acid is called glutamate. These cycles show glutamate involved in many individual reactions occurring at a great many locations. Her Table 7.2 shows the concentration of free amino acids in a variety of retinas. There is no discussion of more complex molecules such as the GARPs, glutamatic acid rich proteins, that have been proposed to support the overall metabolic process.

Most works on physiological chemistry employ the glutamates along with other simple amino acid groups in the energy cycles supplying individual cells and the elements interior to these cells. Overall, these processes do not involve the constant and rapid flow of these materials through cell membranes. Usually, the materials are found on both sides of the membrane and only electrons (and/or holes [H^+depending on the terminology used]) actually transverse the membranes. (The biological community seems to prefer the concept of transporting protons through membranes instead of electrons. In fact, protons almost never transit material with a crystalline lattice and it is doubtful that they actually transit liquid crystalline lattices. Electrons have much higher mobility within lattices and the net result is the same.)

Most of the biological system is powered by reactions involving a series of amino acids and their derivatives. These reactions have been categorized and grouped into a series of cycles by those studying metabolism and nutrition. One of these major cycles is the glutamate cycle. It is normally shown as generating energy by creating glutamic acid and NAD^+. These reactions are characterized by the movement of hydrogen ions (or conversely electrons) between various species in the reactions. These reactions are usually discussed as if they were taking place in solution. However, many of them can take place equally well on a substrate. In this electrostenolytic case, the electron or proton freed or absorbed can be transferred to the substrate and ultimately across the substrate to its opposite surface. This electrostenolytic case is the foundation of the electrical power generation system used to

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[38]Mc Geer, P. Eccles, Sir John. & Mc Geer, E. (1987) Molecular Neurobiology of the Mammalian Brain, 2nd Ed.. NY: Plenum Press pg 176

[39]Lolley, R. Lee, R. Chase, D. L& Racz, E. (1986) Rod photoreceptor cells dissociated from mature mice retinas. Invest. Ophthal. Visual Sci. Vol. 27, no. 3, pp 285-295

[40]Blanks, J & Johnson, L (1983) Selective lectin binding of the developing mouse retina. J Comp. Neurol. vol 221, pp 31

[41]Korschen, H. et. al. (1999) Interaction of glutamic-acid-rich-proteins with the cGMP signaling pathway in rod photoreceptors *Nature*, vol. 400, pp 761-766

[42]Berman, E. (1991) Biochemistry of the Eye, NY: Plenum Chap. 1 & 7

support the electrolytic operations of the neural system.

A broad review of all of the possible sources of energy to support the neural system of an animal could not be found in the literature. Gutmann & Keyzer have addressed selected potential sources and referred to reviews by Kell and by Berry[43]. Their attention appears to be drawn to the potentials and differences between concentration gradient sources and fuel cell sources. Both of these sources involve ion transfer across a membrane.

3.2.2.1 Background

The basic premise to be developed here is; there is an electrostenolytic energy loop occurring at selected locations on the surface lemmas of neurons. At these locations, two members of the glutamate family, glutamic acid in a primary role and aspartic acid in a backup role, are reduced to provide electrical energy to the neuron conduits. The ultimate process may result in the formation of GABA (or a form of alanine, β-amino propionic acid, BAPA). However, there are a variety of intermediate processes and many terminate with glutamic acid. In the process of immediate interest , energy is released that is realized as a voltage potential across the lemma of the neuron. Other simple waste products are also released into the surrounding matrix. It is proposed that this is the mechanism used to power all animal neurons. This premise does not require the physical transport of ***any*** ions through the plasma membrane of the neuron for purposes of powering the neuron. Such transport may occur for other purposes.

The subject of electrostenolysis is too complex to detail here. Eyring[44] and Marino[45] have provided texts including sections on this subject but not in the detail required below. For that, more focused material such as Finkelstein[46] and Gutmann & Keyzer[47] should be reviewed.

3.2.2.1.1 Background related to architecture

The neurons of the visual system are each supported by multiple, individual, limited capacity power sources based on electrostenolytic principles. This reminds one of the old battery radio days when the A battery heated the filaments, the B battery supplied the high voltage and the C battery provided the bias voltage required. To reduce the number of batteries required, the circuits were AC coupled. This allowed certain batteries to be shared. It also avoided another problem associated with DC coupled circuits, supply voltage creep. It is very difficult in DC coupled circuits to avoid a step-wise rise (or fall) in the output circuit voltage of each amplifier stage. This is because of the need to maintain the appropriate voltage difference between the output and input circuits of a given stage. This problem can be overcome in semiconductor circuits by using a combination of PNP and NPN type active devices. To date, no NPN type devices have been found in the neural literature.

In a long string of amplifiers, only two practical solutions to the voltage creep problem exist. One is to introduce at least one stage of AC coupling. The other is to use saturable switching circuits. The last solution is the one used in the vision process. A certain amount of voltage creep is accepted in the analog (electrotonic) signal processing circuits of the retina before the ganglion cells. The ganglion cells encode the previously analog signals to binary pulses in order to avoid additional voltage creep. Subsequent transmission amplifiers operate in a

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[43]Gutmann, F. & Keyzer, H. (1986) Modern Bioelectrochemistry. NY: Plenum Press, pg 90

[44]Eyring, H. (1970) Physical Chemistry: An advanced treatise. Vol IXA/ Electrochemistry NY: Academic Press.

[45]Marino, A. (1988) Modern bioelectricity. NY: Marcel Dekker

[46]Finkelstein, A. (1987) Water movement through lipid bilayers, pores and plasma membranes. NY: John Wiley & Sons. pp-94-114

[47]Gutmann, F. & Keyzer, H. (1986) Modern bioelectrochemistry. NY: Plenum Press, Chapters 2 & 3

saturation mode until the decoding circuits of the brain are reached.

3.2.2.1.2 Role of glutamate and GABA in retinal metabolism

The clinical science course of the American Academy of Ophthalmology has provided a succinct discussion of the metabolism of the retina[48]. It is too general for the purposes of this work. However, it notes the potent role of glutamic acid and GABA on retinal operation. They specifically note the ability of "millimolar concentrations of the compounds to cause an excitation block of the retina, rendering all cells except photoreceptor cells non-responsive to light stimulation." This is clearly due to the presence of the outer limiting membrane that isolates the electrolytic source of the a-wave within the inter photoreceptor matrix from attack by these materials. The article also notes the following with regard to neurotransmitters. "In spite of the data for putative glutamate receptors, there is no clear demonstration of release of glutamate or aspartate from photoreceptors in the dark. Therefore, this identification as photoreceptor cell transmitters is tentative." As noted in this work, the receptors are actually electrostenolytic sites that are not involved in signaling.

The paper also discusses the excess capacity of the retina to produce lactate relative to its metabolic needs, even in the absence of oxygen. It gives the production as 1.12 μmoles/mg dry wt/hr in the presence of oxygen and 80% higher in the absence of oxygen. Although it suggests the excess is removed by diffusion, it indicates the mechanism is unknown. In this work, it is converted into glutamic acid and eventually it is GABA that is removed or recycled.

3.2.2.1.3 The search to define materials used in neural electrostenolytics

Although amino acids are often described as functioning primarily as precursors of proteins and other biomolecules, they are often used as a source of energy. Lehninger[49] devotes two chapters to the oxidation of fatty acids and the oxidative degradation of amino acids. These categories include the glutamates, glycine and GABA. He says that higher animals actively oxidize both exogenous and endogenous amino acids obtained from the metabolic turnover of body proteins. He also says that free amino acids are readily absorbed through cell plasma membranes. It appears this sentence is too broad and should probably be interpreted as at least one region of the plasma membrane is capable of supporting such absorption. Lehninger indicates there are 20 different flow sheets for amino acid oxidation. Several of these sheets include the glutamates, glycine and GABA. Many terminate with the formation of glutamic acid. This material is then transported to the kidney in the form of glutamine, to aid in the excretion of ammonia. Lehninger also devotes a chapter to the biogenesis of the same fatty acids. In essence, these materials are used over and over again within the body through a series of metabolic cycles.

Many of the above bio-energetic processes were being annotated during the 1930-50 time period. Those involving the glutamate cycle appeared to be involved in powering the neurons of the neural system. The presence of the glutamates on the surface of neurons would be expected and is well known. In general, the presence of these materials near the plasma membrane walls of neurons was determined during this same period and prior to the introduction of the electron microscope.

Because of the cyclic uses of many amino acids within the animal system, it is difficult to differentiate between the consumption and the generation of a particular constituent at a given location.

Whereas most of the discussion in Biochemistry, concerns the interaction of the above compounds and the release of energy via the conventional agents (ATP, ADP and $NAD^{+)}$, electrostenolysis provides another path to the release of energy. This release is in the form of electrons subsequently stored on one or more capacitors (the lemma of the neurons). The result is an electrical potential that is used to bias the Activas of the neurons.

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[48]— (1992) Fundamentals and Principles of Ophthalmology, section 2 *in* Basic and Clinical Science Course. San Francisco, CA: American Academy of Ophthalmology pp 191-198

[49]Lehninger, A. (1972) Biochemistry, 6th printing NY: Worth Publishers Chap. 19 & 20

The extensive 1981 review by Puil is of great value in describing the impact of electrostenolytics on the neuron[50]. However, his basic model was of a dynamically porous membrane wall along the lines of Huxley, Hodgkin & Katz (See **Sections 10.8.3 & 10.8.4**). Because of this, he does not differentiate carefully between probing (or stimulating) the individual dendroplasm, the podaplasm and the axoplasm of a given neuron. The paper has a considerable number of 'however," "on the other hand" and "alternately" expressions when discussing the effect of a given chemical on a neuron. This is at least partly due to the wide variety of investigators referenced. Techniques and interpretations varied widely. The use of a three-terminal neural model eliminates many of these ambiguities and inconsistencies.

Puil observed that the topical application of glutamate to a neuron resulted in a hyperpolarization of the associated plasma inside the neuron (pg 234), "an indication of enhanced excitability of these terminals in the frog and the cat." He goes on to note, In the isolated amphibian spinal cord, either super-perfusion by bath application or intra-arterial perfusion of S-glutamate produces a negative DC-potential shift which may be measured with pairs of non-polarizable Ag-AgCl electrodes, and also by the sucrose-gap method, on dorsal as well as ventral roots " (accompanied by a long list of references). He further notes, "The responses are relatively constant, usually showing no evidence of fade or tachyphylaxis and they completely disappear within a few seconds after withdrawing glutamate." Puil also investigated iontophoretic response over a range of concentrations of glutamate, ultimately resulting in toxicity. This demonstrates the care required in discussing the effect of glutamate concentration on the neural system.

It is important to note that in much of Puil's subsequent discussion, he speaks of the hyperpolarization or depolarization of the axon associated with a neuron. There is no one-to-one correlation between the hyperpolarization of a plasma adjacent to an electrostenolytic site and the change in polarization of the distinctly separate axoplasm. The impact on the axoplasm depends on whether the dendroplasm or the podaplasm was hyperpolarized.

Puil performed microiontophoretic experiments to determine the point of action of glutamate on a neuron. While, he discussed a range of difficulties associated with delivering a precise amount of glutamate within a specific volume associated with the surface of a neuron, he did draw several conclusions with respect to motoneurons. He noted, "(1) evidence that the dendritic regions of feline motoneurons are more sensitive to S-glutamate than the soma, (2) the possible diversity or variations in the sites and extent of uptake of glutamate and its analogues by neurons or glia. . . ." And, "Axons of motoneurons have been found to be relatively insensitive to S-glutamate." These observations are easy to rationalize based on the three-terminal model of the Activa and the neuron.

Puil also noted, "The discharges evoked by S-glutamate can be blocked by microiontophoretic applications of procaine to the same cell."

Puil was working with micropipettes having short, <150 microns, and longer, 150-350 micron, intertip distances. These are very large numbers relative to most neurons. His Section 4.1 is also based strictly on a dynamic and porous membrane model.

Puil noted the similar action of aspartic acid to that of glutamic acid. He also noted that the chirality of these two acids had little effect on their actions.

Finally, Puil noted the impact of various analogs of glutamic and aspartic acid on the neurons. "When applied microiontophoretically to spinal neurons only a few amino acids other than the closely related homologues of S-glutamate have been found to produce excitation with exactly the same characteristics as those of S-glutamate." Many of the materials they investigated exhibited a reduction in the root potentials in a reversible manner. However, the rate of recovery following application of these materials was frequently very slow. These materials appear to operate similarly to L-Dopa, the current drug

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[50]Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res Rev* vol. 3, pp 229-332

of choice in Parkinson's Disease (See **Section 18.8.5.3**).

> Puil has provided an extensive list of analogs and chemicals closely associated with the glutamates (pp 304-6).

Puil's paper appears to be highly compatible with the thesis of this work that the electrostenolytic process occurs at specific locations on the surface of the individual lemma of a neuron by stereospecific electrostenolysis. To accomplish this, the portion of the lemma must be electronically asymmetrical and the reactant must be stereochemically compatible with the polar (positive) portion of the phosphoglyceride forming the outer layer of the lemma. To accomplish this, it appears the reactant must be a dicarboxylic compound of specific stereochemistry. Puil stated this requirement somewhat more loosely based only on chemistry and a list of references, "initial studies quickly established the minimal requirements for the excitatory property: one basic and two acidic groups with α-decarboxylation of the parent molecule leading to a substance with depressant action (e.g. α-decarboxylation of glutamate yields GABA, a neutral, inhibitory amino acid. (pg 266)" Only one compound listed by Puil was not dicarboxylic in form (excepting a class where sulphur was substituted for carbon in the radical). When the one carboxylic group was replaced by a tetrazolic group, the resulting chemical showed no neural effect.

The above ground rules limit the primary electrostenolytic reactants to the two dicarboxylic (and negatively charged when in ionic form) amino acids, glutamic and aspartic acid, and there dicarboxylic analogs. Within the current wisdom, these materials are inappropriately labeled neurotransmitters. Within the context of this work, they are neuro-facilitators.

A broad range of other compounds may impact the rate of reaction at the electrostenolytic surface. These have generally been classed as false neurotransmitters in the current common wisdom.

While the proposed electrostenolytic process involves stereochemistry, it only requires a loose interpretation of the "lock and key" model usually used to explain the mechanism. The critical portion of the reactant molecule appears to be limited largely to the area close to the carboxylic group farthest from the amino group.

Polarity is important when discussing the impact of a chemical on a neuron. Except at toxic levels, application of glutamic and/or aspartic acid to an electrostenolytic site lead to a higher negative potential within the associated plasma. This is generally described as hyperpolarization. The change in potential associated with a subsequent action potential may be greater. Such a change is generally described as involving a larger positive going amplitude. This is because, the underlying DC level became more negative. Action potentials do not normally become more positive than the potential of the matrix surrounding a cell. However, determining this local potential is experimentally difficult if the matrix has a significant resistivity. The reference potential, measured at a remote location in the INM, may not reflect the local potential.

Aspartic acid appears to be a minor player in the electrostenolytic process at this time. Subsequent discussion will center on the role of glutamic acid.

As of 1986, Gutmann & Keyzer had not explored the roles of all of the metabolic materials found in the IPM and the interneural matrix of the eye. They do provide relevant material concerning Na^+, Ca^+, ATP and other related materials. Similarly, they were not aware of the active device within the neuron. Their Chapter 17[51] provides a qualitative attempt to explain the action potential based on simple fields and some very complex chemistry. These attempts are not required when the presence of an active device is accepted.

In the current literature, many authors are attempting to relate the metabolites present on the surfaces of the external neural membranes to the signal transmission task instead of the

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[51]Prepared by Kinnunen, K. & Virtanen, J.

electrical power generation task. These metabolites are extremely important to the operation of the nervous system but not as signal amplification and transmitting mechanisms. Further, the metabolites on one or both sides of the membrane control the actual potential produced by the power source. These metabolites are not found concentrated at the synapses. They appear all along the length of many types of neurons.

It is true that the consumption of the metabolites may be approximately related to the signal intensity at the adaptation amplifier. However, this is a very indirect and complex relationship of little theoretical or practical importance. Because of the high degree of negative feedback within the adaptation amplifier, the consumption of metabolites at later points in the signal chain is essentially independent of the signal intensity.

Each metabolic power source can be represented by a three-element electrical network, a perfect rechargeable battery in series with a perfect diode and the combination shunted by a capacitor. The current capability of the battery is dependent on three parameters. First, it depends on the electrical characteristics of the membrane. Second, it depends on the area of the available membrane wall. Third, it depends on the metabolic diffusion rates in the vicinity of the membrane and the sources of additional metabolites. The only available source is the vascular system. Similarly, the capability of both the diode and the capacitor are determined by (other) characteristics of the membrane and the available area of the membrane wall.

Only detailed experimentation can determine the exact parameters of these power supplies. The data would suggest that most of them are tailored to meet the operational requirement with little impact on the operating characteristics. A major exception occurs in the photoreceptor cells. These cells employ a variety of electrostenolytic sources to provide different potentials at different sites. Some of these potentials may only be used at these particular sites. The potential provided to the adaptation amplifier is of particular interest. The impedance associated with this power source has been tailored to provide the extremely wide acceptable signal amplitude range found in vision. The potential sources associated with the distribution amplifier of the photoreceptor cell are also specialized. Genetic errors in the establishment of these potentials appears to play a major role in achromatopsia (See **Section 18.8**).

3.2.2.1.4 GABA as a byproduct of electrostenolysis

Considerable data is available in the literature concerning GABA (gamma amino-butyric acid), Glycine and Glutamine in their various forms. Most of the data is the result of exploratory research. All three of these chemicals are closely related structurally and appear to concentrate in areas associated with neurons after exogenous intake. The functional role played by these materials has never been developed in detail (see 2005 activity by Patel et al. in **Section 3.3.2.2.2**). Recently, it has been proposed that a "glutamate cascade" is present in the signaling function related to vision. The proposal has been that such a conceptual mechanism provides an explanation for the high initial signal amplification process found in dark adapted vision. This work takes an entirely different view.

It is proposed that these materials are bio-energetic sources that participate along with other materials in powering the electrical operation of the neural system in animals. In this role, they are the most common materials involved in electrostenolysis at various specific locations along the outer membrane of the neuron. These sites tend to be grouped in areas designated as manifolds.

Lake et. al[52]. have demonstrated the metabolism of GABA and glutamine in the retina of various mammals. However, the quality of instrumentation available in their era limited the precision with which the location of these materials could be determined. It is proposed by this theory that their compartments are now known as (terminal) manifolds of the vascular system and these manifolds contain glia next to the specialized surfaces of all neurons. By performing uptake experiments, the conclusion was drawn that GABA accumulates in retinas more than in other areas of high neuron density. *If this is true, it would suggest that GABA plays a preferred role to other bioenergetics in the operation of neurons.* However, additional experiments are probably required

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[52]Lake, N. Marshall, J. & Voaden, M. (1977) Metabolic compartmentation and the metabolism of GABA and glutamine in retina pg. 354 *in Synapse, Cottrell & Usherwood* Op. Cit.

to show that GABA did not accumulate similarly in the brain, and the inner ear. Besides uptake experiments involving autoradiography, they showed that GABA reacted to form glutamine that they describe as a non-neuroactive compound. They also showed that the glutamine found in glia transferred to neurons, "where it is subsequently metabolized to GABA via glutamate, thus completing the cycle of GABA uptake by glia following neuronal release." They did not address the energy balance in these transitions or if electrostenolysis was involved. Their investigations suggest that these materials are found on the exterior surface of the axolemma in the area exposed to the interneural matrix. The reversible nature of the reactions involved makes the statement by Lake quite reasonable as part of the metabolic process. It appears the dominant reaction within the neuron, that generates electrons, is carboxylation[53].

More recently, Benson, et. al. have studied the role of glutamic acid in the nervous system[54]. Their concentration was on tracking an enzyme they describe as GAD (glutamic acid decarboxylase). However, they do not describe the reaction chemistry as a result of GAD, e. g. why a carboxyl group should be removed from glutamic acid?

Glutamine, in one form or another is an end product in a variety of bioenergetic reactions. Many of these reactions are very complex, include many steps, and are critical to the metabolism of the animal. As a result, many of these reactions are sufficiently well studies to have specific names. By providing energy to the animal, these reactions are ideal candidates to provide electrical energy to the neural system as well. By releasing energy in small steps, these materials are well suited to the requirement to supply electrical energy at approximately 150 mV to the neural system. The determination of what individual chemical reactions might be employed in the electrostenolytic process at the cell membrane to provide energy at this voltage level is beyond the scope of this work. However, the α-Ketoglutarate pathway is a likely analog. In such a case, the GABA would be transformed into glutamic acid with the release of an electron. The electron released by the reaction would be transferred through the wall of the membrane instead of being transferred to a molecule of nicotinamide adenine dinucleotide, NAD^+.

More recent investigations approach the electrostenolytic process from a different perspective. Steriade, et. al. state, "there is reason to believe, mainly from neurochemical studies, that GABA may be released by afferent pathways. . . ."[55] They also say, "All of the reticular nucleus cells appear to produce gamma-aminobutyric acid (GABA). . . ." This theory proposes that the glutamate-GABA reaction is the source of electrical power for the neural system and *neither* of these chemicals participates directly in the signaling function. In this context, the materials are present primarily in specialized regions on the external surfaces of neurons devoted to the creation and sustenance of the intrinsic membrane potential associated with a given plasma compartment within a neuron. The materials are delivered to the specialized regions from the blood stream by the interneural matrix following ingestion. This electrostenolytic process is the key to the very high thermal efficiency of the neural system. Normally, the material is converted in a reaction cycle. However, the crucial step of supplying electrons to the plasma within a cell by electrostenolysis is reversible. Glutamic acid is well known for its importance in reactions providing energy[56].

3.2.2.1.5 Relation of glutamic acid and GABA to neural metabolism

Whereas the notion of a glutamate cascade requires a mechanism for controlling the level and termination of such a cascade, this theory does not. To interpret the role of this chemical complex in the operation of the photoreceptors of vision, separating the photoexcitation/de-excitation role from the photo-translation role is appropriate as done

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[53]Lehninger, A. (1972) Biochemistry NY: Worth Publishers pg. 446

[54]Benson, D. Isackson, P. Gall, C. & Jones, E. (1992) Contrasting patterns in the localization of glutamic acid decarboxylase and Ca2+/calmodulin protein kinase gene expression in the rat central nervous system *Neurosci*. vol. 46, no. 4, pp 825-849

[55]Steriade, M. Jones, E. & Llinas, R. (1990) Thalamic oscillations and signaling. NY: John Wiley, pg 62 & 84

[56]Lehninger, A. (1972) Op. Cit. Chap. 20, Oxidative degradation of amino acids

earlier. Both processes have been explained without relying upon the presence of the glutamic acid-GABA electrostenolytic reaction explicitly. However, it does support the power requirements of the adaptation amplifier within the photoreceptor cell. This requirement is unusual due to the voltage breakdown and resulting variable gain characteristic of this amplifier.

+ At very low excitation levels, the gain of this amplifier is about 4000:1. Approximately 4000 electrons flow in the collector lead of the Activa within this amplifier for every electron-hole pair created in its base region. As shown earlier, a direct and linear (except in the L-channel) relationship exists between the number of photons incident on the chromophores of the disks and the number of electron-hole pairs created in the base region. Under this very low current level through the adaptation amplifier, the voltage between the collector and base is high. This causes any electrons formed in the base region to be swept out of the region at high speed. This speed is high enough that any collision with other electrons in the lattice can cause their excitation into the valence state. The result is current multiplication by what is known as the avalanche effect. [The term is analogous to the putative molecular "cascade" of the glutamate cascade theory.]

+ as the excitation level rises, one electron-hole pair is still created for every photon absorbed. However, the electrical power supply to the adaptation amplifier is not stiff. It cannot meet the current demands of the amplifier and the collector to base voltage drops. As this voltage drops, the number of electrons generated by the avalanche effect drops, and the overall current gain of the amplifier drops below 4000:1. It eventually reaches 1:1 under high levels of excitation. This level corresponds roughly to the photopic illumination level in vision.

All of the current flowing through the collector of the adaptation amplifier must be supplied from the electrical power supply. The voltage supplied to the collector varies with both the time constant of the power supply and previous consumption levels. The performance of the power supply is best described using a state variable approach. The current supplied at a given instant is a strong function of the current instantaneous level of excitation and the earlier excitation level and its impact on the performance of the power supply.

Assuming each electron flowing in the adaptation amplifier collector must come from an individual bioenergetic reaction, the consumption of bioenergetic material is a variable that can be computed precisely as in every other active semiconductor circuit employing the avalanche effect. The instantaneous consumption, in terms of electrical charges flowing per incident photon, is very high at low excitation levels following dark adaptation. As the adaptation is changed, the instantaneous consumption for the same amount of excitation will decrease. Upon reaching the photopic level of adaptation, the instantaneous current consumption will now reach a level approximating one electron per photon absorbed.

It is interesting that the effect of the avalanche effect is to reduce the current consumption as a function of the photo-excitation level. This is not the image provided by the notion of a cascade. The avalanche effect provides a large amount of negative feedback in the adaptation amplifier circuit. This is done to stabilize the output level of the photoreceptor cell and not overload the remainder of the neural system of vision at high illumination levels. The role of the bioenergetic materials is to provide the current called for by the performance of the overall circuit. No additional governing mechanism is required to control how much bioenergetic material consumed at this location.

3.2.2.1.6 Unique stereochemistry of glutamic and aspartic acids

By reviewing the pharmacological performance of glutamic and aspartic acid in Section 18.8.5.3 and the fundamental structures of the common amino acids, an interesting feature appears. These two amino acids are the only dicarboxylic amino acids. Because of this feature, they can be described as acidic amino acids. They are the only amino acids exhibiting a negative charge in ionic form. These materials also exhibit an ability to engage in a stereochemical relationship with the phosphoglycerides of the membrane walls. They also show a propensity to lose one of their carboxylic groups through the release of carbon dioxide. The aggregate of these properties shows why these two materials play a unique role

in the electrostenolytic powering of the neural system.

3.2.2.2 Underlying physical chemistry of electrostenolytic conversion

The molecular chemistry involved in creating electrical power from metabolites will not be discussed here. However, the concept of "hole" transfer, as an alternative to hydrogen ion transfer, through a membrane is critical to understanding electrostenolytics.

Gutmann & Keyzer[57] have prepared a comprehensive work on the general subject of bioelectrochemistry but have not addressed the more specific field of electrostenolytics. The most important point is that the use of the electrostenolytic effect, or electrodics in the vocabulary of the above authors, can lead to very high operating efficiencies. The second most important point is that ***the electrodic model of gates in a membrane is a caricature.*** **No physical gates controlling the flow of ions exist in the biological membranes corresponding to this caricature.** The caricature is used to represent the actual chemiosmotic situation for a continuous membrane immersed between two different solutes and porous to electrons and/or holes.

> A hole, if discussed at all in biology, is usually thought of as ionized hydrogen atom moving through a membrane. It is actually the site of a missing electron in a crystalline lattice. This hole is continually filled by an electron at a nearby site jumping into the empty site. The result is the apparent movement of an empty site, a hole, in the opposite direction to normal electron flow. At the terminal surface of the lattice, an electron from a neutral hydrogen or other atom may contribute an electron to fill the hole now on the lattice surface. Similarly, at the other surface, an electron may leave the lattice and become associated with a positively ionized atom, thereby neutralizing it. The net result from an external perspective is the apparent movement of a positive ion through the lattice.

3.2.2.2.1 The electrostenolytic mechanism

Berry has described the passage of electrons through a biological membrane. The membrane cannot be of type 1; it must be type 2 or type 4.

Applying the laws of both electrostatics and electrodynamics carefully to the biological plasmalemma is important. It exists in several optimized regions that may operate differently. Hodgkin & Huxley did not differentiate between the possible types of plasmalemma. Their concept is not compatible with either type 1 (symmetrical) or type 2 (asymmetrical) membrane. Whatever its type, each region of a membrane exhibits an electrical capacitance. This capacitance is defined by the potential produced across the membrane per unit of (net) charge deposited on one side of a unit area of the membrane. For asymmetrical (type 2) membranes, the measured capacitance may be a function of the polarity and magnitude of the applied potential.

For a closed membrane, several possible sources of the above charge exist. First, individual electrons may cross the membrane and create a net charge imbalance. Second, at least theoretically, heavy ions can cross the membrane and create a net charge imbalance.

Note that a net electrical charge cannot exist within the volume of a closed membrane filled with an electrolyte. The laws of electrostatics say that all of the individual charges will repel each other. This will cause all of the net charge to migrate through the electrolyte and be deposited on the wall of the enclosing membrane. **The bulk of the plasma within the membrane will remain neutral under any steady state conditions**. Similarly, any excess (net) charge on the plasma outside the membrane will accumulate on the surface of the membrane. **The bulk of the surrounding plasma must remain electrically neutral**. These statements are compatible with the discussion in **Section 0.4.2.7**.

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[57]Gutmann, F. & Keyzer, H. (1986) Modern Bioelectrochemistry. NY: Plenum Press

At least two methods exist to move *electrons* across a BLM. The first involves the transfer of electrons through the membrane by conventional chemical processes. In the case of the biological membrane, the electrons must be moved in opposition to the existing electrical potential. This is achieved using a conventional battery charging circuit that is implemented by the mechanism of electrostenolytics in this work.

The second method of transfer involves the movement of electrons into (or out of) a closed membrane by "transistor action." Organic chemists have been attempting to achieve this type of transfer for at least the last 25 years. However, they have needed an invention. The Activa is the embodiment of the invention they have sought was the subject of **Chapter 2**.

It will be shown that the operation of a neuron depends on the transfer of electrons through a BLM by both methods, electrostenolytics and transistor action.

> This section will not address the question of whether charge is transported through the BLM by electrons in the conduction band or holes in the valance band. This question was addressed in **Sections 1.3** & **1.4**.

3.2.2.2.2 Electrostenolysis vs the role of GAD in metabolism

An enzyme, glutamic acid decarboxylase (GAD) has been identified with respect to the conversion of glutamate to GABA in conventional carbohydrate metabolism. It has been found in plants and animals (in chordates as well as other phyla). GAD is found in many organs of the body that are unrelated to the neural system. GAD has been well characterized and found to exist in at least two forms in humans, one of 65 kDa and one of 67 kDa. The amino acid sequence of one of these proteins is available on the internet[58]. The available literature discusses the above reaction without discussing the energy change involved.

The conversion of glutamic acid to GABA occurs in both the homeostasis and signaling oriented portions of the neuron. The conversion associated with homeostasis probably does involve GAD. However, the conversion associated with signaling appears to be significantly different. The conversion relies upon a portion of type 2 BLM to act as a substrate and in other aspects support the generation of electrical power for the neuron.

Care must be employed in the semantics used here. An enzyme is an organic catalyst. A substrate in inorganic chemistry can also act as a catalyst. In the case of GAD, the mechanism most discussed in the literature is that of a simple catalyst encouraging a carbohydrate metabolism reaction to take place without regard to the energy either released or absorbed. On the other hand, the type 2 BLM supports the same reaction while supporting the transfer of an electron through the membrane as a method of using the energy released in the reaction.

The participation of GAD in carbohydrate metabolism does not conflict with the conversion of glutamic acid to GABA in the absence of GAD as part of electrostenolytic metabolism.

3.2.2.2.3 The role of N-acetyl aspartate in neural operation

N-acetyl aspartate has recently become a subject of major study because of its appearance as a marker in magnetic resonance spectroscopy, a variant of MRI. It appears near lactate, creatine and choline in these recordings. Its prominence in recordings made of the brain using this technique have generated considerable clinical effort designed to understand its role. The material is associated with the tricarboxylic acid cycle and may be formed in a variety of ways. Most reactions appear to involve the important component acetyl CoA. However, N-acetyl aspartate does not appear to be directly associated with the glutamate-GABA shunt that is critically related to the operation of the neural system (**Section 3.2.3**).

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[58] harvester.embl.de/harvester/Q992/Q99259.htm

Many amplitude ratios between the signature of this chemical and others have been reported when comparing patients suffering from various diseases and the normal condition. To date, no specific role has been defined for this chemical in the operation of neurons. It remains only a marker.

3.2.2.2.4 Free energy of the electrostenolyitc process

Stone & Oliver provide course estimates of the free energy change parameter for the acidic amino acids that may be useful[59]. See **Section 8.5.6.3.2**.

3.2.2.3 The specific energy sources of the neural power supplies

A neuron under cutoff conditions exhibits a high negative axoplasm potential. It also exhibits the highest potential differences between plasmas. The high axoplasm potential suggests that an electrical source of about 150-154 mV (measured at 37° Celsius) is a primary requirement. If necessary, all other potentials can be obtained from this source. Alternately, a lower potential source of about 25-30 mV would be useful in supporting the needs of the neurites of a particular neuron. In both cases, the source must provide a negative potential to the plasma compared with the surrounding matrix.

The glutamate family plays a large role in providing energy for use in animal system. However, the actual chemical reactions involved in powering the neurological system have not been defined previously.

The generic name glutamate is frequently used in pharmacology but is not found in formal biochemistry, except with an anion partner. Although used as a specific term in most discussions of the glutamate cascade theory, it is usually used as a shorthand notation for glutamic acid in other disciplines.

The glutamate family, as defined below, contains a variety of members. They are all obtained ultimately from glucose by using a variety of citrate (Kreb) cycles. The glutamates appear to be derived locally along the neural pathways of the PNS. This ubiquitousness along the peripheral nervous system led to the unfortunate conclusion that it must be a major neurotransmitter of neurology. Later, it was found to be not only ubiquitous, but dominant among the amino acids within the brain cavity of the CNS. However, the literature remains committed to its role as a neurotransmitter. This work recognizes the role of glutamate as a neuro-facilitator and not a neurotransmitter. GABA is the reactive product of electrostenolysis of glutamate. Since its presence tends to inhibit the glutamate/GABA reaction, GABA has frequently been called a neuro-inhibitor.

Within the CNS, its presence is so general that determining its origin is difficult. It may be manufactured locally with respect to each neuron, in association with a nearby glia, or more generally within the volume of the CNS. One author has chosen to speak about one or more pools of glutamate within the CNS. However, he does not arrive at a location for such a physical pool.

Finding anything in the literature providing a concise comparison of the physiological metabolism of the neuron with other cell types is virtually impossible. Cantarow & Schepartz has provided a comparison of a variety of cell types (with the notable exception of the neuron)[60]. **Figure 3.2.2-1** places the neuron in perspective with respect to these other types of cells. The neuron exhibits a unique capability associated with the glutamate shunt. This

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[59]Stone, H. & Oliver, S. (1966) Beidler's theory and human taste stimulation *Percept Psychophysics* vol 1, pp 358-360

[60]Cantarow, A. & Schepartz, B. (1967) Biochemistry, 4th Ed. London: W. B. Saunders. pg 422

shunt is the source of power for the neural portion of the cell. It is the analog of the putative ion-pump of Hodgkin & Huxley. In the operation of the neuron, most of the activity associated with the Krebs cycle is devoted to supplying power to the signaling function. This activity is so intense that it has been suggested that the typical neuron cannot provide sufficient pyruvate via the glycolysis mechanism beginning with glycogen. The suggestion is that additional lactate is acquired from adjacent glial cells. See **Section 3.2.6.2.3**.

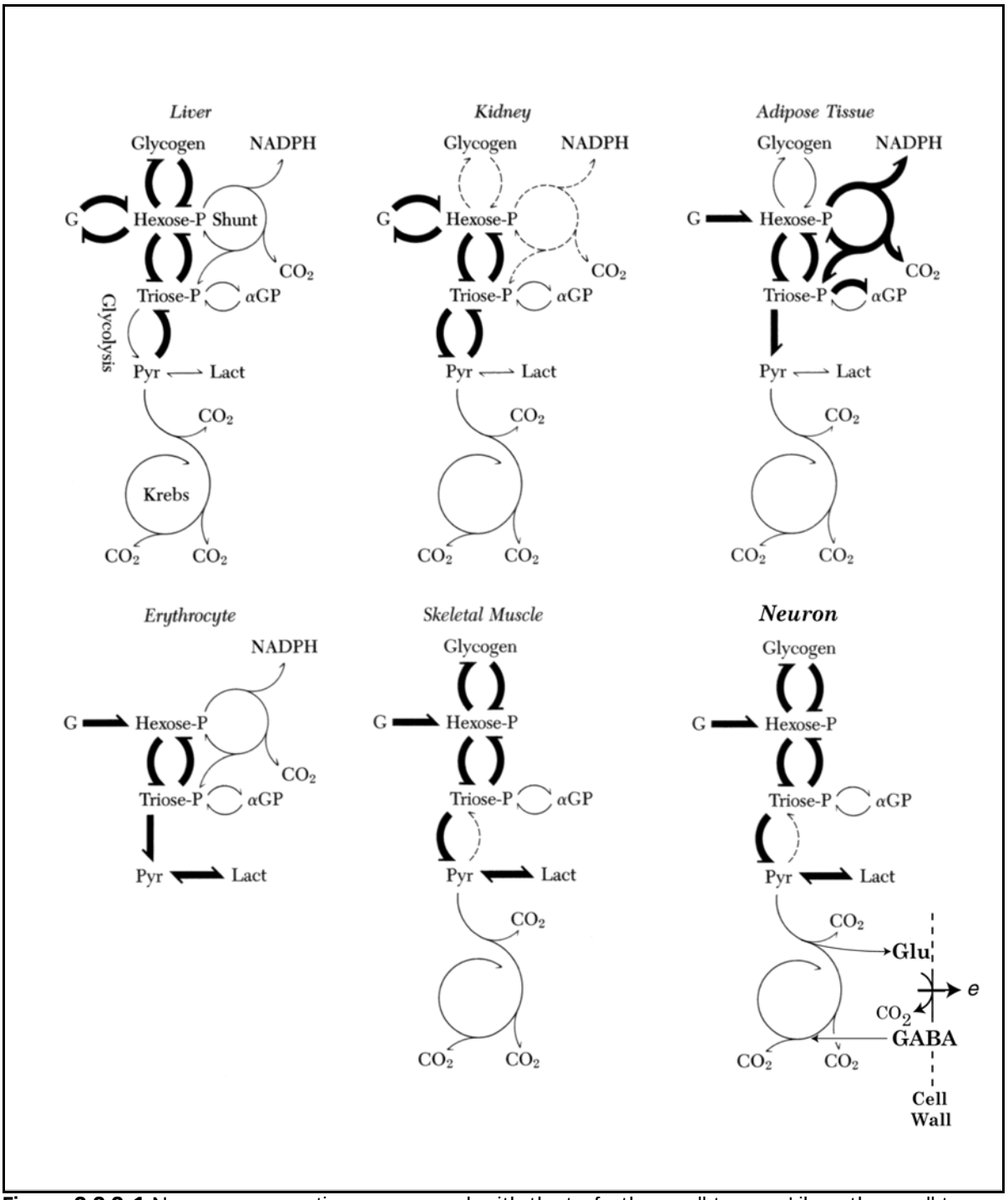

Figure 3.2.2-1 Neuron energetics compared with that of other cell types. Like other cell types, the neuron employs its own variant of the nominal glycolysis and tri-carboxylic-acid (Krebs) cycle. The glutamate shunt provides free electrons required to power the signaling capability of the neuron. Modified from Cantarow & Schepartz, 1967.

3.2.2.3.1 Background

White, et. al[61]. provide a variety of electrochemical information related to the energy sources of biochemistry. It includes a table of the free energies of hydrolysis for many compounds of biological interest. Glutamine is shown as releasing 3,400 calories/mole at pH = 7. They also provide a series of electrode potentials of some reduction-oxidation systems. Two values of particular interest are the α–ketoglutaric acid + NH_4^+/glutamic acid system at -140 mV (pH=7) and the α–ketoglutaric acid/ succinic acid + CO_2 system at -670 mV. The first system suggests that changes of about 140 mV are available within the glutamate shunt. The two together suggest that the glutamate to GABA conversion might provide the desired -154 to -140 mV potential.

White, et. al. also provide a flow chart of amino acid metabolism in the brain (pg. 973). The glutamates and GABA play a major role in this flow diagram.

The conversion of glutamic acid into GABA with the release of CO_2 is diagramed in Harper, but no numerical data is provided on the available energy[62]. Pyridoxal phosphate is given as a coenzyme but no other details are given. Harper discusses a variety of reactions involving the glutamates. This aspect of the tricarboxylic acid cycle is described in Hertz using the designation GABA shunt[63]. The ionization constants and pH values at the isoelectric point of glutamic and aparatic acids are given in Pethig[64]. Their isoelectric points are significantly lower than the other amino acids listed. He shows how easy it is to isolate glutamic and asparitic acid in the laboratory based on this factor. He also presents the hydration number for these amino acids and their residues. For the acids, their hydration number is two. Interestingly, the residue of glutamic acid, GABA, is shown as non-polar and without a hydration number.

Puil has provided a massive, well referenced and invaluable paper published in an obscure review[65].

Dowling provides a useful pedagogical description of glutamate and its potential conversion into GABA, aspartate and glycine[66]. No discussion of the mechanisms or energy required to perform these changes is given.

Recently, Korschen has proposed an alternate source of glutamic acid. He has proposed that the glutamates are provided by glutamic acid rich proteins (GARP) that presumably could cross the BBB. This approach is discussed briefly below.

While the treatment of the glutamates in the literature is large, little attention appears to have been placed on the stereochemistry of the family. In this work, this is a key mechanism that appears to eliminate the need for enzymatic mechanisms in the process of providing electrical power.

3.2.2.3.2 Potential reactants in primary electrostenolytics

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[61]White, A. Handler, P & Smith, E. (1973) Principles of Biochemistry, 5th ed. McGraw-Hill Chapters 14, 15, 23, & 25 [my library]

[62]Harper, H. (1975) Review of Physiological Chemistry, 15th ed. Los Altos, CA: Lange Medical Publications. pg 377

[63]Hertz, L. (1969) The biochemistry of brain tissue *in* Bittar, E. & Bittar, N. *eds*. The Biological Basis of Medicine NY: Academic Press pp 20

[64]Pethig, R. (1979) Op. Cit. pg 73

[65]Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res. Rev*. vol. 3, pp 229-332

[66]Dowling, J. (1992) Neurons and Networks. Cambridge, MA: Harvard University Press, pg 143

Having a ready reference to the chemical structure of the material important to this section is helpful. **Figure 3.2.2-2** presents several equations and formula, taken mostly from Lehninger, that should be helpful. Puil has provided an extensive list of analogs and chemicals closely associated with the glutamates (pp 304-6). His discussion of their actions is extensive. See **Section 1.2.1.3**.

The top four lines show the two major neuro-facilitators of the primary electrostenolytic process, glutamic acid and its backup aspartic acid, and their principle reaction products, GABA and β-amino propionic acid (BAPA) respectively. The shaded area shows how both neuro-facilitators lose CO_2 as part of the reaction. GABA and BAPA are shown in slightly non-standard form to indicate the source of the hydrogen remaining from the carboxyl group.

The transition from the simple blood sugar, glucose to the glutamates is described conceptually in McGeer, Eccles & McGeer as a variant of the tricarboxylic acid cycle[67]. Their paragraph on page 177 is quite enlightening. Although they are discussing glutamate from the perspective of a known neurotransmitter, they note its unusual characteristic in that it is not exclusively a neurotransmitter and appears to be used for other functions. A more profound discussion of the term neurotransmitter will be found in **Section 3.5.4**.

McGeer, Eccles & McGeer have provided considerably material on the glutamates and GABA. They profess that "Glutamate and aspartate are nonessential amino acids that do not cross the blood-brain barrier (BBB); therefore, they are not supplied to the brain by the blood. Instead, they are synthesized from glucose and other precursors by several routes." Not all investigators agree with the first assertion. These routes have been described by many authors, usually using top-level block diagrams because of their complexity. These diagrams are frequently accompanied by considerable text to describe all of the putative enzymatic activity involved. They suggest that GABA is also prepared from glucose and that its location of highest concentration within the retina is near the ganglion cells. It could be prepared by virtually the same process as glutamic acid. In fact it is prepared by an extension of the process, the electrostenolytic mechanism. A feature of glutamate generation is that all of the steps involve carbohydrates up to the point where α-keto-glutaric acid is converted to L-keto-glutamic acid (α-amino glutaric acid) by the introduction of an amine group. Their findings would suggest that the glutamates may also be formed within the retina and along the neural pathways throughout the body rather than being supplied by the blood.

There is a semantics problem related to the designation GABA. While it is the short form of gamma-amin(e)-o-butyric acid, the chemical is structurally different from the primary (α–) amino acid which might be described by the label butyric amino acid. GABA does not exhibit an amino acid group. Nor does it exhibit the primary properties of an amino acid. In the more recent literature, GABA is described as 4-aminobutanoate.

The formation of many of these compounds from GABA in the laboratory is quite straightforward and documented in many texts dealing with the nutritional aspects of biochemistry. However, these reactions are largely irrelevant to the operation of the neural system.

The consumption of these materials as a part of metabolism is less widely discussed. Their metabolism plays a key role in the operation of the neural system through the electrostenolytic process. This process releases the CO_2, shown shaded in this figure, and in the process transfers an electron thorough the membrane wall in order to bias regular cells and to electrically power neural cell.

The conversion of glutamic acid to GABA (alt. 4-aminobutanoate) on the surface of a plasmalemma can be considered a pseudo-enzymatic process, in which case, the pseudo-reaction would be described as pseudo-E4.1.1.5 in the formal listing of enzymatic reactions. It is also described as R00261 in the list of reactions, although the presence of an enzyme is

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[67]McGeer, P. Eccles, J. & McGeer, E. (1987) Molecular Neurobiology of the Mammalian Brain. NY: Plenum Press. pg 177

apparently not required.
http://www.chem.qmul.ac.uk/iubmb/enzyme/

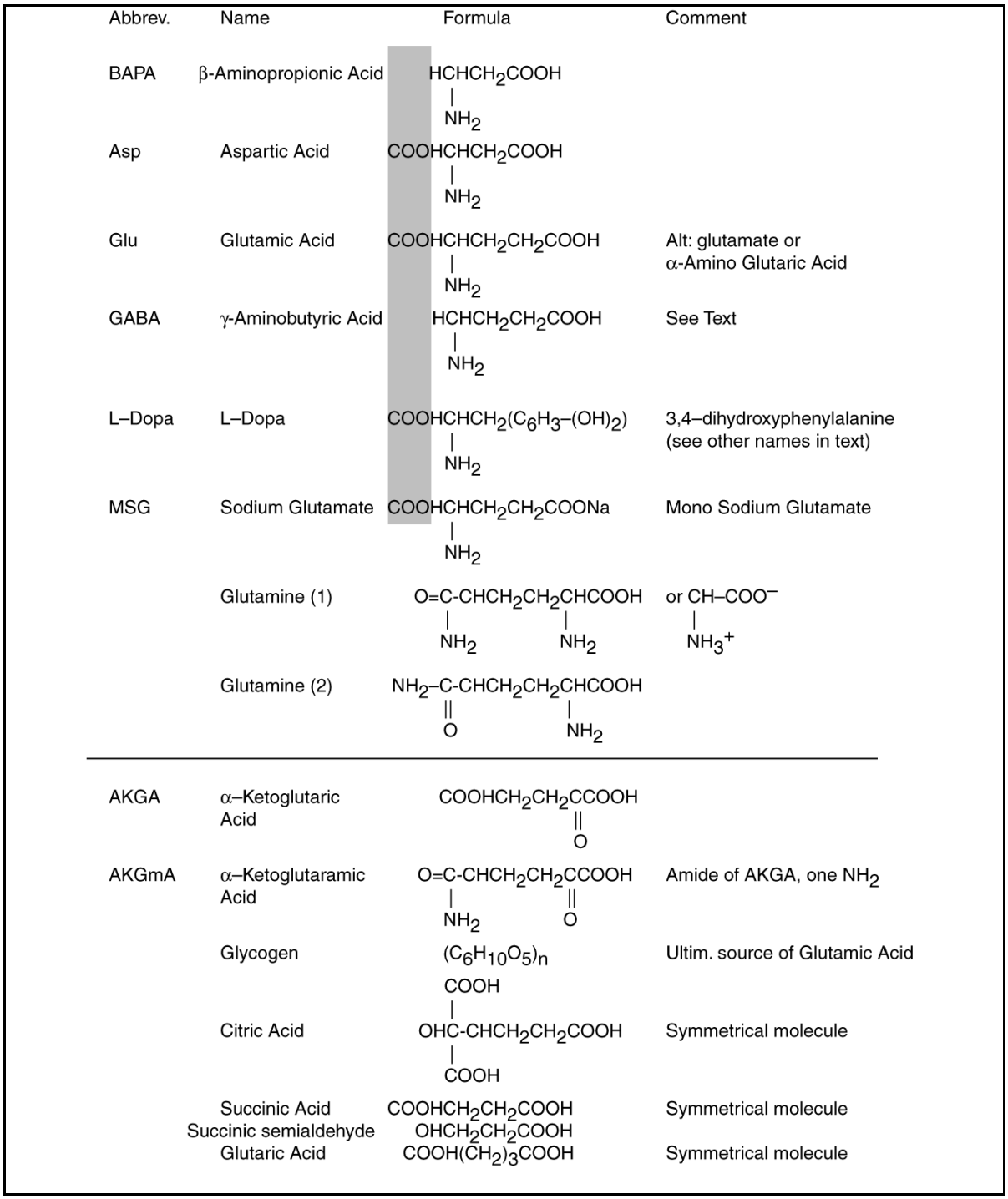

Figure 3.2.2-2 Bio-energetic compounds of premier importance in neuroscience. Top; the primary participants, and potential antagonists, in the electrostenolytic process. The shading shows the CO_2 lost in the electrostenolytic reaction powering the neural system. It is the carboxyl (or carboxyl-like) group at the other end of the molecule that is stereo-chemically associated with the receptor sites on the bilayer membrane of the cell. Bottom; other formula present in the glycogen and tricarboxylic acid cycles leading to glutamic acid. The symmetry of succinic acid is particularly noteworthy.

Glutamine is easily formed from glutamic acid. The two forms of Glutamine shown are merely to adapt to two-dimensional paper. They are the same compounds. Glutamine is easily hydrolyzed to produce glutamic acid (glutamate) and NH_4^+. AKGA is an intermediate form frequently mentioned in discussions of the other materials. These materials are all complex enough to support many different electronic configurations and participate in reactions involving transitions between their different electronic isomers.

When employed in an electrostenolytic process, the above materials can be used to create an electrical potential. The hydrolysis of Glutamic acid to form GABA releases one molecule of CO_2 and energy. It appears the energy is released in the form of an electron being released on the other side of the energy barrier formed by the biological membrane.

3.2.2.3.3 Fundamental reaction of electrostenolysis

The term substrate has an entirely different meaning in inorganic and organic chemistry. The substrate of inorganic chemistry becomes the receptor in organic chemistry and the term (first) reactant of inorganic chemistry becomes the substrate of organic chemistry.

In the following discussion, the terminology of inorganic chemistry is used. The substrate is a part of the lemma of the cell and not a separate "receptor" of organic chemistry. The reactant is attracted to the substrate and forms a covalent bond with it. The reactant then participates in covalent catalysis as described by Silverman[68].

Providing the electrical power required by an individual plasma of a neuron appears to involve three steps. First, the reactant material must be transported to the appropriate specialized site of the neurolemma and allowed to unite with that site (substrate) stereo-chemically. Second, the reactant must react, releasing carbon dioxide and injecting an electron through the electrically asymmetrical lemma into the adjoining plasma. Third, the reaction product must be released from its stereochemical relationship with the substrate and removed from the site.

The basic electrostenolytic reaction supporting the supply of electrical power to each plasma of each neuron is shown in **Figure 3.2.2-3** The reaction occurs on the surface of the lemma, surrounding the plasma, acting as a substrate. It appears that the glutamic acid molecule attaches itself stereo-chemically to the substrate via the carboxyl group farthest from the amine group. Although McIlwain & Bachelard speak of an enzyme (decarboxylase, pg 167) catalyzing the glutamate to GABA reaction, it is not clear any additional enzymatic support is required in the presence of a substrate. The process releases one molecule of carbon dioxide for each molecule of glutamic acid converted to GABA. Simultaneously, the process injects a free electron into the plasma on the opposite side of the lemma forming the substrate. The GABA is then released from the substrate. As discussed in **Section 18.8.5.3**, this reaction may operate with aspartic acid as the initial reactant. While CO_2 is still released, the other residue changes accordingly. Selinsky noted the close relationship formed between aspartic acid and the choline headgroup of the membrane[69]. "These interactions range in strength from several kcal/mol for charge-charge interactions, as might occur between a charged amine headgroup such as choline with a negatively charged amino acid side chain such as aspartic acid, . . ." It is proposed the same relationship exists between BLMs and the "other" negatively charged amino acid, glutamate. The introduction of L-Dopa into the blood stream is found to have beneficial results in Parkinson's Disease and possibly in nystagmus. It appears it is able to cross the blood-brain barrier and to replace, or inhibit the

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[68]Silverman, R. (1992) The Organic Chemistry of Drug Design and Drug Action. NY: Academic Press pg 104

[69]Selinsky, B. (1992) Protein-lipid interactions and membrane function *In* Yeagle, P. The Structure of Biological Membranes. NY: Academic Press pg 607

participation of, glutamic acid (and aspartic acid) in at least some of the electrostenolytic reactions supporting the neural system.

The figure was drawn with software tools showing the constituents unionized. It is likely both constituents are ionized with the loss of the hydrogen associated with the oxygen in the lower carboxyl group. This would allow a more significant stereo-chemical binding of the reactants to the substrate.

The rate of the production of free electrons is directly related to the concentration of glutamate and GABA at the surface of such a electrostenolytic mechanism. The presence of 2-5% glutamate and 1.5-3% GABA result in a typical neural axon potential, under cutoff conditions, of between 150 and 154 mV. A lower concentration of glutamate or a higher concentration of GABA may be due to an impedance to the progress of the reaction.

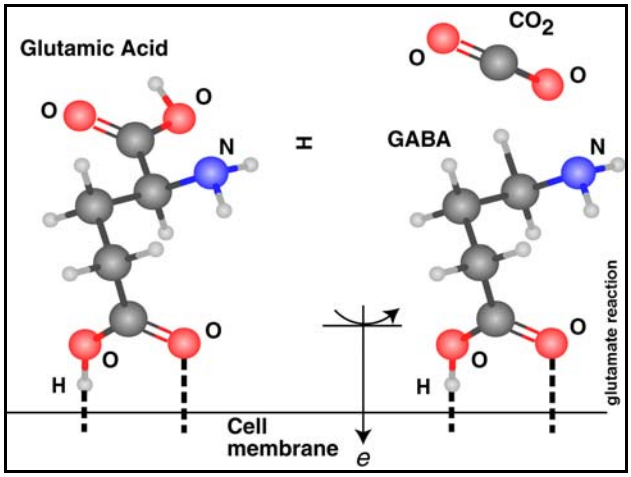

Figure 3.2.2-3 The fundamental electrostenolytic process powering the neural system. Glutamic acid becomes associated with the cell membrane in a highly selective stereo chemical relationship (dashed vertical lines). A reduction then occurs. The process releases carbon dioxide as shown. It also injects a free electron into the plasma on the other side of the cell membrane. GABA is then released from the stereo-chemical bond.

Frelin has provided excellent data related to the consumption of glutamic acid in isolated post-natal heart cells of mice, and similar data for lysine utilization[70]. It is not clear why he reported *de novo* alanine production from glutamic acid, with the release of CO_2, unless his testing was not able to separate alanine and GABA (one additional aliphatic CH_2 group). GABA was little known in the 1980 time period and he did not report its presence in his experiments.

The electrostenolytic process as described in the figure can be described in a more operational sense usingthe standard symbology of electrical engineering. **Figure 3.2.2-4** shows the roles of glutamate and GABA separated into their neuro-facilitator and neuro-inhibitor roles (replacing their archaic labels of neurotransmitters). Glutamic acid (glutamate) is shown as being provided by the source of power to the neuron (shown as the triangular amplifier symbol here) with GABA being produced as a residue, along with CO_2, and being drawn off at the drain terminal of the power supply. Every neuron exhibits a positive going, non-inverting, amplifier input and a negative going, inverting, amplifier input. These inputs are unrelated to activity at the source and drain terminals of the neuron. When operating in stage 3 pulse mode (generating action potentials), the neuron's consumption of glutamate and creation of GABA are proportional; and both the consumption and creation are proportional to the pulse rate driving the neuron. This interpretation explains the ubiquitous presence of glutamic acid and GABA throughout the neural system.

[70]Frelin, C. (1980) Amino acid metabolism by new-born rat heart cells in monolayer cultures *J Mol Cell Card* vol 12, pp 479-491

3.2.2.3.4 The DACB geometry & the electrostenolytic process

Subsequent to the development of this material on the electrostenolytic process powering the neurons, the sections of Chapter 8 related to the chemical senses showed that a unique feature of those sensory receptors was their ability to form dual antiparallel coordinate bonds (DACB) precisely as defined above for the carboxylic group of glutamic acid. Note the location of the hydrogen atom associated with the hydroxyl group of the carboxylic acid group. This hydrogen atom is capable of forming a hydrogen bond (or London bond) with another atom associated with the external lemma of the neuron (or other cell type). The dual bond oxygen of the carboxylic group is also capable of forming a hydrogen bond with another structure within the external lemma of the neuron.

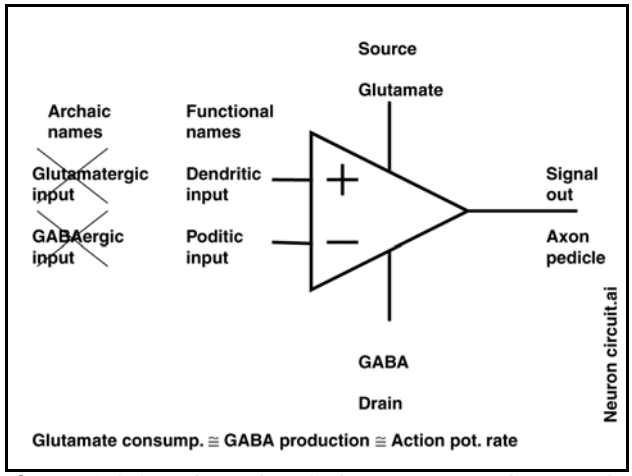

Figure 3.2.2-4 The role of glutamate and GABA in powering the neuron using the symbology of electrical engineering. The signal inputs are labeled +, non-inverting (or excitatory) and –, inverting (or inhibitory) in line with their function. Glutamate is shown as the source of energy to the circuit (neuro-facilitator) with GABA shown as a residue being drained away (neuro-inhibitor). See text.

It appears the DACB is an important functional form used repeatedly throughout the neural system and probably the non-neural cells as well. **Section 3.2.4** will develop the utilization of the DACB form in powering the neurons. See **Section 8.4.8** for a preview of that aplication and **Sections 8.5.1.2** and **8.6** for a detailed discussion of this functional form related to the sensory neurons and its operating mechanism.

A critical feature of the receptor-stimulant coordinate pairing is the perpendicular distance between the two hydrogen bonds, defined in this work as the d-value. The d-value of carboxylic acid is 2.078 Angstrom. It is necessary that the receptor site also exhibit a d-value close to that of carboxylic acid if it is to be receptive to the glutamic acid molecule.

3.2.2.3.5 Definition/location of Glutamate & GABA receptors

Glutamate without a prefix is a historical name that describes the radical of glutamic acid, rather than the salt or ester. It generally refers to glutamic acid in the biological sciences and pharmacology.[71] Glutamic acid can be described as α-amino glutaric acid under the IUPAC rules. Bending the rules slightly would suggest the name γ-amino glutaric acid is equally representative. This description will be found quite useful in **Section 3.3.2.2**.

The literature has identified congregations of glutamate molecules and GABA molecules on the surface of various neuron elements. This has resulted in the designation of putative materials at these sites as glutamate receptors and GABA receptors (sometimes of multiple types). Based on the Electrolytic Theory of the Neuron, these two chemicals are the reactant and residue of a reaction occurring at a single receptor site. Two separate sites are not supported in this work.

The pharmaceutical literature has gone farther and defined two types of glutamate sites and two types of GABA sites using various prefixes and suffixes. This work suggests all of these "types" can be replaced by one type site potentially present on the lemma of separate

[71]Dowling, J. (1992) Pg. 143

compartments of the neuron.

The literature has also frequently conceptualized these sites as formed by proteins. It is very clear the common electrostenolytic sites are of lipid origin and probably formed of phosphatidyl serine.

Unfortunately, it has been inferred that these sites are related to the neural signaling process even though they are not found within the small area associated with the primary synaptic gap (defined more explicitly in **Section 2.4**). Based on this inference, and the myriad reports that topical application of these materials to the surface of a neuron affect the operation of the neuron, these materials have been described as neurotransmitters in the literature. The term neurotransmitters is highly suggestive of a role in transmitting neural signals. However, these locations are actually the stereochemical sites associated with the above electrostenolytic process that powers the neurons. These materials only indirectly affect the signaling operation of the neurons. The sites are scattered over the surface of every neuron (but outside the signaling path), as will be shown in **Chapter 10** and the remainder of this section, and are stereo-specific for the dicarboxylic amino acids and their close relatives including the medically controversial L-Dopa and the socially denigrated MSG, mono-sodium glutamate. It is useful to note that MSG, the glutamate of pharmacology and glutamic acid are identical when in ionized form.

It is yet to be determined whether these glutamate receptor sites are formed by the hydrophilic ligands of the phosphotriglycerides forming the external bilayer of the external membranes of the neurons. It is possible that an additional molecule is required as an intermediary. Nawy & Copenhagen have described a multi-class family of glutamate receptors, but primarily at the conceptual level[72]. Their experiments covered only a very narrow range of bias potentials that did not show the diode characteristic of the typical voltage transfer function of these cells. Vardi et al. have described an antibody that may be useful in locating any potential adjunct to the receptor site formed of lemma molecules[73]. Although their study falsified the hypothesis in the title of the article, they did identify an antibody that did stain the bipolar neurons, probably the proximal neurites disproportionately. However, they did not identify what component of the neurite structure was associated with the staining.

In a later paper[74], Vardi et al. pursued the location of the receptor site stained by their antibodies. They prepared antibodies selective for the C-terminus of the human mGluR6 receptor and used confocal and electron microscopy to study the patterns of immunostaining in retina of monkey, cat, and rabbit. They arrived at the surprising conclusion based on their hypothesis, that the area stained was not associated with the synaptic region but with a region 400-800 nanometers distant from the synapse. This is a considerable distance on a neurite that is typically less than 100 nanometers in diameter.

> "These were identified as dendrites of the ON S-cone bipolar cell by immunostaining for the marker cholecystokinin precursor. The staining pattern suggests that all types of ON bipolar cells, despite their marked differences in function, express a single isoform of mGluR6. Ultrastructurally, mGluR6 was located not on the tip of the central element, near the site of vesicle release, but on its base at the mouth of the invagination, 400–800 nm from the release site. Thus, the mGluR6 receptors of ON bipolar cells lie at about the same distance from sites of vesicle release as the iGluR receptors of OFF bipolar cells at the basal contacts."

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[72]Nawy, S. & Copenhagen, D. (1987) Multiple classes of glutamate receptor on depolarizing bipolar cells in retina *Nature* vol 325, pp 56-58

[73]Vardi, N. Matesic, D. et al. (1993) Identification of a G-protein in depolarizing rod bipolar cells *Vis Neurosci* vol 10, pp 473-478

[74]Vardi, N. Duvoisin, R. Wu, G. & Sterling, P. (2000) Localization of mGluR6 to Dendrites of ON Bipolar Cells in Primate Retina *J Comp Neurol* vol 423, pp 402-412

> "We had expected mGluR6 staining to localize at the extreme tip of the ON bipolar dendrite, where it most closely approaches the active zone. However, in more than 30 examples of ON cone bipolar dendrites, this region was devoid of stain or else stained only weakly. Instead, stain was concentrated 200–600 nm more proximally. Where an ON dendrite ascended vertically to penetrate."
>
> "That one mGluR6 isoform serves all ON bipolar types suggests that their functional differences are generated further downstream and that it excludes glutamate receptors from being the origin of the slow responses in the short wavelength perception."

These findings clearly support the proposal of this work that the mGluR6 sites are the sites of electrostenolytic activity supporting the electrical power needs of the cell and are not related to the synaptic transmission of signals. As noted above, the mGluR6 sites were not in the synaptic region. The findings also suggest the iGluR and mGluR receptor families are probably identical.

The development of stage 2 signal processing in this work (Chapter 8) will demonstrate the bipolar neurons are all non-inverting amplifiers and that the differentiation between ON and OFF bipolar cells is a false one. It is the more complex differencing neurons that offer the ability to create "OFF" neurons. Thus, a premise of many of these pharmacology based papers is also false. In the absence of this difference, the designations $GABA_A$ and $GABA_B$, and iGluR and mGluR are unrealizable differentiations.

"We noticed that the rod and cone membranes that face the mGluR6 receptor always display a "fluffy" density. This density is so distinctive that it could be used as a marker for the location of the mGluR6 receptor in ON dendrites that are not immunostained. Given that many of the densities and particles originally described for these synapses (Raviola and Gilula, 1975) correspond to specific ion channels, receptors, etc. (Vardi et al., 1998), one would expect this density to also represent some important macromolecules."

A review of the literature of electron microscopy of operating man-made microcircuits will show the "fluffy" density observed by Vardi et al. is due to the defocusing of the microscope by the presence of electronic charge on the surface of the specimen (Search Vardi in **Chapter 5**). The "fluffy" density of Vardi et al. continues to represent the excess electrical charge at the sites of significant electrostenolytic activity according to this work. It is not indicative of a particular macromolecule.

Recently, Hu et al. have reported on their efforts to locate and describe the operation of the glutamate receptor sites, based on the chemical theory of the neuron and a group of proteins as the likely receptors[75]. While the quality of the experimental work is excellent, they fail to show how the glutamate is captured by the putative GPCR receptors on the surface of a neuron, and what the result of capturing glutamate is with respect to the neuron.

3.2.2.3.6 The stereo specific cytology of the electrostenolytic process

When a portion of the type 1 BLM forming a lemma is converted to a type 2 membrane, it is capable of entering into a stereo-specific coupling with glutamic acid (glutamate) as shown schematically in **Figure 3.2.2-5**. The detailed molecular character of the membranes forming the stereo-specific type 2 BLM are unknown at this time. However, it is likely that the lipid participating in the stereo-specific process is choline related (See **Section 1.4.2**). The geometric characteristics and the electrical polarization of glutamate make this union quite strong. However, after the release of the carbon dioxide ligand and the transfer of an electron to the intracellular side of the BLM, the situation is changed. The reaction product, GABA, does not exhibit the required structural and polarization properties to maintain the union and it diffuses away from the BLM surface (along with the carbon dioxide). The strength of this union and the energy of the reaction can be inferred from the potential

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[75]Hu, J-H. Yang, L. Kammermeier, P. et al. (2012) Preso1 dynamically regulates group I metabotropic glutamate receptors *Nature Neurosci* vol 15(6), pp 836-846

generated in connection with the transfer of the charge through the BLM.

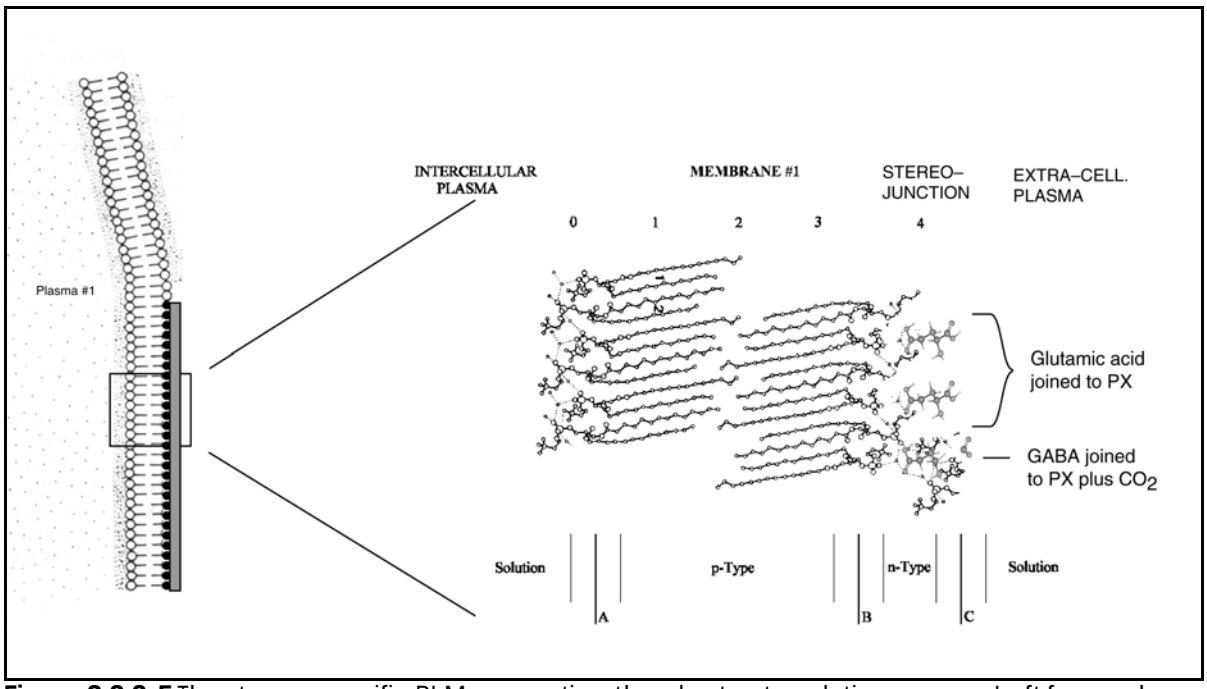

Figure 3.2.2-5 The stereo specific BLM supporting the electrostenolytic process. Left frame shows the stereo specific materials aggregating to the membrane. Right frame shows an expanded view. Glutamate is shown joined to the lipid forming the external surface of the membrane at upper right. GABA is shown joined more loosely to the surface of the membrane after release of the carbon dioxide ligand at lower right.

- - - -

The glutamates, glutamic acid, GABA, glycine and aspartic acid are highly concentrated at a multitude of locations along all neural pathways of the PNS . Within the CNS, glutamic acid is the most prevalent amino acid of all. At these points, it is proposed that a modified glutamate cycle functions on the surface of the plasma membranes to generate the electrical potential found between the plasmas of each cell and the surrounding matrices. Because of the reversibility of the glutamate cycle, the quantity of each constituent of these reactions varies as a function of signaling level (and hence of time). Because of the solubility of these materials in the surrounding matrix, they also tend to equalize their individual concentrations in response to their consumption or generation at a given location.

This work has surfaced the requirement for a positive electrical source to support the cardiocytes. It is proposed that this electrostenolytic source is the di-amino acid, lysine. **Section 3.4** will discuss its conversion to iso-leucine and ammonia while charging the podaplasm of the cardiocyte to a nominal +52 mV potential.

Still earlier, McGeer, et. al. said "Nevertheless, it must be recognized that truly definitive markers that can be applied at the cellular level do not exist for glutamate and asparate as they do for several other neurotransmitters. Therefore, evidence for neuronal identification and for pathways involving these amino acids must in all cases be considered as tentative." Their chapter 6 describes the role of glutamate and aspartate primarily in metabotropic terms which are completely consistent with the above sections of this work. Their table of

metaboloid concentrations by location within the nervous system is very useful. They also note the ubiquitous ability of glutamate and aspartate to excite multiple neural "receptors" in response to topical application. The problem of markers has been overcome through nuclear chemistry as discussed in **Sections 7.7.5** & **18.8.5 xxx**.

3.2.2.4 Toxicity of glutamate in excess

There is a general recognition that excess glutamate is toxic to neurons. Fields noted[76], "Too much glutamate and the brain not only becomes hyperactive, but neurons, like engines revved beyond redline, are damaged or killed." This is particularly important in topical applications of glutamate during *in-vitro* experiments. During normal *in-vivo* operation, the hydraulic conductance of the external neural matrix limits the application of glutamate to neural tissue.

Lau & Tymianski have provided a recent survey of the subject of glutamate toxicity along with a variety of other neuro-modulators[77]. No models or schematics are provided but a long bibliography is.

3.2.3 Combining the type 2 membrane with electrostenolysis–*powering the neural system*

[xxx refocus and move to new chapter 4,5 or 6.]
By repeating the work of Eliasof using a Ussing apparatus, it is relatively straight forward to continue the experiments to determine the quiescent electrical potential of a membrane in combination with its native electrostenolytic process (See **Section 3.2** on electrostenolysis). The equivalent circuit diagram is still relatively simple as shown in **Figure 3.2.3-1**. Assuming a saturated solution of the electrostenolytic reactants in the INM, a finite circulating current will be found within the loop formed by the electrostenolytic source and the membrane. It may be extremely small for a small conduit. By measuring the quiescent potential, $v_{quiescent}$, of the terminal shown in the upper electrolyte relative to the INM using a finite and controlled impedance voltmeter (at least one order of magnitude higher than the impedance of the compartment lemma. and knowing the diode characteristic and equivalent battery potential (q–m battery) of the membrane, it is possible to compute the electrostenolytic source voltage and impedance. The equivalent batter potential is commonly known as the cutin, offset or threshold potential of the diode. The electrostenolytic impedance is assumed to be a simple resistance in the absence of any other data.

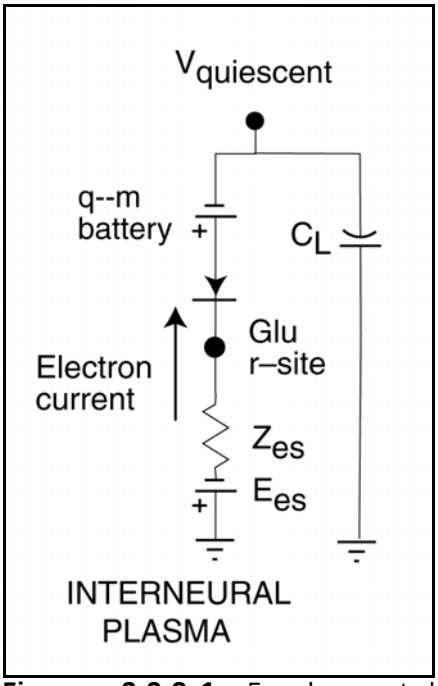

Figure 3.2.3-1 Fundamental membrane with electrostenolysis support. The capacitance shown consists of both the bulk capacitance and the displacement capacitance of the diode. Glu r–site; glutamate receptor site. es; electrostenolytic site. q–m battery; quantum mechanical battery.

It should be noted that the electrostenolytic potential is generally higher than the intrinsic membrane potential. When making the above measurement with a high impedance voltmeter relative to any circuit element, it is important to specify that a quiescent voltage is being

[76]Fields, R. (2009) The Other Brain. NY: Simon & Schuster page 155

[77]Lau, A. & Tymianski, M. (2010) Glutamate receptors, neurotoxicity and gneurodegeneration *Eur J Physiol* vol 460, pp 525-542

measured not the intrinsic membrane potential or the intrinsic electrostenolytic potential.

The available evidence suggests electrostenolysis occurs at glutamate receptor sites on the external surface of type 2 BLM occupied by phosphatidyl serine (PS).

3.2.3.1 The apparent intrinsic potential and impedance of a biological membrane combined with electrostenolysis

Many experiments have been carried out treating the circuit in the above figure as a lumped circuit. The voltage at the upper terminal has been measured as a function of an external load impedance between that point and the INM (or as the case of one variant of the voltage clamp experiment, a current has been introduced into the circuit via this terminal while holding the voltage constant). The resulting voltage-current characteristic has been used to compute a single voltage and impedance representative of the combined membrane and electrostenolytic system. The result may be interesting but it lacks precision. It blatantly conflicts with the requirements of Kirchoff's Laws that require circuit linearity before the application of Ohm's Law..

3.2.3.2 The electron-pump replaces the putative ion-pump in charging a biological membrane

Many authors have attempted to define the mechanism powering the neural system. They have explored a variety of mechanisms familiar to the physiology of nutrition. This area of physiology normally concentrates on chemical energy stored as ATP and similar materials. It does not normally focus on the creation of an electrical potential. However, many of the same materials can participate in an electrostenolytic process producing free electrons. These electrons can traverse the substrate.

This work proposes that a portion or portions of the glutamate cycle of nutrition can take place at an appropriate reaction site on the surface of a membrane conduit. This reaction is of the electrostenolytic type and provides electrical bias to the conduit.

It is proposed that the nominal reaction takes place at a glutamate receptor site formed of type 2 lemma with an outer surface of phosphatidyl serine (PS) and involves the transformation of the simple amino acid, glutamic acid into GABA (gamma-amino butyric acid). The desired potential can be maintained indefinitely with minimal continuous consumption of energy. Only the presence of glutamate on the exterior surface of the type 2 membrane is required.

By broadening the designation ion-pump, to charge-pump, the processes of electrostenolytics and transistor action provide demonstrable solutions to the charge-pump problem associated with the polarization of neuron plasmas.

> The transfer of electrons across a membrane by electrostenolytics is analogous to and is in fact the solution to the long quest for an ion-pump that could polarize the interior of a neurite or axon structure. This finding is even more profound than the earlier one of Habib & Bockris. **No requirement exists for an ion-pump to polarize the interior of a cell. Neither is there a requirement for the polarization of the interior of a cell to pump ions through the cell membrane for signaling purposes.**
>
> According to this formulation, no requirement exists for the transfer of alkali or alkali-earth ions or large particles across the lemma of the fundamental biological conduit to support neural signaling. Although such transfer obviously occurs during some phase of the genesis and metastasis of the conduit, it will not be addressed further in the context of neural signaling.

While a continuous symmetrical BLM forms a very high quality insulator, an asymmetrical membrane forms an electrical diode. When associated with a charge-pump and the capacitance of the membrane, this diode can sustain a potential between the two sides of the membrane of one polarity but not the other. The simple non-neurological cell

incorporates this feature to insure its interior is always polarized negatively with respect to the surrounding electrolytes.

3.2.4 The role of the protein, mGluR and its variants

The literature has developed a role for a series of proteins described by the labels mGluR, mGluR1, mGluR5 & mGluR6 that are believed to be intimately associated with the utilization of glutamic acid (glutamate) in the neural system. With the identification of the functional receptor of the carboxylic group as the lemma phospholipid, phosphatidylserine (**Section 8.5**), the role of the proteins of the mGluR family must be re-examined. These proteins have been closely linked to glutamate in the neural process. However, the linkage has been at the conceptual level based heavily on recent genetic progress in identifying the linkage between a segment of mRNA and the manufacture of the protein within cells.

> In the following discussion, the role of the proteins of the mGluR family will be described as enzymatic. They are now believed to insure that only a selected group of carboxyl containing molecules can bind to the electrolytic power producing regions of type 2 lemma associated with multiple neural conduits, specifically both dendritic and axonal conduits (including axon segments as conduits).

Glutamate has been found intimately associated with the neurons of the peripheral neural system at the histological level. In addition, its presence within the CNS is ubiquitous (**Section xxx**). Its location at the cytological level has been less clear. The literature has long asserted that glutamate was a neurotransmitter within the synaptic gap. However, the fact that glutamate actually powers the neurons electrolytically, demonstrates that glutamate is not a neurotransmitter but a neuro-facilitator (**Section 3.5.4**).

3.2.4.1 The role of the mGluR family of enzymes in electrostenolytics

The role of the mGluR family of proteins in electrostenolytics appears to be enzymatic and not that of a direct functional "receptor." This hypothesis is asserted based on the role of glutamate in the glutamate to GABA conversion described in **Section 3.2.2**. One aspect missing from the role of phosphatidylserine in its role as the receptor of glutamate in power generation, particularly within the CNS, is how most other chemicals with a carboxylic group (other than the dopamines and the alternate fuel aspartate) are prevented from occupying the receptor site. The obvious solution would be the presence of another chemical on the external surface of the neural lemma acting as the "lock cylinder" in a stereochemical relationship where selected carboxylic containing molecules could act as the "key" and become attached to the phospholipid, facilitating a chemical reaction. The resulting proposed situation is shown in **Figure 3.2.4-1**. This figure follows directly from the figures of preceding sections and the description of the phospholipid receptor with the carboxylic group as found in the gustatory (taste) modality, **Section 8.5.xxx**. Since the gustatory modality is designed to sense all carboxylic acid groups, the mGLUR enzymes play no role in the sensory neurons of gustation. In its electrostenolytic role, the MGluR enzyme attaches to the surface of the lemma, probably to the same phospholipid receptor that provides a receptor for glutamate in the electrostenolytic reaction. Since details of this attachment are missing, the enzyme is shown in two-dimensional caricature.

The mGluR insures that the glutamate (or its backup, aspartate) is properly oriented to release a specific one of its two carboxyl groups thereby producing GABA and a free molecule of CO_2. Technically, the CO_2 should be shown with two conjugate bonds. As a result of this reaction, a nominal 154 milli-electron–volts of energy is transferred through the wall of the lemma into the plasma of the neuron. This energy is able to polarize the plasma to a maximum of 154 millivolts under quiescent conditions. The GABA is no longer able to maintain its relationship to the receptor and drifts away, thereby allowing the process to be repeated endlessly as needed.

> As the precise structure of the mGluR family of proteins becomes known, it may become possible to determine the particular features of the structure that allow the enzyme to select glutamate, aspartate, a few members of the dopamine family (and possibly the amino acid analog, L-quisqualic acid (see the next section) that can occupy the electrostenolytic site.

The spacing of the two oxygen atoms that hydrogen bond to the serine group of phosphatidylserine is the same 2.1 Angstrom as for the carboxylic acid gustaphore/receptor combination of the gustatory modality.

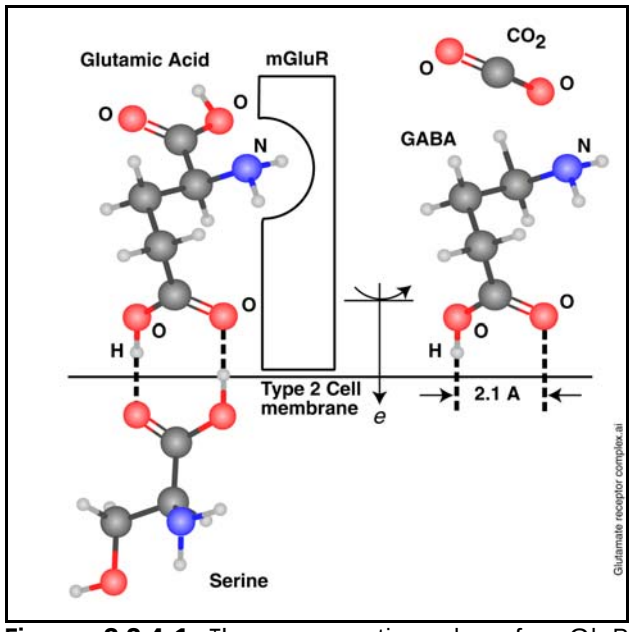

Figure 3.2.4-1 The enzymatic role of mGluR proteins in powering the neurons. Left; before reacting. Right; after reacting. Center, electrolytic symbol of the reaction. MGluR insures that only glutamate and aspartate can productively occupy the phosphatidylserine (PdtSer) receptor site on the type 2 lemma of the neuron. After reacting, the remaining GABA can no longer occupy the receptor via the hydrogen bonds shown.

As in other enzymatic mechanisms, the mGluR is unaffected by the glutamate/GABA reaction and is available to support capture of another glutamate molecule by the receptor site following dispersal of the GABA molecule.

3.2.4.2 The details of the mGluR family of enzymes

The conventional understanding is, "The metabotropic glutamate receptors, or mGluRs, are a type of glutamate receptor that are active through an indirect metabotropic process. They are members of the group C family of G-protein-coupled receptors, or GPCRs.[2] Like all glutamate receptors, mGluRs bind with glutamate, an amino acid that functions as an excitatory neurotransmitter." Wikipedia presents a useful table organizing the mGluR family[78]. However, several of the column headings are not supported here. Only the left two columns are reliable.

[78] http://en.wikipedia.org/wiki/Metabotropic_glutamate_receptor

Family	Receptors[79]	Gene
Group I	mGluR1	GRM1
	mGluR5	GRM5
Group II	mGluR2	GRM2
	mGluR3	GRM3
Group III	mGluR4	GRM4
	mGluR6	GRM6
	mGluR7	GRM7
	mGluR8	GRM8

As noted in this section, the MGluR proteins of Group I act as enzymes supporting the electrostenolytic powering of the neurons. Lujan et al. have provided an extensive bibliography of the research into the mGluR family of proteins as of 1996[80]. That work suggests the mGluR1 and mGluR5 are involved in the stereo-chemical selection and presentation of glutamate to the electrostenolyitc receptor, phosphatidylserine. Chu & Hablitz have shown the amino acid analog, L-quisqualic acid can react in some way with the Group I mGluR's[81] This analog has a structure similar to the dopamines, **Figure 3.2.4-2**.

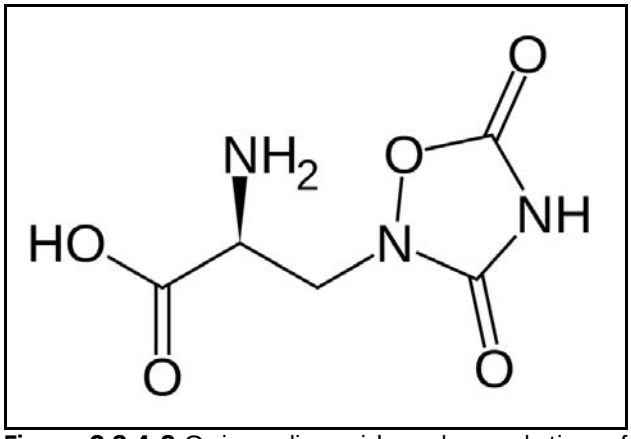

Figure 3.2.4-2 Quisqualic acid, a close relative of the dopamines and a reactive with Group I mGluR's.

San Gabriel et al. have provided some discussion of the structure of Group I mGluR proteins[82]. Their focus was on demonstrating its association with the putative gustaphores associated with the perception of umami. They did note, "Metabotropic glutamate receptor 1 (mGluR1), which is widely expressed throughout the central nervous system and regulates synaptic signaling, is another L-glutamate receptor candidate. It is found within taste buds, although the amount of L-glutamate in the perisynaptic region is in the order of μol/L, whereas free dietary L-glutamate is in the mmol/L range." This quotation can be reinterpreted to indicate the mGluR1 found within the taste buds (in the absence of any glutamate as a gustaphore) is supporting glutamates role in electrostenolytics within the fluid milieu of the body. When applied as a gustaphore, the glutamate is stimulating the C–Best and

[79]Swanson, C. Bures, M. Johnson, M. Linden, A. Monn, J. & Schoepp, D. (2005). Metabotropic glutamate receptors as novel targets for anxiety and stress disorders *Nat Rev Drug Discov* vol 4(2), pp 131–44. doi:10.1038/nrd1630. PMID 15665858

[80]Lujan, R. Nusser, Z. et al. (1996) Perisynaptic location of metabotropic glutamate receptors mGluR1 and mGluR5 on dendrites and dendritic spines in the rat hippocampus *Euro J Neurosci*

[81]Chu, Z. Hablitz, J. (2000). "Quisqualate induces an inward current via mGluR activation in neocortical pyramidal neurons". *Brain Res* vol 879(1-2), pp 88–92. doi:10.1016/S0006-8993(00)02752-9. PMID 11011009.

[82]San Gabriel, A. Maekawa, T.Uneyama, H. &Torii, K. (2009) Metabotropic glutamate receptor type 1 in taste tissue1–3 *Am J Clin Nutr* vol;90(suppl):743S–6S

N–Best receptors of the gustatory modality. This reading of the above quotation is totally compatible with the operation of the gustatory receptors of the Electrolytic Theory of the Neuron (**Section 8.5**). Their assertion, "The GPCR mGluR1 is an excitatory receptor mainly known to be expressed in the postsynaptic somatodendritic region . In the central nervous system, it mediates the action of the neurotransmitter L-glutamate." This is particularly true if the term "excitatory receptor" is replaced with "enzyme" and the term "neurotransmitter" is replaced by neuro-facilitator."

San Gabriel et al. presented a schematic of the mGluR protein but did not provide a detailed structure. They encountered difficulty attempting to read the genetic code for their material,

> "The first 170 nucleotides from the amplified sequence of taste mGluR1 corresponded to the very end of the last intron sequence. There was a stop codon in-frame with the long open reading frame, which suggested that there is an initial sequence that is not translated. No traditional ATG codon to indicate initiation of translation was found near by the stop codon (40). The closest methionine resided one exon away from the stop codon, which would result in an excessively long untranslated sequence. We suggested that a (GTG) codon within the same frame may be the initiation site. Although GTG is not a frequent sequence of initiation, it is possible that GTG can function as a tentative start codon."

The molecule is obviously quite large (>170 nucleotides). Belenikin et al. have also provided structural information on this molecule as of 2003[83].

Metabotropic glutamate receptors (mGluR1) discovered a little more than a decade ago belong to the subclass of G-protein-conjugated glutamate receptors, which comprises, to date, eight subtypes (mGluR1–mGluR8). The complete structure of an mGluR receptor comprises an N-terminal domain (NTD) involved in binding competitive antagonists and agonists; a cysteine-rich domain; a transmembrane domain (TMD) containing a binding site for noncompetitive antagonists, which are more selective and effective than competitive ones; and a C-terminal domain, whose size varies in different subtypes. Only the structures of the mGluR1 NTD [1] and its complexes with the agonist [1, 2] and antagonists [2] have been determined experimentally.

The purpose of this study was to construct the spatial structural models of the mGluR1 TMD and its dimer, as well as the modeling of the noncompetitive-antagonist binding site.

Whether one of the defined binding sites can be shown to capture glutamate appears undetermined at that time. Their article is quite detailed and requires an expert to interpret the text precisely.

3.2.4.3 Distribution of glutamate receptors on a neuron

Lujan et al has reported some very carefully documented work on the distribution of mGluR1 and mGluR5 on the dendrites and dendritic spines of the rat hippocampus *in-vitro*. They described their purpose clearly. "In the present study we investigated the cellular and subcellular distribution of group I mGluRs in relation to specific glutamatergic inputs. Antibodies that selectively recognize all known splice variants of mGluR1 or mGluR5 were employed in high resolution methods." They included a set of definitions to insure correct interpretation of their findings.

• Synaptic specialization– Their term for the active (signaling) surface area of a post synaptic region of a membrane of a dendrite or dendritic spine; the active surface area of a synapse.

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[83]Belenikin, M. Costantino, G. Palyulin, V. Pellicciari, R. & Zefirov, N. (2003) Molecular modeling of the mGluR1 metabotropic glutamate receptor transmembrane domain and construction of the model of its dimer *Doklady Biochem Biophys* vol 393(1-6), pp 341-345

• Extrasynaptic region– the region distinctly distant from the synaptic specialization.
• Perisynaptic positions– the region immediately surrounding the synaptic specialization.
• Perforated synapses– synaptic junctions with an irregular outline resulting in postsynaptic densities which appear as isolated segments in cross-section.

They employed both light and electron microscopy and noted, “From the light microscopic analysis it was not possible to predict whether any of the immunoreactivity was associated with synapses or distributed uniformly on the neural surface.”

“All dendritic spines with a clear synaptic specialization were counted and assessed for the presence of immunoparticles.” **Figure 3.2.4-3** shows their unexpected position of immunoreactive mGluR5 on the head of dendritic spines (n = 207) relative to the postsynaptic membrane specialization as measured by pre-embedding immunogold labeling in the statum radiation of the CA1 area of the rat hippocampus.”

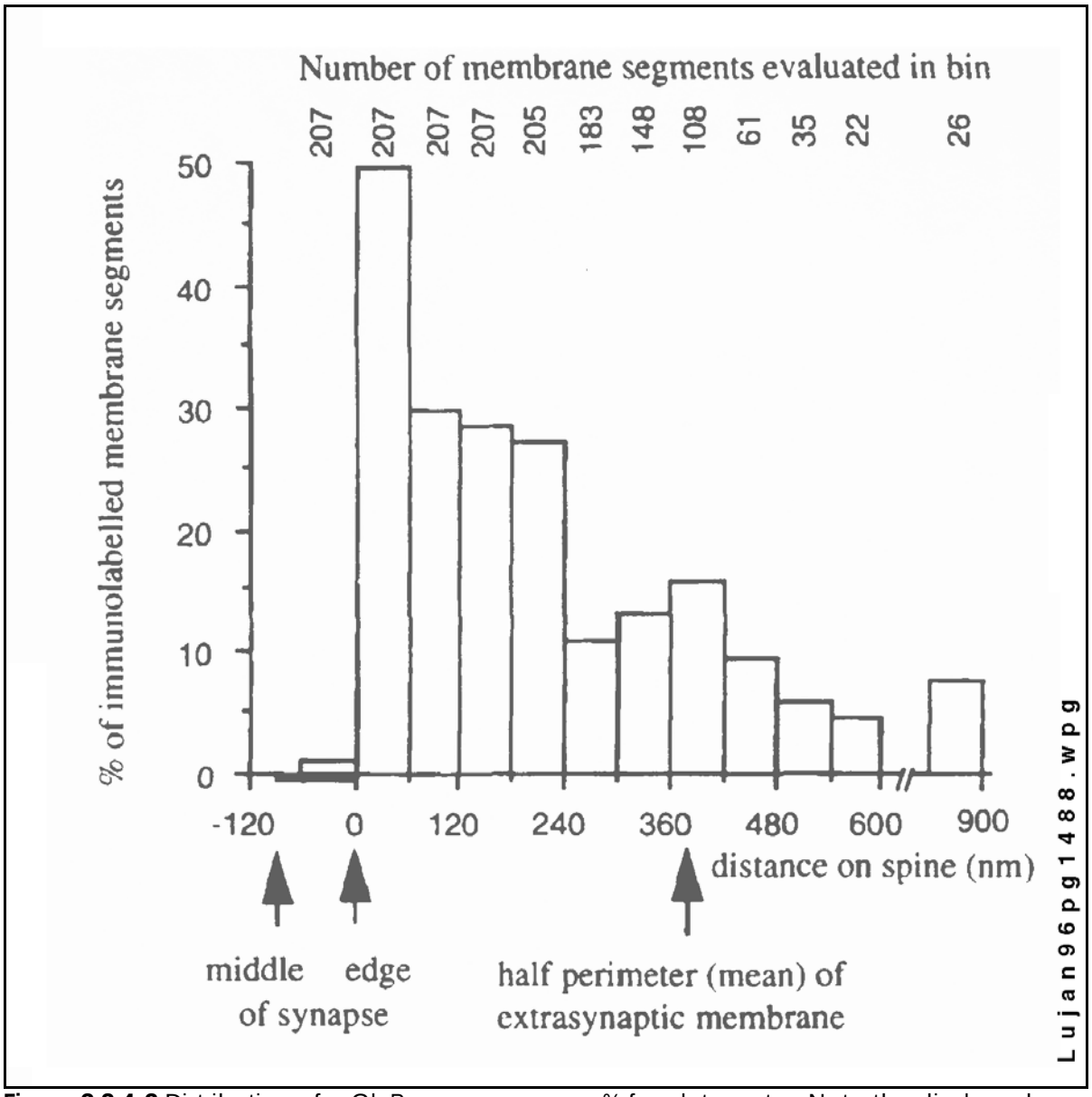

Figure 3.2.4-3 Distribution of mGluR on neurons as a % for glutamate. Note the displaced zero and the break in the abscissa scale. Absence of glutamate within the synapse reinforces the assertion that it is not a neurotransmitter. It is a neurofacilitator. See text. From Lujan et al., 1996.

The ordinate displays the percent of membrane segments exhibiting immunolabeled particles associated with mGluR5, acting as surrogates for the actual glutamate receptors, phosphatidylserine. The abscissa shows distance from the edge of the synapse, the demarcation between the synapse specialization and the perisynaptic region.

Virtually no enzymatic mGlur5 is found within the radius of the synaptic specialization. It is essentially all located outside of the synapse where it can support the electrostenolytic power process.

The figure is quite clear mGluR5 is not found within the synapse itself. The enzymatic material is dispersed on the extra–synaptic region of the dendritic spine lemma.

They noted in their abstract, "The density of immunolabelling was highest on dendritic spines."

Lujan et al. also noted that, "In the case of mGluR1, peroxidase reaction end–product was present on the extracellular surface of extrasynaptic somatic, dendritic and spine membranes, confirming previous results obtained with the G18 antibody (Shigemoto et al, 1994) and in agreement with the predicted extracelluar location of residues 104-154."

At a more detailed level, they note, "The diffusion of the peroxidase reaction end–product prevents the determination of the precise location of the 'receptors'." They conclude, "The results obtained by the immunoperoxidase method support the presence of receptors everywhere along the plasma membrane." And, "Immunoparticles were mainly associated with the plasma membrane for both mGluR5 and mGluR1." And, "The higher density of immunoreactive mGluRs in the extrasynaptic spine membrane indicates that neurons have mechanisms which differentially regulate the density of extrasynaptic neurotransmitter [glutamate acting as a neuro-facilitator, *editor*] receptors in addition to synaptic ones in different parts of the somato-dendritic domain." Their paper did not address the detailed functional (signaling) role of the putative synaptic receptors for glutamate.

Their summary remark on page 1496 appears determinative, "Immunoparticles were always found outside the synaptic membrane specialization, often appearing in a perisynaptic position at the edge of asymmetrical synapses. In the rare cases when a particle appears to overlap the lateral part of the synaptic specialization it is probably due to the superimposition of the image of the particle on the postsynaptic density in different depths of the section."

> **It can be concluded that glutamate is clearly acting as a neuro-facilitator in the perisynaptic and extrasynaptic regions of the neuron, and not a neurotransmitter within the synaptic specialization in the case of rat hippocampus cells explored by Lujan et al. The role of the mGluR family of proteins appears to be enzymatic in facilitating the electrostenolytic powering of the neurons through the glutamate to GABA chemical reaction.**

More specifically, and formally;

• The null hypothesis that the mGluR family (specifically mGluR1 and mGluR5) are present in the synaptic specialization as the receptor of the neurotransmitter, glutamate, is falsified by Lujan et al.

• In the absence of a recognized receptor in the synaptic specialization, the null hypothesis that glutamate is a neurotransmitter (carrier of signal information) is open to question if not falsified.

• An alternate null hypothesis is offered that glutamate is a primary neuro-facilitator providing electrical power to the individual neuron via a phosphatidylserine receptor located outside of the synaptic specialization.

On the other hand, the following null hypotheses related to glutamate (alternate aspartate) are offered,

• Glutamate is the primary neuro-facilitator powering the individual neuron through its presence on the external surface of type 2 lemma outside of any synaptic region of the neuron.

• Glutamate provides electrolytic power to the neuron through the oxidation of glutamate to GABA (alternate alanine), the release of CO_2 and the transfer of electrical energy to the plasma of the neuron.

• The power provided to the neuron by the oxidation of glutamate results in the polarization of the plasma to a maximum of –154 mV under quiescent conditions.

• The receptor for glutamate is the phospholipid, phosphaditylserine, an integral part of the type 2 lemma of every neuron.

The following null hypotheses related to the mGluR family of proteins (specifically mGluR1 and mGluR5 based on Lujan et al.) are also offered,

• The mGluR family of proteins are involved in supporting the electrolytic powering of the individual neurons.

• The mGluR family of proteins are found on the surface of type 2 lemma outside of the synaptic specialization.

• The mGluR family are present on the surface of type 2 lemma located outside the synaptic specialization.

• The mGluR family are enzymes supporting the stereo chemical capture of properly oriented glutamate by the phospholipid glutamate receptor, phosphatidylserine..

•The mGluR family are more than decarboxylase enzymes in that they support the transfer of energy through a lemma into an electrolytic plasma.

3.2.4.4 Distribution of glutamate receptors in the neural system

The distinction between the perisynaptic and extrasynaptic regions made by Lujan et al. is an important one that can be used to answer questions related to the axonal segments of stage 3 neurons and that can be extended to the axonal elements of all neurons. As developed in **Section xxx**, all axonal segments are myelinated. As such, the extrasynaptic region at the dendrite-like portion of the axon segment is unavailable for electrostenolytic processes. However, the perisynaptic region is available. Similarly at the opposite, axon-like portion of the axon segment; the extrasynaptic portion is protected by myelin but the perisynaptic portion is accessible for electrostenolytic processes. By extension, the unmyelinated perisynaptic portion of any axon is available for electrostenolytic processes, and in fact, the perisynaptic region of any axon is available to support electrostenolytic processes.

3.2.4.5 Requirements on Group I mGluR's as enzymes

To be maximally effective in electrostenolytics, the group I mGluR enzymes should exhibit the following properties;

• Migrate to, and associated with, the external surface of the type 2 lemma region(s) of neural lemma within the fluid milieu of the organism.

• Preferentially sequester the negatively charged dual carboxylic amino acids (glutamic acid and aspartic acid).

• Orient the two amino acids to present the carboxylic group farthest from the nitrogen moiety to the PtdSer lipid of the type 2 lemma of the neuron.

• Aid in the formation of dual hydrogen bonds between the amino acids and the serine ligand of the phospholipid.

• Support the decarboxylation of the amino acids at their terminal closest to the nitrogen moiety.

• Support the release of the residue, GABA or Alanine, following the decarboxylation back into the fluid milieu (thereby making the receptor site available for a repeat of the later steps in the above sequence..

3.2.5 Proposed schematic of the axoplasm and electrostenolytic supply

[xxx may need to be simplified if full fig used earlier in chapter 2]
Figure 3.2.5-1 shows the proposed electrostenolytic circuit of the axoplasm when supplied with

the nominal –154 mV potential required by neurons.

It suggests the axolemma changes from type 1 to type 2 in the area of electrostenolytic activity. The resulting axolemma is capable of supporting the charging of the axoplasm to a negative potential by an external source as shown. It remains impervious to negative charges attempting to return to the extra neural matrix in the absence of the electrostenolytic source.

The ability of the outer bilayer to form a double coordinate stereo-chemical bond (d = 2.07 Angstrom) with the carboxylic group of glutamate suggests this outer layer is a form of phosphatidyl serine (**Section 1.4.2**, as it is also in the case of the positive potential supply in cardiocytes (**Section 3.4**).

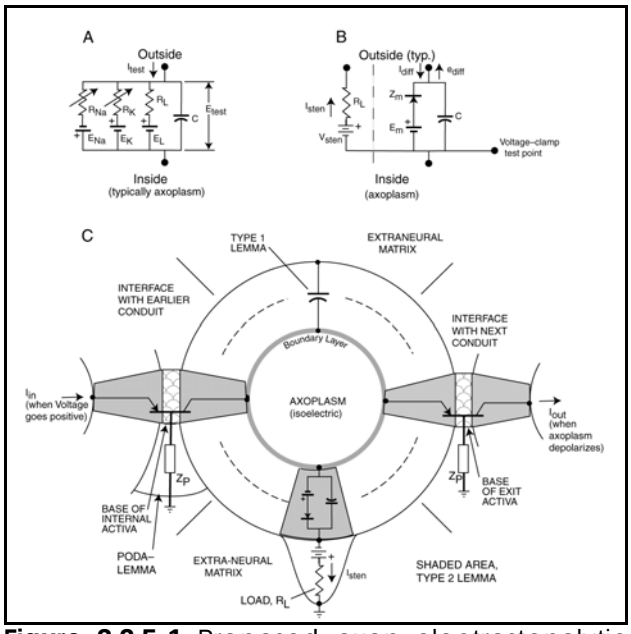

Figure 3.2.5-1 Proposed axon electrostenolytic schematic. The orientation of the diode within the type 2 axolemma, and the associated quantum-mechanical battery is optimal for supporting the charging of the axoplasm to a negative potential by the electrostenolytic supply shown in the bottom quadrant.

3.3 The sources of glutamic acid

The "blood-brain barrier" plays a crucial role in understanding the potential sources of the glutamates. The glutamates must be available to neurons both within the CNS and along the length of the PNS. The majority of the neuroscience literature says the glutamates cannot cross the blood/brain barrier. If correct, the glutamates must be synthesized within the CNS. It must also be formed within the immediate vicinity of each neuron of the PNS. Conversely, the general literature of nutrition suggests that glutamate derived from oral ingestion of mono-sodium glutamate passes the blood-brain barrier easily. A careful analysis of the effect of oral ingestion of mono-sodium glutamate (MSG) on the CNS could shed a definitive light on this question. The clinical literature also suggests that GABA crosses the blood-brain barrier readily.

At least three alternate sources of the glutamates have been proposed in the literature. One involves the synthesis of glutamic acid from glycogen, via a Kreb (or tricarboxylic acid) cycle. The second would create the glutamates from other complex molecules via a variant of the Krebs cycle. This method is particularly awkward because of the multiple variations presented in the literature. The third involves the local decomposition of proteins. This section will rationalize some of this material. Form here forward, the tricarboxylic acid (TCA) cycle will be used in preference to the older notations, the Kreb cycle or the citric acid cycle.

Fonnum provided a comprehensive review of potential sources of glutamate in 1984[84]. Unfortunately, his discussion was limited to text. He defines two different "compartments" for the processing of glucose. The compartments appear to process glucose through two different versions of a TCA cycle. He says that under normal conditions, the glucose metabolized in the large glutamate "compartment" results in large amounts of glutamate and lesser amounts of glutamine. Alternately, the glucose metabolized in the small glutamate "compartment" results in a higher percentage of glutamine. He references other work that states the large compartment contains 85-90% of the total glutamate pool in brain.

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[84]Fonnum, F. (1984) Glutamate: a neurotransmitter in mammalian brain *J. Neurochem.* Vol. 42, no. 1, pp 1-11

Defining the above compartments becomes another matter. Fonnum speaks of two sub-compartments supporting the production of glutamate. One is for glutamate as a neurotransmitter. The second is for glutamate destined to react and form GABA. Fonnum closes with the observation that "the relative contribution of glutamine or glucose to transmitter glutamate in-vivo remains an open question." McGeer, et. al. comment that, "Unfortunately, it has not yet been possible to associate definitively any of these metabolic pools [compartments] with anatomical structures such as neurons, or glia or with distinct glutamate or aspartate neuronal systems."[85] In this work, based on the electrolytic model of the neural system, glutamate as a neurotransmitter is not necessary. The processing of glutamate into GABA occurs in the normal electrostenolytic process of powering the neural system.

Recalling that glutamate and GABA are ubiquitous in the peripheral nervous system is important. Conceptualizing unique compartments where glutamate is found may not be necessary. It is also important to note Fonnum's comment that until about 15 years ago, ". . . it was at first difficult to believe that glutamate could be a neurotransmitter." This work will show glutamate is not a neurotransmitter as defined within the chemical theory of the neuron. It is more appropriately described as a neuro-facilitator within the electrolytic theory of the neuron.

Fonnum briefly addresses the formation of glutamate from glutamine, possibly from that formed via the small compartment defined above. In that case, the original source would still be glucose, despite the citrate cycle used.

McGeer, et. al. note that glutamic acid is the precursor of GABA and that glutamic acid can be formed from either glutamine or α-ketoglutarate (pg 198). These are only two of the potential precursors of glutamate. The literature contains many TCA cycles which could be used to create glutamate from glucose. Fonnum lists three routes[86]. The paths of Fonnum and of McGeer, et. al. typically suggest 8-10 precursors between glucose and glutamate and a large variety of accompanying enzymes facilitating the individual reactions. Lehninger illustrates about a dozen paths from various amino acids or intermediaries to glutamate.[87] Enumerating the ways of forming glutamate appears to be primarily an intellectual exercise.

The concentrations of the glutamates, their precursors and their reaction products can be very high within the CNS. Paul notes the concentration of GABA in vertebrate CNS can reach millimolar levels[88]. These high concentrations are allowing very valuable data to be acquired from humans of all ages, *in-vivo,* using optimized MRI imaging techniques[89].

The discussions to follow uncover some potentially important information of great interest to medicine. These ramifications will be discussed in **Section 3.2.3.4**.

3.3.1 Glycogen as the principal source of glutamate

In brief, the general plan begins with conversion of glucose into pyruvate and then a citrate

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[85]McGeer, P. Eccles, Sir J. & McGeer, E. (1987) Molecular Neurobiology of the Mammalian Brain, 2nd ed. NY: Plenum, pg 177

[86]Fonnum, F. (1984) Op. Cit. pg 1

[87]Lehninger, A. (1970) Biochemistry. NY: Worth Publishers, pp 445-452

[88]Paul, S. (1995) GABA and glycine *Chapter 8 In* Bloom, F. & Kupfer, D. *ed*. Psychopharmacology: the Fourth Generation of Progress. NY: Raven Press pg 87

[89]Ross, B. Lin, A. Harris, K. Bhattacharya, P. & Schweinsburg, B. (2003) Clinical experience with ^{13}C MRS *in vivo* vol 16(6-7), pages 358–369)

leading to α-ketoglutarate. The α-ketoglutarate is then converted to glutamate. The electrostenolytic reaction converts this glutamate into GABA and carbon dioxide. Any enzyme or other chemical impacting (either positively or negatively) on the supply of glutamate or the removal of the reaction product GABA, relative to their normal concentration near a neuron, can be considered an important neuro-facilitator or neuro-inhibitor. Such a facilitator or inhibitor indirectly affects the operation of the neural system.

McIlwain & Bachelard reported on a probable a method of forming glutamate, and eventually GABA, in 1985. They injected radio-nucleotide labeled glucose into cerebral tissue and observed the distribution of the nucleotides in various compounds after one hour. Their figure 4.7 is reproduced as **Figure 3.3.1-1**. Although this is a transient measurement, it can be compared with their table 1.1 of steady state concentrations. The concentrations are consistent between their two data sets. The label α-ketoglutarate has been added to this figure as discussed below. The figure supports the first claim in the following quotation from Hertz[90]. "This concept is in agreement with the finding that pyruvate and lactate is almost as effective a substrate as glucose in the maintenance of not only the resting and the stimulated respiration, but also of a reasonably high concentration of energy-rich phosphates." It is also compatible with the two compartment model of Fonnum. The lower right path representing his large compartment and the upper right path representing his small compartment. Ruscak & Ruscakova have provided compatible data from a variety of investigators on the ratios found in rat brains for glutamic acid, GABA and glutamine[91]. They have also commented more positively on the relative permeability of the blood-brain barrier by glutamic acid.

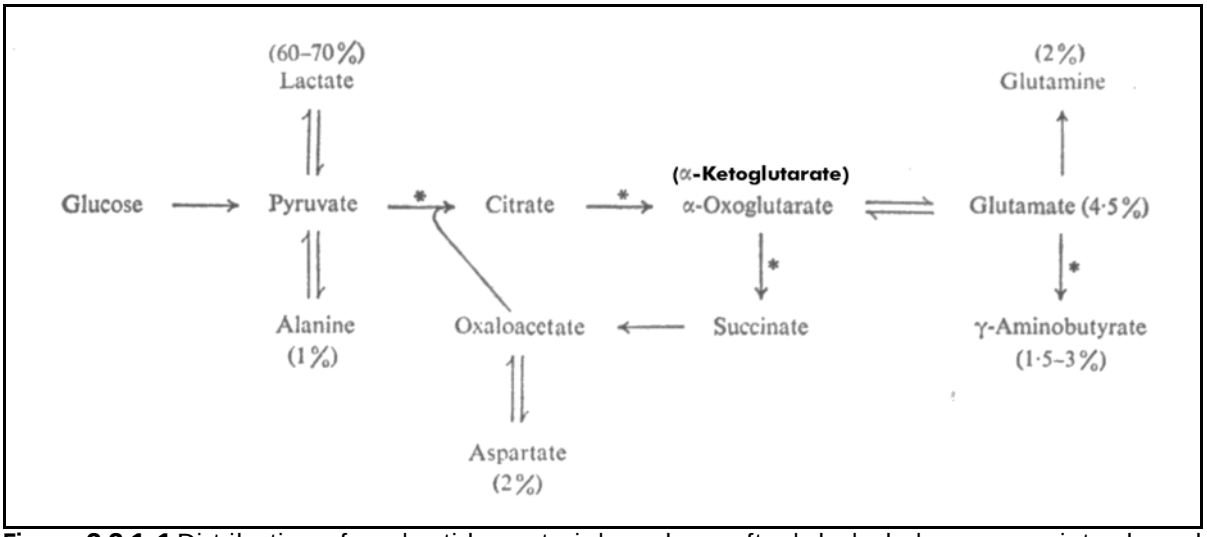

Figure 3.3.1-1 Distribution of nucleotide material one hour after labeled glucose was introduced into cerebral tissue. The asterisks indicate the release of carbon dioxide (in total, about 20% of the labeled material). From McIlwain & Bachelard, 1985.

Lehninger lists nine steps, in two stages, in the conversion of glucose into pyruvate (pg 316). The reversible reaction to form lactate is a major method of intermediary storage. Only a few steps are needed to go from pyruvate to citrate at the entry to the TCA cycle. Most descriptions of the TCA cycle begin with citrate at the top of the loop and rely upon an extension to glutamate. This glutamate shunt is shown in Figure 6.1 of McGeer, et. al. Nomenclature remains a problem in this area. McIlwain & Bachelard use the designation α-

[90]Hertz, L. (1969) Op. Cit. pg 21

[91]Ruscak, M. & Ruscakova, D. (1971) Metabolism of the nerve tissue in relation to ion movements in vitro and in situ. Baltimore, MD: University Park Press pp 85-98

oxoglutarate while McGeer, et. al. use α-ketoglutarate and Fonnum uses 2-oxoglutarate for the same material.

The reaction of glutamate to GABA is not addressed in Lehninger since it is not a metabolic step in his context. However, it is the fundamental step in powering all neurons. This difference highlights a critical distinction related to glutamate. When speaking of the metabolism of glutamate, it is critically important to distinguish between carbohydrate metabolism and electrostenolytic metabolism. The former, related to the small compartment of Fonnum, is concerned with the homeostasis and growth of the cell and organism. The latter, related to the large compartment of Fonnum, is focused on providing electrical power to the neural signaling system. Bachelard, recently highlighted this difference[92]. He provide a TCA cycle applicable to the astrocyte cell (carbohydrate metabolism producing glutamine) in figure 4a and to the neuron cell (electrostenolytic metabolism producing GABA) in figure 4b.

The electrostenolytic metabolism of glutamate is directly related to the glutamate shunt described in a variety of biochemistry texts. The schematics in figures 4(b) and 5(b) on pages 18 & 19 of Bachelard appear to be the only TCA cycles of interest in neural signaling. Figure 4(b) occurs naturally while 5(b) is artificial. Figure 5(b) does highlight an idiosyncracy introduced by the IUPAC naming rules that will be addressed further below. The same carbon atoms in glutamate and GABA are numbered differently. As noted in the footnote to **Figure 3.3.1-4**, the carbon atoms of glutamate are numbered as if it were α-amino glutaric acid. If it were defined as γ-amino glutaric acid (in parallel with γ-amino butyric acid or GABA), the same carbon atom would have the same number in both formulas.

The distinction between carbohydrate metabolism and electrostenolytic metabolism is not always recognized in the literature. The schematic TCA cycle described in Ross, Lin, et. al. (lower frame of figure 5) only applies to astrocyte cell (carbohydrate) metabolism.

3.3.1.1 Fundamental steps leading from glucose to glutamic acid

While glutamic acid can be obtained from nearly any simple sugar, it is usually obtained from glucose, or glucose stored as the polysaccharide glycogen. Obtaining glutamic acid from glucose involves three and one-half major stages of biological chemical processing.

Stage one involves the collection of the simple sugars and their conversion into glyceraldehyde. Glucose, the formal name for the dominant constituent being α-D glucopyranose, is converted to glucose 6-phosphate by hexokinase and then to fructose 6-phosphate. The fructose 6-phosphate is then converted to D-glyceraldehyde-3-phosphate.

Stage two requires six steps to convert the D-glyceraldehyde-3-phosphate into pyruvate and then into acetyl CoA, a very complex thioester of acetic acid and a very complex enzyme known as coenzyme A.

Stage three introduces acetyl CoA into the tricarboxylic acid cycle that can produce a variety of biochemicals including α-ketoglutarate. A shunt associated with this cycle, and labeled stage 3.5 here, is used to produce glutamic acid. The steady-state compositions of these materials found in the brain are shown in the above figure.

A more detailed discussion of these chemical processes appears in **Section 3.5.4**.

3.3.2 The Source of electrostenolytic reactants–glycolysis, TCA and shunt

Figure 3.1.3-2 has presented an extended Citric Acid cycle (or Kreb's cycle) to introduce how glutamate is prepared within the vicinity of each individual neuron. Aspartate can be

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[92]Bachelard, H. (1997) Op. Cit. Figures 4a & 4b and 5a & 5b

prepared by essentially the same cycle, with only minor modification. The overall process has been studied in detail and is well documented and straight forward. This section will address additional features of these processes in greater detail.

3.3.2.1 Probable reconstitution of glutamic acid

McIlwain & Bachelard provide an additional discussion of potential TCA cycle operations that could regenerate glutamic acid[93]. GABA is easily converted to succinic semialdehyde through transamination. This chemical is a participant in the TCA cycle originally used to create α-ketoglutarate and then glutamic acid (see **Section 3.2.3.2** and **Section 3.2.6**).

Lake, Marshall & Voaden[94] have discussed a "glutamate pool" within the retina and shown, using radioactive labeling, that GABA is converted into glutamine within this pool. They indicate the initial site of uptake of exogenous GABA varied by species. It was the Muller fibers (glial cells) within the retina of mammals, e.g., rat and cat. The site was the actual neuron of the retina in the non-mammalian frog and pigeon. However, these results from autoradiography are not as specific as could be obtained via more modern techniques. They also introduced labeled glutamine into retinal tissue and obtained the following results.

TABLE 3.3.2-1
Presence of reaction products following Glutamine injection

Time	Glutamate	GABA	Glutamine	Unaccounted for
0 min.	—	—	100%	—
25	30%	30%	30%	10%
55	—	60%	10%	30%

There is every likelihood that glutamic acid is consumed in electrostenolysis and reconstituted by a short loop near the point of electrostenolysis. It may proceed as suggested by Lake, et. al: However, this does not appear to be the case. Glutamine contains two NH_2 groups. Going to this level of amination appears unnecessary. An alternative approach would recognize glutamine as an alternate source of glutamic acid as suggested by:

glutamic acid –>GABA–>α-ketoglutaramic acid–>glutamic acid
↕
glutamine

This reaction eliminates the glutamine step with the re-carboxylation of the GABA to α-ketoglutaramic acid followed by hydrogenation to glutamic acid. Any glutamine produced from GABA would then be incidental (or auxiliary) to the reconstitution process.

Both processes are totally anaerobic.

3.3.2.2 The dynamics of glutamate generation and electrostenolytic metabolism

The separate discussions of **Sections 3.2.2.2** and **3.2.3.2** need to be harmonized into a single schematic of the TCA cycle including the glutamate-GABA shunt. This has been done and was presented in [**Figure 3.1.3-2**] as part of an earlier discussion.

That figure only addresses the large compartment of Fonnum and one of the two

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[93]McIlwain, H. & Bachelard, H. (1985) Op. Cit. pp 168-180

[94]Lake, N. Marshall, J. & Voaden, M. (1977) Metabolic compartmentation and the metabolism of GABA and glutamine in retina: A species comparison. *In* Synapse, Cottrell & Usherwood ed. London: Blackie pg.354

compartments of Lake, Marshall & Voaden. The actual "compartments" take on a different conceptual framework here. While most of the steps in the combined operations of glycolysis and the TCA cycle probably take place within near by glia cells (probably of the astrocyte type within the CNS) , the electrostenolytic process occurring within the glutamate-GABA shunt occurs on the exterior surface of the multiple lemmas associated with the individual conduits of the signaling portion of each neuron. To aid in understanding the operation of this specialized version of the glycolytic/TCA chain, the number of carbon atoms and oxygen atoms associated with each constituent have been added to their names. This modification highlights the fact that the electrostenolytic metabolism of glutamate(5,4) into GABA(4,2) with the release of one molecule of carbon dioxide. The goal of the specialized TCA cycle shown is to regenerate glutamate(5,4) from the degraded GABA.

Note the potential economy related to the use of ammonia in the transamination and re-amination process external to the cell. This opportunity would suggest that the amination of α-ketoglutaric acid, and the subsequent rearrangement to form glutamate may occur in the inter neural matrix, rather than within a cell.

> The sharing of ammonia in the extra-neural matrix may also play a significant role in the operation of the cardiocytes of the heart. In that situation, the release of NH_2 in the conversion of lysine to isoleucine* would provide a readily available source of ammonia for the conversion of GABA to α-ketoglutaramate(5,4). See **Section 3.4**.

Aspartate, if present, can play another role in the TCA shown above. In the presence of the enzyme, aspartate (formerly glutamic-oxaloacetic) transaminase, the following reversible reaction becomes available[95];

aspartate + ketoglutarate —> oxaloacetate + glutamate

This reaction relates to the diagonal of the cycle described above. It allows the presence of aspartate to support the formation of additional glutamate while increasing the store of available oxaloacetate. Aspartate is apparently more important in the formation of various nucleic acids than it is in the operation of neurons. However, it remains an alternate neuro-facilitator of neuron operation.

3.3.2.2.1 Confirmation of the glutamate shunt cycle

Bachelard, et. al. have provided a unique insight into the operation of the electrostenolytic metabolism cycle by radioactively labeling a variety of precursors found in the cycle and the preceding glycolysis chain. Their figure 4b has been expanded for presentation as **Figure 3.3.2-1**

[95]Cantarow, A. & Schepartz, B. (1967) Biochemistry, 4th Ed. London: W. B. Saunders. pg 234

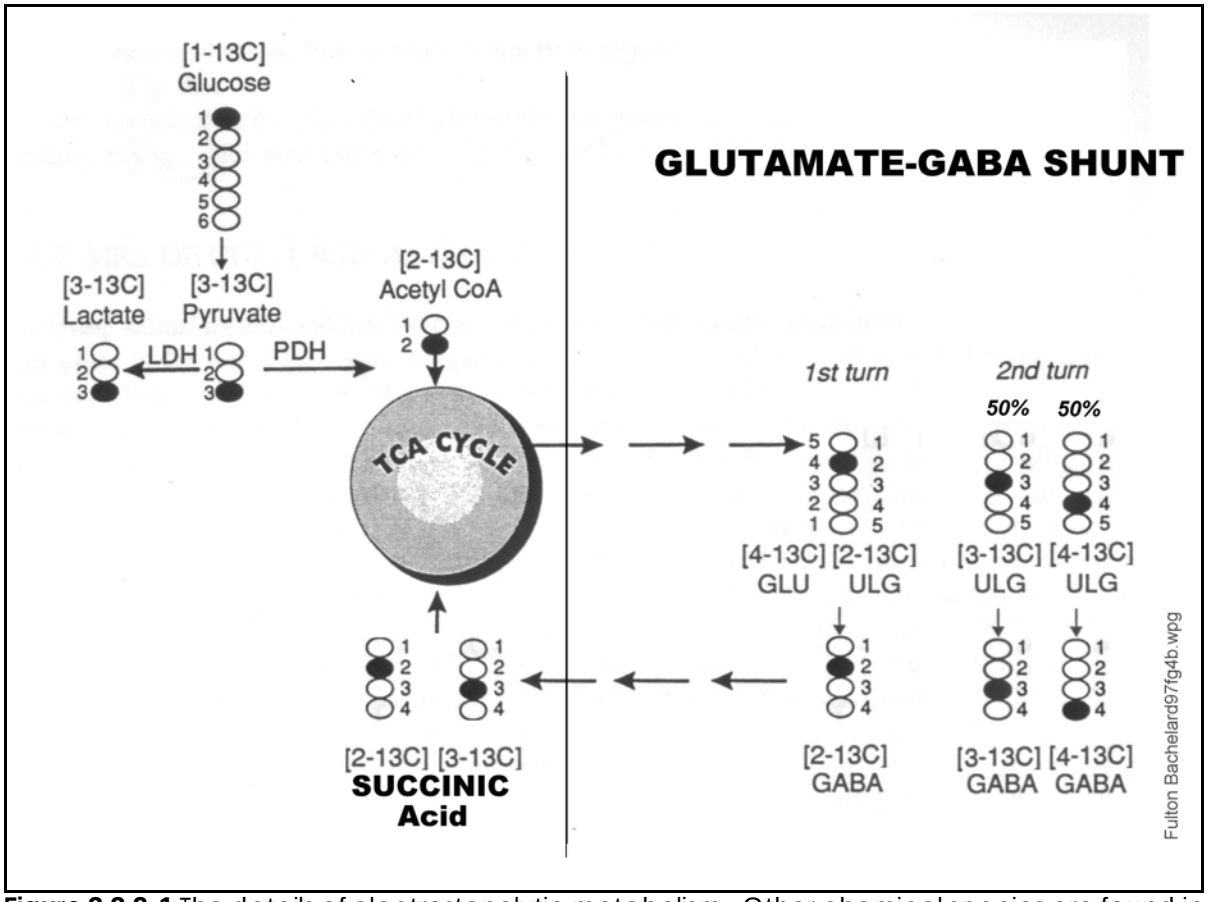

Figure 3.3.2-1 The details of electrostenolytic metabolism. Other chemical species are found in the space between the arrows. The first key to understanding the operation of the glutamate–GABA shunt is recognizing the symmetrical nature of Succinic acid. See text. Compare with Bachelard, et. al., 1997.

The figure describes two "turns" of a modified TCA cycle, including the glutamate-GABA shunt. The first partial turn consists of the introduction of new glutamate into the system that is fabricated from glucose or previously stored lactate. Only a small portion of the TCA cycle is involved in this process. The glutamate is converted to GABA as part of the electrostenolytic process powering the neurons. The black dots indicate the observed positions of radioactively labeled carbon in each of the molecules when they are all derived from a common source, [1-^{13}C] glucose.

> A problem of nomenclature arises at this point. The numbers on the left of the carbons representing glutamate correspond to the IUPAC designation of glutamate as α-amino glutaric acid. However, to be consistent in this representation, it would be better if glutamate were defined as γ-amino glutaric acid. This nomenclature would agree with that used for γ-amino butyric acid (GABA) and results in the numbering system shown to the right of the glutamate carbons. To avoid confusion, the renumbered glutamate will be labeled ULG in the following discussion. This nomenclature allows the labeled carbons to be tracked much more easily in the following discussion.

The second turn is shown as a complete turn via the glutamate-GABA shunt. It begins with the GABA produced in the first turn being converted to succinic acid. This acid is processed further within the TCA cycle resulting in the production of additional GLU/ULG as shown on the right. The new glutamate appears in two different labeled forms due to the symmetry of succinic acid, as shown at the bottom left. When the symmetrical succinic acid molecule

formed from GABA is converted into an asymmetrical molecule through further processing within the TCA cycle, there is a 50/50% chance that the labeled carbon will appear in either of two positions. This is reflected in the two forms of glutamate and GABA produce in this second turn.

Figure 3.3.2-2 provides a more detailed look at the progression of the labeled carbons through the system as a result of additional turns of the modified TCA. The top row shows all of the principle constituents involved in the introduction of new glutamate derived from glucose and the removal of its fifth carbon in the electrostenolytic reaction forming GABA. The second row shows the conversion of GABA into either of two symmetrical forms of succinic acid. Subsequent processing causes the formation of two forms of α-ketoglutaric acid through the addition of new carbon at the new position 1, using the IUPAC notation. After rearrangement to form glutamate, glutamate loses the fifth carbon in forming GABA. This GABA exhibits labeled carbon at old locations 2 & 3, now re-labeled as locations 3 & 4 using the IUPAC rules.

The lower row of the figure carries this processing one step farther in order to understand the long term operation of the modified TCA cycle. The two forms of labeled GABA are now converted into four different "species" of succinic acid. Each species forms 25% of the total amount of succinic acid present. After addition of new carbon and its subsequent removal in the formation of GABA, the resulting GABA exhibits no labeled carbon at location one. This labeled carbon has been transferred to a radioactive molecule of carbon dioxide, the first radioactive residue of the electrostenolytic process resulting from ingestion of [1-^{13}C] glucose.

Bluml et al, have also provided recent information on the role of glia in providing glutamate to the neurons[96]. However, their discussion does not involve the glutamate shunt. They claim the metabolism associated with neurons can be tracked by using acetate. They assert that acetate is converted to acetyl-CoA only in the glial compartment (and not in the analogous neural compartment). Experiments can be designed to isolate the contribution of glutamate from these individual compartments. It is asserted in this work that glutamate is metabolized to GABA and GABA is recycled within the glutamate shunt. Glutamine plays no role in the proposed metabolism.

Additional research will be needed to determine whether glia support signaling in the neuron by supplying lactate or by supplying glutamate to the neuron.

[96]Bluml, S. Moreno-Torres, A. Shic, F. Nguy, C-H. & Ross, B. (2002) Tricarboxylic acid cycle of glia in the in vivo human brain *NMR Biomed* vol 15(1) , pp 1-5

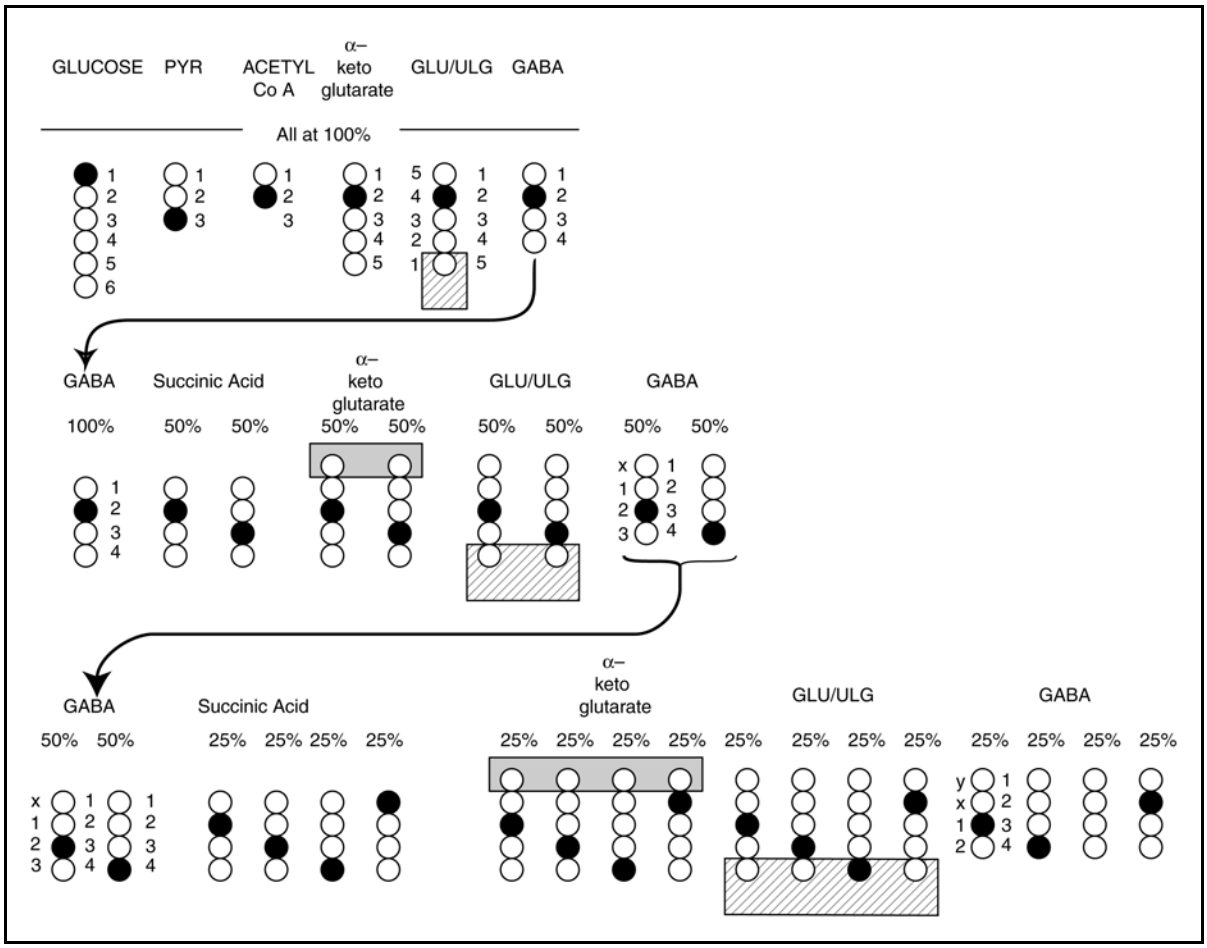

Figure 3.3.2-2 Species found during electrostenolytic metabolism. Top row; initial generation of glutamate from glucose. Middle; first turn of the regeneration cycle. Bottom; second turn of the regeneration process. The label GLU/ULG has been used to highlight the nomenclature problem. The numbers to the left of the carbon symbols refer to GLU when described by IUPAC rules as α-glutaramic acid. The numbers on the right describe glutamate (ULG) when described as γ-glutaramic acid. The shaded boxes show the addition of carbon to the specific species during the generation/regeneration process. The hatched boxes show the removal of carbon dioxide from the species as part of the electrostenolysis process. The second key to understanding the operation of the glutamate-GABA shunt is to recognize the "cycling" of the labels for the carbons of GABA. This cycling is due to the addition of a carbon at one end of the molecules and its removal at the other end. See text.

3.3.2.2.2 Augmentation of the glutamate shunt via glutamine

As noted in **Section 3.2.3.2**,, and developed in **Section 3.1.3.3**, glutamine does not participate in the routine formation of glutamate either directly from glucose or in its regeneration from GABA via the TCA and the glutamate shunt (**Section 3.1.3.3**). However, glutamine can provide a reserve source of glutamate. Glutamine is easily formed from excess glutamate and excess NH_4^+ by amination. Glutamine is a non-toxic form convenient for the storage and transport of ammonia. Being non-toxic, it can be present in the inter neural matrix without causing difficulty. In this role, glutamine supports a wide variety of metabolic reactions. Glutamine is easily converted back to glutamate by hydrolysis. Ross,

Lin, et. al. show this mode of storage in the lower frame of their figure 5[97]. They show how the recovered glutamate differs in molecular sequence from the original glutamate participating in glutamine storage.

Patel et al. have performed an exemplary set of experiments designed to evaluate the roles of glutamic acid (glutamate), glutamine and GABA separately in rat neurons. They used nuclear chemistry to track each material through the tricarboxylic acid cycle (TCA)[98]. Their purpose was to collect data aiding in the analysis of BOLD fMRI data. Unfortunately, their analyses reflect the terminology of the day where a non-inverting input (or dendritic) terminal of a neuron is labeled glutamatergic and an inverting input (or poditic) terminal of a neuron is labeled GABAergic. They apparently did not concern themselves as to why glutamate and GABA were associated with neurons or if there was a direct mechanism coupling the two chemicals. They also appear to use the term "isoelectric" in place of quiescent. The work can be compared to this work and the earlier work in the 1987 paper of McGeer, Eccles & McGeer (**Section 3.1.3.3**) and the 1997 paper of Bachelard et al. (**Section 3.3.2.2.1**).

Their figure 1 is shown as **Figure 3.3.2-3(A)** with additional labels and a revised caption. The support material for their paper provides greater detail regarding these two TCA cycles. Figure 1 essentially duplicates [**Figure 3.1.2.2**] of this work by using two leaves to represent the main TCA cycle associated with the neuron and a separate support TCA cycle associated with a separate astroglia. The block arrows and three letter codes in the central portion of the diagram are at a different level of detail than in the loops. The orange arrow is an artist's artifact since there is no known reservoir of Glu (glutamate) associated with the astroglia and the label under the arrow is not descriptive. An alternate rendition is offered in frame (**B**) of the figure.

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[97]Ross, B. Lin, A. Harris, K. et al. (2003) Clinical experience with ^{13}C MRS *in vivo*, *NMR Biomed* vol 16, pp 358–369 DOI:10.1002/nbm.852 *A Review Article*

[98]Patel A. de Graaf, R. Mason, G. et al. (2005) The contribution of GABA to glutamate/glutamine cycling and energy metabolism in the rat cortex *in vivo PNAS* vol 102 (15), pp 5588-5593

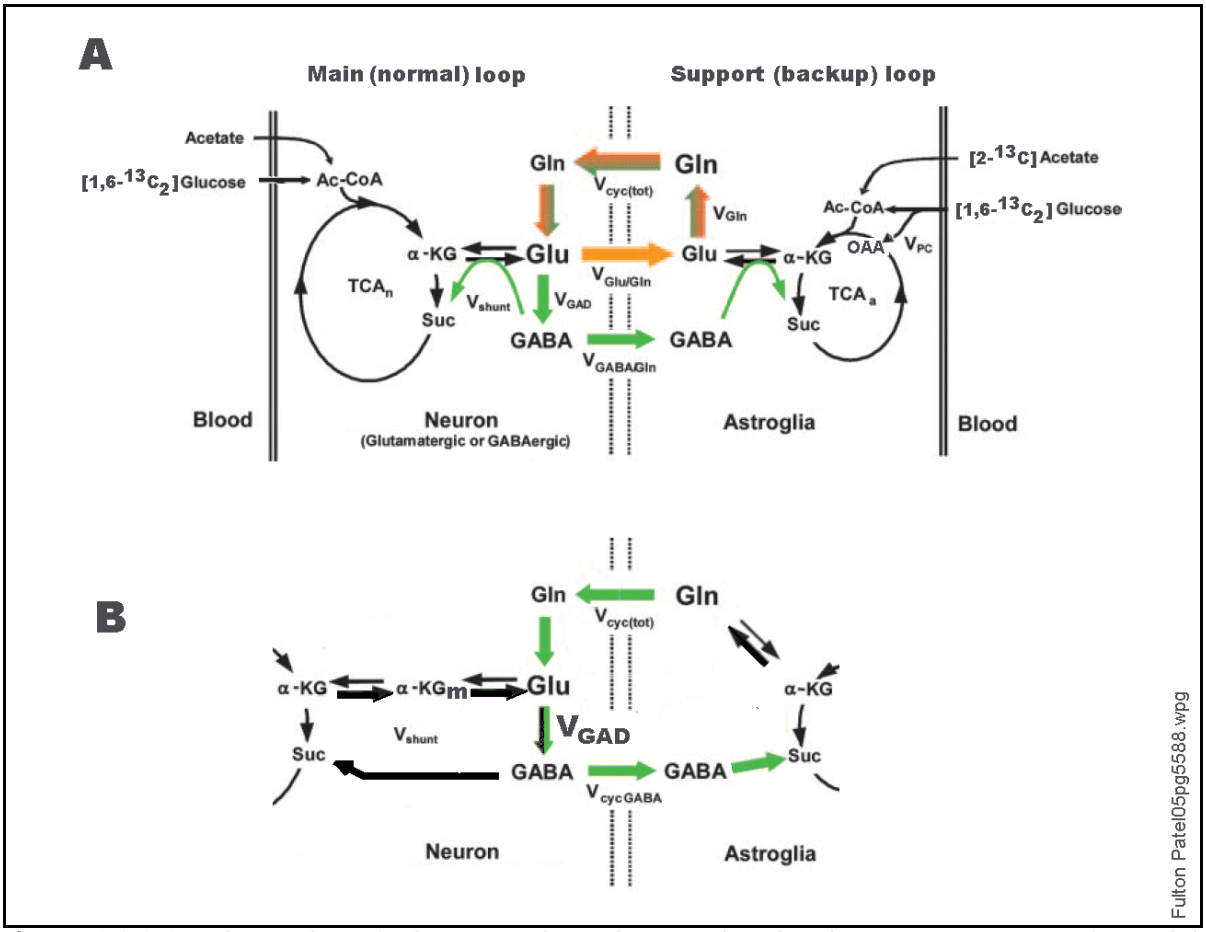

Figure 3.3.2-3 Schematics of glutamate-based normal & backup power generation. (**A**) Schematic depiction of Glu/Gln and GABA/Gln cycling between glutamatergic (orange) and GABAergic (green) neurons and astroglia by Patel et al., 2005. Note different means of forming Ac-CoA on left and right. The acetate on the left is not tagged with a nucleotide. (**B**) Alternate interpretation of the central portion of their figure applicable to all neurons. V_{GAD} is the electrostenolytic process powering the individual neuron(s) although not functionally defined as such by Patel et al. The sub-label below neuron has been removed and the bi-colored (orange/black) arrows discarded. The glutamate shunt, V_{shunt}, has been reoriented. The goal of the Patel et al. investigation was to determine how much of the glutamate participating in V_{GAD} is from each of the sources shown. See text.

Frame (**B**) stresses the functional fact that the flux labeled V_{GAD} is associated with the actual electrostenolytic process occurring on the surface of, and providing power to, ***all*** of the individual neuron(s). The rest of the chemical processing shown to the left of V_{GAD} may occur in the "housekeeping" portion, separate from the signaling portion, of each neuron or within the chemical milieu associated with the neurons. Additional support for glutamate production may be provided by nearby astroglia drawing GABA from the milieu and returning glutamine to the milieu.

The novel element in their protocol is the use of two different nucleotides to label Acetyl-CoA so that the source of glutamate originating within the TCA and the glutamate shunt can be separated from that produced from glutamine originating in the astroglia. Note the two Ac-CoA labels in their figure 1 should carry distinctive nuclear chemistry designations (as in the modified figure above and the caption to their figure). Their work can then be more easily compared to the nucleotide work of McIlwain & Bachelard in **Figure 3.3.1-1** and Bachelard, et. al. in **Section 3.3.2.2.1**. They specifically note "Whereas glucose is oxidized in both neurons

and glia, acetate is metabolized almost exclusively in glia (with citations)."

In this work, the regeneration of GABA to glutamic acid does not require such clear delineation as described by Patel et al. The astroglia and the right loop of their figure 1 acts more as a backup to the electrostenolytic supply of the neural cell and its local environment according to this hypothesis. See **Sections 3.2.2.3.2**, **3.3.2.2.3** & **3.3.3.1.4**.

Patel et al. identified V_{GAD} only as a convenient term in their equation 9 applicable only to GABAergic neurons. In fact, this flux is present, and describes the electrostenolytic process on the external surface of the signaling portion of ***all*** neurons (**Section 3.2.2.3.3**).

Figure 5B(right) of the supplement conforms to the operation of the electrostenolytic process relating to every neuron proposed in the hypothesis of this work with exceptions due to transcription problems related to the diagram as described below. It essentially reproduces just the left half of their figure 1(as represented by the "green" labeling, without the green arrow labeled $V_{GABABin}$ and the green hairpin on the right). Their goal may have been a representation of the TCA loop including the glutamate shunt of McGeer, Eccles & McGeer, 1987 shown in [**Figure 3.1.3-2**]. There are other "shunts" associated with the TCA and clarity requires an adjective in front of shunt when describing the TCA role associated with the neurons. [**Figure 3.1.3-2**]shows the normal conversion of GABA back to Glu via the TCA by the heavy arrow proceeding to Suc.

The supplement provides the differential equations they "solved" in support of their work. These equations were never solved explicitly.

The term V_{GAD} was identified only as the "GABA synthesis rate" and given by the equation $V_{GAD} = V_{cyc(Gaba/Gln)} + V_{shunt}$ based on frame 5(B)(right). From that figure, it is seen that V_{GAD} is the flux associated with the forward kinetics of the molar equation Glu $\rightleftarrows$ GABA $+CO_2$ developed and illustrated functionally in **Section 3.2.2.3.3**. This molar equation is consistent with their statements regarding the relatively equal consumption of GLU and creation of GABA. It says nothing about the relative concentrations of the species under quiescent conditions. They attribute V_{GAD} to the action of Glu decarboxylase (GAD) in accordance with the conventional chemical theory of the neuron (page 5592) rather than to the electrostenolytic process of the Electrolytic Theory of the Neuron supported here. $V_{cyc(Gaba/Gln)}$ is shortened to $V_{(Gaba/Gln)}$ in the upper frame of their figure 1.

A long list of differential equations are defined in the supplement. No physiological model supporting these equations was presented and no effort was made to solve these equations by either analytic or numerical computation techniques. They did note the equations applied to an iterative process. Providing information concerning the iterations ala Bachelard would have been useful. No input path associated with either the putative glutamatergic or GABAergic input paths are shown in figure 5. There are problems with the artwork related to figure 5 (particularly where tenses are used differently than in figure 1). No GABA appears in the digram of figure 5(A)(right). A differential equation associated with the Glutamate node leading to V_{GAD} is needed but not described explicitly. Many estimates were included in the descriptions of the terms in the differential equations at the end of the supplement. However, no citations were provided supporting these values..

V_{GAD} is directly related to the effective forward kinetics of the electrostenolytic process of this hypothesis. It is a function of the pulse rate of any stage 3 neuron generating (and each Node of Ranvier regenerating) action potentials. For stage 2 and stage 4 & higher neurons, the functional relationship is more complex.

Figure 5B(left) of the Patel et al. supplement represents the backup (storage) loop supporting electrostenolysis within the neural system approximately as shown by the TCA on the right in the above figure.

3.3.2.2.3 Glutamine as a reserve source of glutamate

3.3.2.3 Protein as a potential source of glutamate–the GARPS

A protein-based source of the glutamic acid supporting the above reactions has recently been proposed by Korschen, et. al[99]. While their configuration (based on the existence of a lemma surrounding the outer segment of the photoreceptor) and their concept of the gated cGMP channel are not supported in this work, their physical chemistry deserves review. They define "an unusual set of glutamic-acid-rich-proteins (GARPs) of unknown function." Because their starting assumptions are so different, interpretation of their data may be difficult. However, several features of their work standout. First, the materials were found to congregate intimately with the outer segments of the "rod photoreceptors" and were not found close to "cones." This would be consistent with the premise of this work that the so-called cone is a non-functional or immature photoreceptor.

Second, the materials were found within the notches along the periphery of the outer segment, the precise location of the microtubules (neural dendrites) of the inner segment.

Third, the GARPs were found in two forms, "GARP2 lacks the carboxyl-terminal glutamic-acid-rich region." This feature and the proposition that electrostenolysis of glutamate acid to GABA is key to neuronal activity, would suggest that GARP1 is in fact a glutamic-acid-rich-material. However, GARP2, without a carboxyl group attached to each glutamate, would be more appropriately described as a GABA-rich-material (GABARP). This proposition would lead to the question of whether the GARPs are actually proteins or other large molecular complexes. Such complexes would have a ratio of molecular weights of 147:103 just due to glutamate in the former and GABA in the latter. Korschen, et. al. report a ratio of GARP1 to GARP2 of 130K:62K.

They conclude their extensive paper with a question, "What is the function of GARPs?"

It is difficult to rationalize the presence of glutamate residues with the requirement for complete glutamate acid molecules to satisfy the stereochemical and dipole potential requirements defined in this work. Alternately, Korschen et al. have labeled a simple amino acid, possibly clumped, as a protein, rather than the potentially shorter amino acid chains called peptides.

3.3.3 Toxic effects of glutamate during *in-vitro* experiments

The literature has reported negative consequences on neuron operation of topical application of glutamic acid to neurons. Similar effects have been reported for the topical application of Aspartic acid, GABA, presumably BAPA and other chemicals that can interfere with the fundamental electrostenolytic processes. This effect can be explained if the hydraulic impedances of the extra-neural matrix related to these chemicals is found to have an effect on the nominal collector impedance of the Activa within the neuron. This impedance is associated with the electrostenolytic conversion of glutamic acid to GABA (alternately aspartic acid to BAPA). As noted in **Section 3.2.2.3**, under normal conditions, glutamic acid is only available to the individual neuron at a concentration of a few percent in the extra-neural matrix.

3.4 The secondary electrostenolytic process powering the neurons

Examination of the operation of the cardiocytes of the heart suggest the requirement for a positive electrostenolytic power supply to serve the base (poditic) terminal of the Activa of

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[99]Korschen, H. et. al. (1999) Interaction of glutamic-acid-rich-proteins with the cGMP signaling pathway in rod photoreceptors *Nature*, vol. 400, pp 761-766

those cells. The requirement appears to arise from the need to allow the collector terminal of the Activa to go closer to zero potential when saturated than allowed by a poditic terminal at zero potential.

This requirement can be satisfied by a secondary electrostenolytic process and employing a specialized asymmetrical lemma supporting a positive potential within the podalemma. This specialized lemma may require the definition of a type 5 lemma for clarity.

Figure 3.4.1-1 shows the bio-energetic compounds pertinent to the secondary electrostenolytic process. The isomer of leucine (δ–methyl leucine or α–amino caproic acid) shown in the figure may be subject to further rearrangement to the textbook configuration (α-methyl leucine). As in the case of the primary neuro-facilitators, the stereochemical receptor site for the secondary process also seeks to hold the carboxylic group of the secondary neuro-facilitator. The loss of the NH_3 group causes the residue to be released from the receptor site.

The reaction of lysine to form iso-leucine with the release of NH_3 into solution involves the release of a very small amount of free energy, believed to be less than 1000kCal/mole.

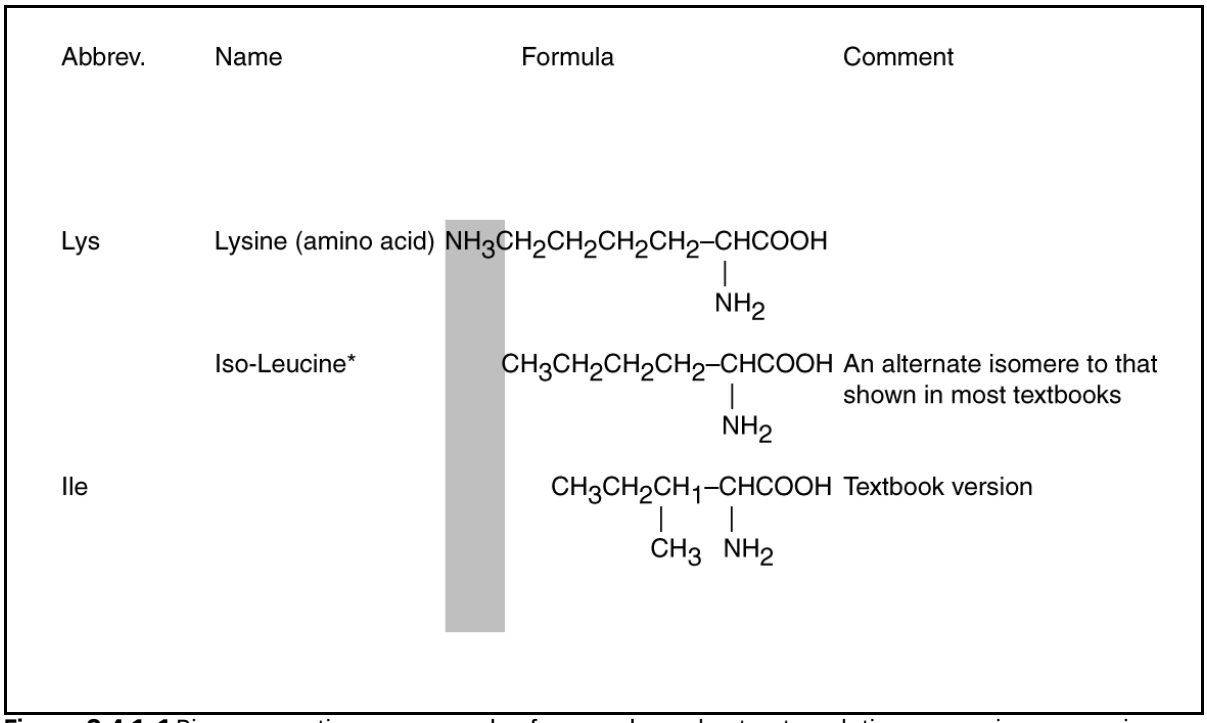

Figure 3.4.1-1 Bio-energetic compounds of secondary electrostenolytic sources in neuroscience. The major participants, and potential antagonists, in the secondary electrostenolytic process. The shading shows the NH_3 lost in the secondary electrostenolytic reaction powering the neural system. It is the carboxyl (or carboxyl-like) group at the other end of the molecule that is stereo-chemically associated with the receptor sites on the bilayer membrane of the cell. Bottom; other formula associated with the formation or interference with the secondary electrostenolytic process.

3.4.1 Supplying positive potentials near 50 mV

Section 16.8 has described the requirement for a positive electrostenolytic process to bias the poditic terminal of a majority of the cardiocytes of the heart. It appears this process involves the conversion of lysine to isoleucine + ammonia by the extraction of an electron from the podaplasm space and the establishment of a potential on the order of +52 mV within the podalemma under static conditions. The value is not known precisely because the precise saturation potential of the Activa within the cardiocyte is not known at this time.

The proposed electrostenolytic reaction is not well documented as the isomer of leucine produced is possibly undocumented. However, based on;

• the success of the analysis of the negative potential electrostenolytic process and
• the very limited availability of amino acids capable of providing a positive potential using the same mechanism,

the assumption of a lysine to isoleucine conversion with the release of the isolated amine group and establishment of a positive potential in the 50 mV range appears prudent.

3.4.2 Characteristics of lysine and leucine

Extensive studies on the free energy of lysine have appeared in the literature, employing different source material and utilizing different states of the lysine, even to different levels of

compaction of the powder[100]. The complexity of the forms of lysine studied is immense and it is not clear which forms are relevant to the electrostenolytic process of interest. Many of the free energies reported are less than one kcal/mole (compatible with a + 50 meV free energy of conversion).

Wittmann & Becker have described the development of lysine as an industrial product (800,000 tons/year production)[101]. It is an essential amino acid not produced internally by animals. They describe lysine as a member of the aspartate family, although this seems superficial based on this work. Lysine is a "basic" amino acid while aspartic is an "acidic" amino acid.. Aspartic acid is a di-amino, while lysine is not.

King has noted the uniqueness of the two amino acids of interest in positive potential generation by electrostenolysis[102]. "All 20 of the amino acids, excepting leucine and lysine, can be degraded to TCA cycle intermediates as discussed in the metabolism of amino acids. This allows the carbon skeletons of the amino acids to be converted to those in oxaloacetate and subsequently into pyruvate." Lysine and leucine appear isolated from a wide range of chemical processing "cycles" within the biological organism. TCA = Tricarboxylic Acid cycle, originally the citric acid cycle or Kreb's cycle.

Chen and Calvo have given the following values for leucine in their abstract[103], "The Gibbs free energy change for leucine binding to the high-affinity site is about –7.0 kcal/mol. Binding of two leucine molecules to low-affinity sites on the hexadecamer or one leucine molecule to one octamer induces the dissociation of hexadecamer to leucine-bound octamer. The Gibbs free energy change for leucine binding to the low-affinity site was estimated to be in the range –4.66 to –5.03 kcal/mol for leucine binding to an octamer or –6.01 to –6.75 kcal/mol for leucine binding to a hexadecamer." The free energy is obviously dependent on what substrate is involved in the measurement. They did not provide any information on isomers of leucine.

Gaudin et al[104]. have provided an extensive binding study related to leucine and at least one form of isoleucine.

3.4.3 Proposed electrostenolytic conversion of lysine to isoleucine

Figure 3.4.3-1 shows the proposed conversion of lysine (shown in its neutral form) to the standard form of isoleucine, with a potentially intermediate form shown to focus on the removal of NH_2. Nitrogen is highly susceptible to the formation of coordinate bonds when hydrogen is available. Thus, lysine is frequently shown with an NH_3^+ group at its extremity. Similar, the released NH_2 is susceptible of coordinate bonding with two hydrogens to form an NH_4^+ group.

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[100]Arumugam, B. Kadir, H. & Tayyab, S. (2010) Effect of charge neutralization at lysine residues on the free energy of stabilization of hen egg white lysozyme *Rom. J. Biochem* vol 47(2), pp 115–133

[101]Wittmann, C. * Becker, J. (2007) The L-lysine story: from metabolic pathways to industrial production *In* Wendisch, V.*ed*. Amino Acid Biosynthesis–pathways, regulation and metabolic engineering. NY: Springer pp 38–65

[102]http://themedicalbiochemistrypage.org/gluconeogenesis.html

[103]Chen, S. & Calvo, J. (2002) Leucine-induced Dissociation of Escherichia coli Lrp Hexadecamers to Octamers *J Molec Biol* vol 318(4), pp 1031-1042

[104]Gaudin, C. Marty, B. Belaich, A. Sari, J. & Belaich, J. (1977) Microcalorimetric study of substrate fixation on the Leucine-Isoleucine-Valine-binding protein from *Eescherichia coli Biochem Biophys Res Comm* vol 78(1), pp 377-382

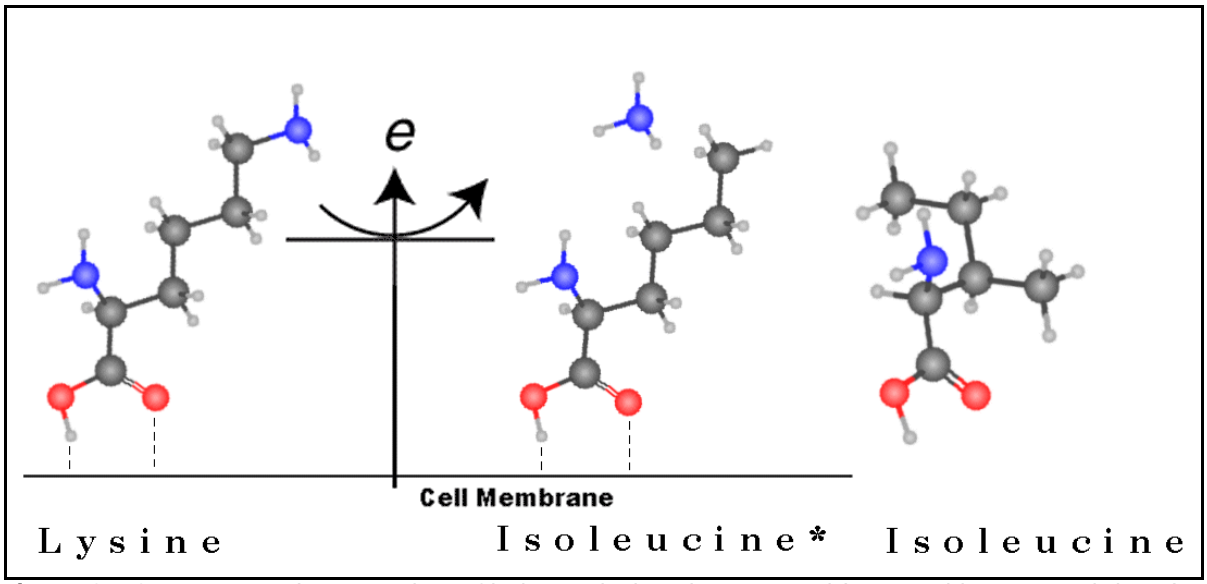

Figure 3.4.3-1 Proposed conversion of lysine to isoleucine to provide a positive potential to the podaplasm.

The three constituents are shown oriented as if coordinate bonded to a type 2 lemma via their carboxyl group. This is the same arrangement as for the coordinate bonding of glutamate to its receptor of other type 2 lemma. It involves a pair of coordinate chemical bonds with a spacing between the bonds of 2.07 Angstrom (essentially the spacing between the two oxygen atoms when the carboxyl group is in solution).

Lysine is believed to exhibit a dipole potential that is attractive to the exterior bilayer of the type 2 lemma where it bonds coordinately.

Upon stereo-chemically bonding with the type 2 lemma, the lysine is capable of releasing the NH_2 group and simultaneously supplying approximately 52 milli electron volts of energy to the lemma. The orientation of the lysine molecule and its dipole potential support the removal of one electron from the interior of the podalemma and the establishment of a more positive potential within the podaplasm. The reaction is analogous to the glutamate reaction diagramed above. The isoleucine is no longer of the correct dipole potential and is released by the lemma. The isoleucine* shown is not reported in the amino acid literature and its lifetime may be short.

Estimates of the specific free energy available from the reaction of lysine to form any isomer of isoleucine at the surface of a lemma formed of amphiphilic bilayers, have not been found in the literature. The energy of this reaction in the specific environment of the podalemma involves many variables. However, it appears the free energy involved is much less than the free energy of formation of the individual reactants and products. It is estimated here as about 1000 cal/mole or 52 milli electron-volts. Thus, this reaction can force an electron through a potential of 52 millivolts if present on a semiconducting lemma of correct polarity. With the lemma of opposite polarity to other type 2 lemma, it will provide a nominal quiescent potential of +52 millivolts to the adjacent podaplasm.

Frelin has provided excellent data related to the consumption of lysine in isolated post-natal heart cells of rats, and similar data for glutamate utilization[105]. Unfortunately, he used lysine as his reference level of activity when describing other reactions rather than describing lysine consumption in its own right.

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[105]Frelin, C. (1980) Amino acid metabolism by new-born rat heart cells in monolayer cultures *J Mol Cell Card* vol 12, pp 479-491

3.4.4 Proposed electrostenolytic schematic of positive supply & poda

Figure 3.4.4-1 shows the proposed electrostenolytic circuit of the podaplasm when supplied with the nominal +52 mV potential required by cardiocytes.

The reversal of the type 2 lemma in the area of the electrostenolytic supply while maintaining the capability to stereo-chemically capture the carboxylic group of lysine suggests the exterior bilayer has not changed from the phospholipid used in the exterior bilayer of the axolemma membrane associated with the negative electrostenolytic supply. Rather it suggests the inner layer of the type 2 lemma changes from the type 1 lemma in both cases.

The ability of the outer bilayer to form a double coordinate stereo-chemical bond (d = 2.07 Angstrom) with the carboxylic group of either lysine or glutamate suggests this outer layer is a form of phosphatidyl serine in both cases. See **Sections 1.4.2** & **3.2.4.**

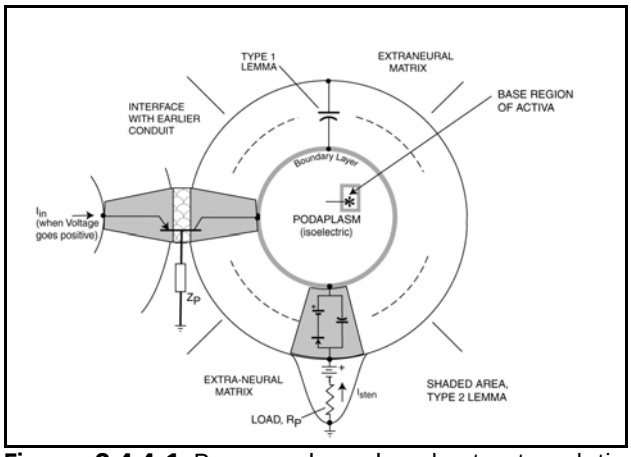

Figure 3.4.4-1 Proposed poda electrostenolytic schematic. Note the reversal of polarity of the diode and battery within the type 2 lemma of the podalemma involved in electrostenolytics. Note the polarity of the electrostenolytic supply establishing a positive potential within the podaplasm.

3.4.5 The sources of lysine

Several texts have asserted that lysine is an essential amino acid, which means that the human body cannot synthesize it. On the other hand, a variety of texts show how its formation is very closely associated with glutamate and/or aspartate in plants and fungi. Its codons are AAA and AAG.

Lysine is in very high industrial production and it is used in a wide variety of foods and as a food supplement. Hence, it is generally not in short supply in the normal diet.

There has been considerable study of the quantum-mechanical aspects of lysine but many of the laboratory studies and calculations have been very narrowly focused. Obtaining a viable free energy value for lysine and isoleucine* or isoleucine will require a very detailed analysis of the literature with someone with a background in the subject matter.

3.5 Principle chemicals affecting neuron operation

This section will address a broad range of non-pharmaceutical chemicals associated primarily, and directly, with the neural system. It will introduce the intimate role of the neural system as the progenitor of the system, but this subject will be developed in detail in **Chapter 16.**

This work will not attempt to address the full range of the pharmacy related to the neural system. The literature is vast, primarily exploratory, and difficult to rationalize. McGeer, et. al. devote considerable space to this subject.[106] McIlwain & Bachelard have also devoted much space to the subject.[107] Their page 413 provides a generic list of the various chemical

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[106]McGeer, P. Eccles, J. & McGeer, E. (1987) Molecular Neurobiology of the Mammalian Brain, 2nd ed. NY: Plenum Press. Chapters 6 through 12

[107]McIlwain, H. & Bachelard, H. (1985) Biochemistry and the Central Nervous System. NY: Churchill & Livingstone. Chapters 14 through 18

classes associated with putative neurotransmitters.

3.5.1 Major chemical equations of neural metabolism

The above figures bring the major chemical events and equations related to neural metabolism into better focus. The primary mechanism powering the neurons is the electrostenolytic process. It involves the conversion of glutamate into GABA. It is glutamate that is the primary neuro-facilitator of biological neurons. It is GABA that is the major reaction product of electrostenolysis. The availability of glutamate and the removal of GABA are the primary controlling factors in the operation of the neural system.

Many authors speak in terms of the complete oxidative reduction of glucose when speaking about neuron operation. The steps in the complete process of reducing glucose to water and CO_2 are shown in **Figure 3.5.1-1**. This figure is exceedingly complex. While it shows the consumption of energy in considerable detail, it does not illustrate the vast number of enzymes and cofactors considered necessary to complete these processes. The figure can be divideded into three major functions. The first is the production of pyruvate or lactate from glucose or glycogen. This overall process is called glycolysis and it occupies the left half of the figure. The process is generally associated with the nucleus of a cell. The upper right portion of the figure centers on the tri-carboxylic-acid (Krebs) cycle. This cycle is responsible for the creation of many precursors to other chemicals used in the organism. Most of these are not involved in neural signaling. However, the glutamate shunt is of particular importance in neural signaling. It is the source of the electrical potential used to power the Activas within and between neurons. This glutamate shunt is described in detail in **Section 8.6**. The operation of the tri-carboxylic-acid cycle is generally associated with the mitochondria of the cell. The lower right of the figure is generally associated with the ribosomes of the cell. It is the area of protein formation and is associated with the ultimate oxidation of the myriad of residue molecules from this process.

The nominal operation of any neuron depends on the nominal operation of all of the manufacturing steps shown in the above figure. Such operation requires the presence of nominal amounts of the reactants and the resulting reaction byproducts. *This requirement in turn requires the nominal rate of supply and removal of all of the involved products*. The availability, reaction, and removal of all of these products are key to the homeostasis of the organism. **Section 8.6.3** presents the homoeostatic concentration of several of the critical metabolic element derived from glucose (glycogen).

As indicated above, providing power to the neurons for signaling purposes is centered on the glutamate shunt shown on the right of the figure. This shunt draws upon α-ketoglutarate from the TCA. This material is aminated to form glutamate. Following amination, the glutamate can participate in an electrostenolytic process on specialized asymmetrical regions of the lemma of neurons. In this stereospecific process, the glutamate is decarboxylated to GABA. The process releases an electron on the inside of the lemma. Multiples of such electrons are the source of electrical potential between the inside and outside of the lemma. It is this electrostenolytic electron pump that is the realization of the ion-pump conceptualized by Hodgkin & Huxley in 1952.

The glutamate shunt occupies a very limited section of the TCA cycle. It only releases a few units of ATP in order to achieve a potential across the substrate membrane of about 154 mV. Hence a single operation of the electrostenolysis process at the molecular level does not account for the complete oxidation of any glucose. However, repeated operation of the TCA cycle via the glutamate shunt will consume all of the energy equivalent to the oxidation of a complete molecule of glucose. Similarly, the operation of multiple electrostenolytic sites simultaneously will consume ATP at a rate that can be related back to the complete oxidation of multiple glucose molecules within the same time period.

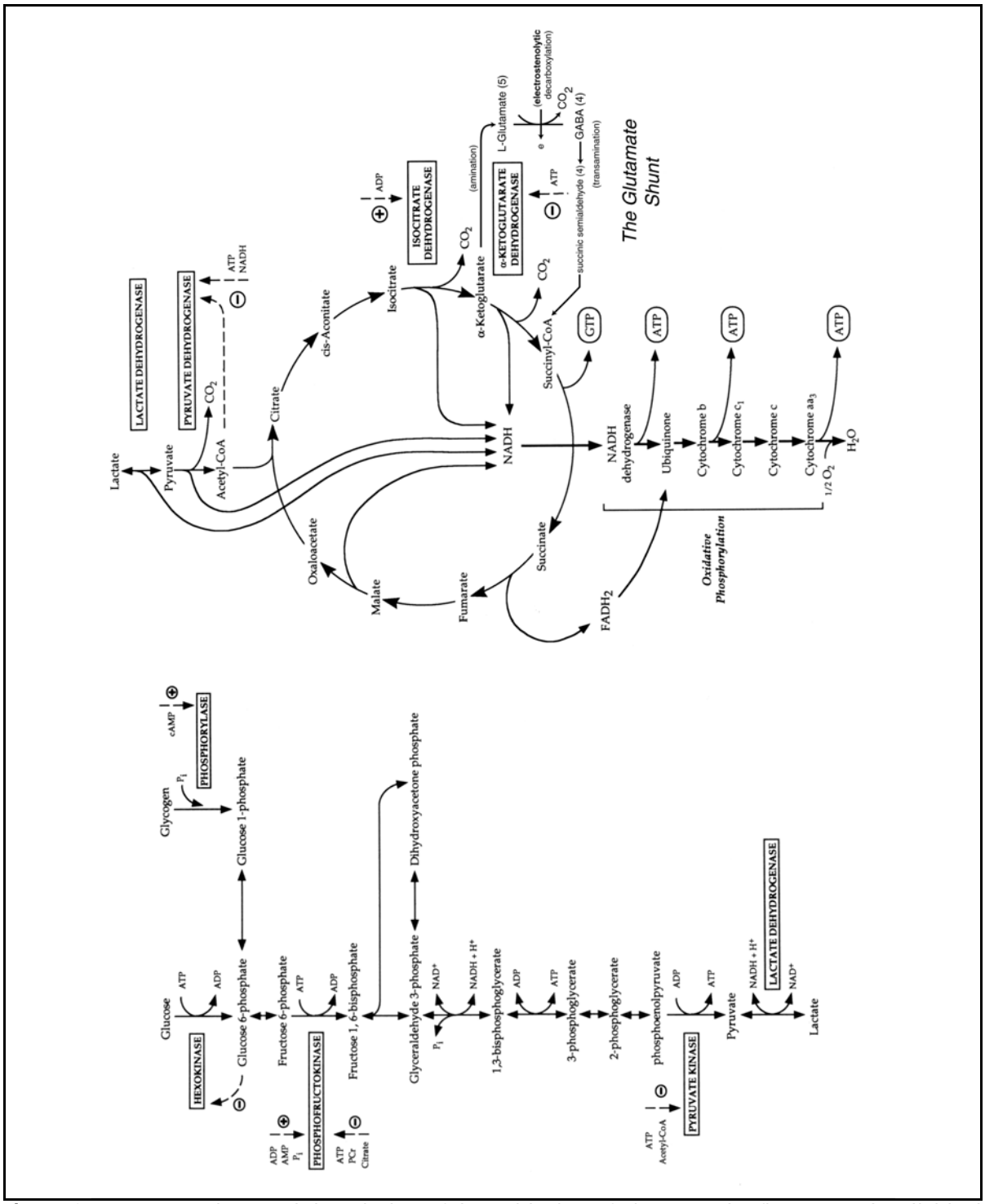

Figure 3.5.1-1 An end-to-end description of the oxidation of glucose. The figure can be divided into three portions. The left portion represents the glycolysis of glucose or glycogen to pyruvate or lactate. The upper right represents one variant of the tri-carboxylic-acid (Krebs) cycle. It includes the glutamate shunt so critical to the operation of the neural system. The lower right represents the oxidative phosphorylation of the residues from the earlier chemical operations. Modified from Magistretti, et. al., 1995.

As defined here, the following equations summarize the steps involved in the operation of providing power to each neuron in the neural system.

Supply of glycogen by diffusion Eq. 3.5.1-1

Glycogen —> pyruvate (aerobic conditions) Eq. 3.5.1-2a

Glycogen—> lactate (anaerobic conditions) Eq. 3.5.1-2b

lactate—>pyruvate (as required)

pyruvate—> α-ketoglutarate (TCA) Eq. 3.5.1-3

a-ketoglutarate—> glutamate (glutamate shunt) Eq. 3.5.1-4

glutamate—>GABA + CO2 (electrostenolysis) Eq. 3.5.1.-5

GABA—> glutamate (transamination) Eq. 3.5.1-6

GABA removal by diffusion (alternate) Eq. 3.5.1-7

GABA removal by transamination to succinic semialdehyde Eq. 3.5.1-8

Many of the above steps generate CO_2 as a byproduct (**Section 7.7.3**). This material must also be removed, primarily by diffusion back to the blood stream.

3.5.2 The stereo-chemistry of many neuro-active materials

Figure 3.5.2-1 describes the stereo-chemistry of several important neuro-active materials. The top row is designed to show the similarity of the two polar nutritionally non-esential amino acids, aspartic acid and glutamic acid. It also shows the result of the electrostenolytic process. By the removal of one CO_2, glutamic acid produces the reaction product, GABA. Aspartic acid can participate in the electrostenolytic process by producing CO_2 and β-amino propionic acid (BAPA).

The lower row shows two materials, L-dopamine and L- dopa, known to have significant impact on the neurons of the CNS in particular. Their glucol group appears able to interface with a receptor on the lemma of a neuron. It is not clear whether this receptor is that associated with electrostenolytics. It may be a distinct receptor used specifically to control the operation of the neuron under stressful conditions.

> A glucol group is defined more stereo-specifically than the similar glycol group. Glucol is a 1,2 *cis*-glycol. It has d = 2.6 Angstrom.

Also shown for completeness is glycine. It is frequently reported as affecting neural operations when applied topically. It appears to be a neuro-inhibitor capable of occupying the stereo-specific receptor designed for glutamate..

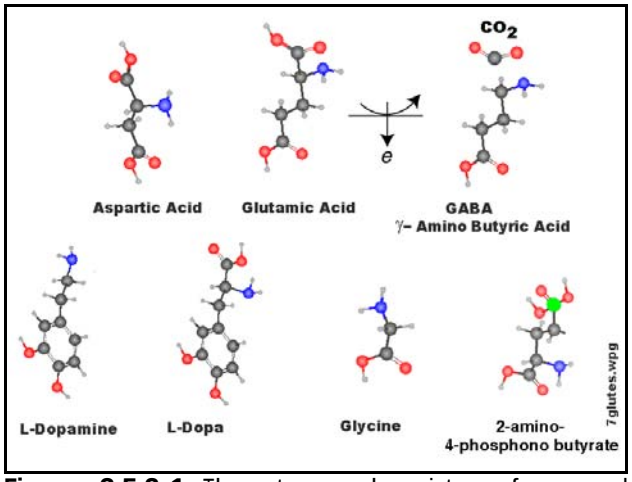

Figure 3.5.2-1 The stereo-chemistry of several neuro-active materials. The normal reaction is the conversion of glutamic acid into GABA. The alternate reaction is the conversion of aspartic acid into BAPA. Both reactions free a molecule of carbon dioxide.

Recently, 2-amino-4-phosphonobutyrate (23052-81-5), abbreviated either L-AP4 or APB in different communities, has been reported to stop the electrostenolytic reaction in many situations, probably due to occupying the stereo-specific receptor for glutamic acid (glutamate)[108]. It includes the necessary carboxylic group and the spine of glutamic/butyric acid. However, the amino group is moved and the highly reactive phosphono group is present in place of the second carboxyl group.

The phosphono group is the same as that found in the polar portion of the membrane lipids of all neurons. Thus, the polar portion of the molecule may look like the phosphatidic portion of a polar lipid receptor site that it has already occupied (a class 1 neuro-inhibitor). Alternately, it may look like a polar lipid membrane site and compete with those sites for the available glutamic acid supply (a class 2 neuro-inhibitor).

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[108]Schiller, P. Sandell, J. & Maunsell, J. (1986) Functions of the ON and OFF channels of the visual system *Nature* vol 322, pp 824-825

Figure 3.5.2-2 shows the structure of epinephrine and norepinephrine; two other important neuro-affectors distributed via the endocrine system. These agents also incorporate a glucol group and a nitrogen separated from their ring structure by two carbons.

These structures are not compatible with the electrostenolytic receptors of the neurons. It is possible that neurons as a class contain a separate receptor site for the glucol group on one or more of their lemma and that these receptor sites play a critical role with respect to a variety of potent neuro-modulators and class 2 neuro-inhibitors.

Lehninger addresses the unique concentration of plasmalogens in the tissue of neurons[109]. The plasmalogens exhibit one long chain fatty acid esterfied to one hydroxyl group of the overall phosphoglyceride and one long aliphatic chain in an α,β-unsaturated ether linkage with the other hydroxyl group. The unsaturated chain suggests electrical (hole) conduction along the length of the aliphatic chain.

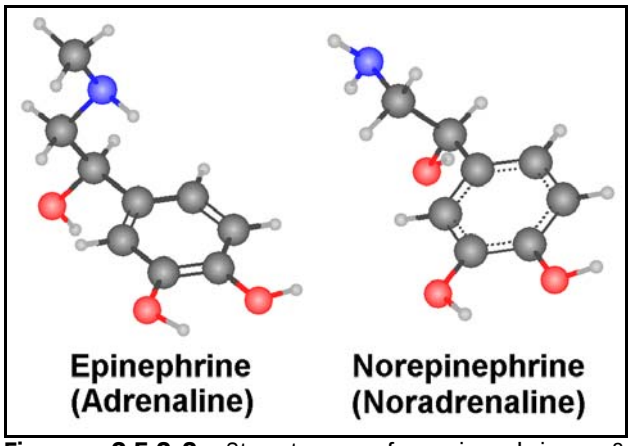

Figure 3.5.2-2 Structure of epinephrine & norepinephrine. The two oxygen atoms of each molecule are separated by a glucol group that makes them incompatible with the electrostenolytic receptor sites designed for glutamate..

3.5.2.1 Lidocaine and its derivatives as glutamate blockers

The question has arisen as to whether Lidocaine and its derivatives could act as a glutamate blocker in the electrical powering of the neurons.

The pharmacological agent Lidocaine (a.k.a. lignocaine_3548 in the Royal Society of Chemistry Jmol data base) is a complex molecule. Like dopamine, it does exhibit one d-value of 2.125 Angstrom, similar to that of glutamate, along with two others at 2.991 and 3.634 Angstrom. It is possible that it can occupy the electrostenolytic receptor site designed to accept glutamate and thereby deprive the individual neuron of electrical power for a period of time until the dual anti-parallel coordinate bond (DACB) is broken by other probably thermodynamic considerations. I will need to explore this further later xxx. As noted below, the DACB between glutamate and the electrostenolytic receptor is broken following the release of CO_2 from the glutamate. This release undoubtedly changes the polarity (specifically the electrostatic potential) of the remaining GABA and may hasten its release from the binding site. Dopamine and Lidocaine do not participate in a similar decomposition and may remain in a stronger DACB relationship for a longer period of time until other mechanism degrade the compounds or other thermodynamic mechanisms cause the breaking of the DACB.

Discussion of the time profile of lidocaine with a medical doctor colleague suggests the observed profile is compatible with the above discussion. If correct individual molecules of lidocaine could disrupt individual neural signal paths for a period of time, possibly on the order of minutes to tens of minutes. Lidocain is typically injected but may be applied topically. Derivatives like bupivacaine and carbocaine have similar anesthetic effect but the effect lasts longer. Xylocaine is a brand name for lidocaine.

3.5.3 The role of ACh & NO as pericrine neuro-affectors

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[109]Lehninger, A. (1970) Biochemistry. NY: Worth Publishers page 197

80 Neurons & the Nervous System

While the role of acetylcholine as a neuroaffector at the striate muscle interface has been extensively studied, the studies of nitric oxide at the interface with smooth muscle is far less well investigated. These two materials form the principle pericrine neuro-affectors at the neuron-muscle interface.

Donnerer & Lembeck (pages 96-97) have provided an important discussion relative to the role of acetylcholine in the 1930's. They noted that nearly all of the publications on the subject either listed Dale as an author or bore his distinctive style.

> Dale had first defined acetylcholine as a muscarine neurotransmitter. "However, the discovery of the nicotinic transmitter function of acetylcholine entailed a much wider implication – it came as a real shock. The finding that acetylcholine was the neuromuscular transmitter at the motor endplate of striated muscle AND the synaptic transmitter in a sympathetic ganglion went against all the, often ingenious, ideas which had been propounded up to that time by those working in this field because it had been taken for granted that these transmission processes were physical – purely electrical events."
>
> When these discoveries were made, Dale at once realized the necessity, on order 'to promote clear idea,' of a terminology which would distinguish nerve fibres not with regard to the anatomical origin, but with regard to their chemical transmission, due in one case to acetylcholine, in the other to a substance line adrenaline, now known to be noradrenaline."

"Therefore, as early as 1933, Dale coined the new terms 'cholinergic' and 'adrenergic' for use in this sense and to be applied to nerve fibres, neurons or transmission processes." The results caused a major stir within the community. Quoting Donnerer & Lembeck, "we again admire the pungency of his style when refuting the suggestions of his opponents." Donnerer & Lembeck make an attempt to organize the resultant terminology using words instead of a table of clearly independent definitions.

By recognizing the three-terminal character of the electrolytic neuron, and the differential inputs provided by that configuration, the dual role of acetylcholine can be more readily explained. Acetylcholine only has one set of characteristics. The action generated by its application to a neuron depends on whether it is topically applied to a dendritic terminal or a poditic terminal.

Sutor & Zolles have noted the role of acetylcholine[110], "Within the mammalian central nervous system (CNS), acetylcholine (ACh) acts as a neurotransmitter that modulates neuronal activity via two subtypes of receptors: (1) the metabotropic muscarinic acetylcholine receptors (mACh-
Rs) and (2) the ionotropic neuronal nicotinic AChRs (nAChRs)." Their description is consistent with this work if the term "neurotransmitter that modulates neuronal activity" is replaced by the simpler neuro-modulator or neuro-affector. Since the role of ACh extends well beyond the neural system, the label neuro-affector is the more general term preferred in this work.

> The use of the terms ionotropic and metabotropic by Sutor & Zolles appear poorly chosen. Ionotropic is undefined in the Medline Medical Dictionary provided by Webster's Dictionary and the term metabotropic is specifically defined as relating to glutamate and its receptors. The extension -tropic is generally defined as relating to a physical reorientation by an organism and not molecular chemistry.

Sarter & Bruno have explored alternative hypotheses related to the role of acetylcholine in

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[110]Sutor, B. & Zolles, G. (2001) Neuronal nicotinic acetylcholine receptors and autosomal dominant nocturnal frontal lobe epilepsy: a critical review *Pflügers Arch - Eur J Physiol* vol 442, pp 642–651

the CNS in what is labeled a review[111]. "Previous efforts aimed at attributing discrete behavioral functions to cortical cholinergic afferents have not resulted in a generally accepted hypothesis about the behavioral functions mediated by this system. Moreover, attempts to develop such a unifying hypothesis have been presumed to be unproductive considering the widespread innervation of the cortex by basal forebrain cholinergic neurons. In contrast to previous descriptions of the role of cortical acetylcholine ACh in specific behavioral phenomena e.g., mediation of the behavioral effects of reward loss, or mnemonic entities e.g., working or reference memory., cortical ACh is hypothesized to modulate the general efficacy of the cortical processing of sensory or associational information." Their premise resolves into acetylcholine acts as a paracrine neuro-affector (hormone) within the CNS.

Figure 3.5.3-1 illustrates the structure of ACh but provides little indication of how it is able to stimulate muscle tissue or affect neural tissue. The presence of oxygen and nitrogen atoms always suggest a potential coordinate chemistry role. Its specific stereochemical arrangement deserves further investigation and measurement of its dipole potential is desirable.

The conventional wisdom is that acetylcholine receptors (AChR) are "integral membrane proteins." This appears unlikely since so many receptors, both sensory and parametric, are now known to be phosphoglyceride–based (See receptor discussion in **Sections 8.4**).

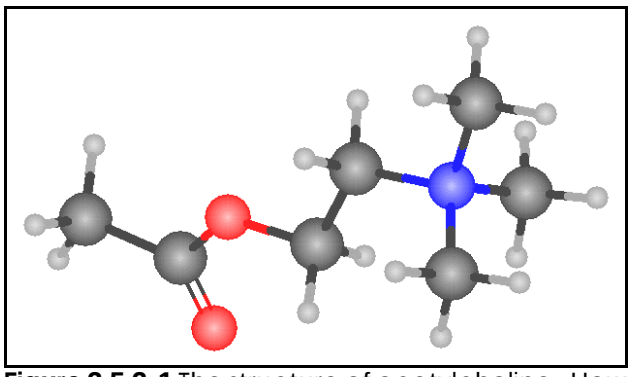

Figure 3.5.3-1 The structure of acetylcholine. How it stimulates both muscle and neural tissue is not obvious but the presence of both oxygen and nitrogen atoms suggests coordinate chemistry plays a role.

The lack of significant details on how ACh is captured by protein-based AChR's is troubling. The subject is generally described at the conceptual level, frequently involving cartoons. While the single bond between the carboxyl carbon and oxygen is considered the weakest, separation of the molecule into acetate and choline offers little indication of how those chemicals might function as neuro-affectors. In fact, the general view is that their separation leads to loss of any stimulation capability. The enzyme, Acetylcholinesterase, also known as AChE, is claimed to degrade ACh in this way in order to terminate its capability. AChE has a very high catalytic activity — each molecule of AChE degrades about 25000 molecules of acetylcholine per second.

The role of nitric oxide as a neuro-affector has recently come under intensive study. Schmidt & Walter have provided a review in 1994 that shows modern study in this field essentially starting in 1990-91[112]. NO was only recently identified as the chemical previously described as EDRF (the endothelium dependent relaxation factor). The paper addresses the options of how to describe NO, even to whether it is or is not a neurotransmitter, or is or is not a hormone, or is or is not a toxin. All of these questions find a ready answer under the Electrolytic Theory of the Neuron presented here. NO is a neuro-affector designed to operate primarily in a pericrine space and act to relax smooth and cardiac muscle. It does circulate to a degree within the cardiovascular system but its lifetime in that environment is so short, its presence in the category of an endocrine hormone can be considered incidental. It plays a major role in the visceral organs that employ smooth muscle widely.

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[111]Sarter, M. & Bruno, J. (1997) Cognitive functions of cortical acetylcholine: toward a unifying hypothesis *Brain Research Reviews* vol 23, pp 28–46

[112]Schmidt, H. & Walter, U. (1994) NO at work *Cell* vol (78, pp 919-925.

Like glutamate, topical application of NO in super-normal concentrations leads to toxicity. Since NO is normally produced by the neuro-affectors on demand, it is rare to encounter toxic levels of NO in-vivo.

NO is primarily released from the electrostenolytic conversion of l-arginine to NO and a residue within pericrine spaces associated with smooth muscle stimulation. Arginine is a particularly rich source of NH_2 that can participate in hydrolysis in order to release NO. A variety of residues can result. The release is under axoplasm potential control and its effect extends over a marginally larger volume than does acetylcholine when released within and end plate. However, NO is a free radical. Its lifetime is largely determined by how well it is isolated from the extra-neural environment. Its life time is typically short (probably measured in milliseconds) after intermixing with the extra-neural environment. The role of NO as a neuro-affector/pericrine–hormone will be developed in detail in **Chapter 20**.

The free energy of reaction of arginine and its dipole potential could not be found in a cursory search of the literature.

3.5.4 Redefinition of neuro-transmitters and neuro-facilitators

The neurosciences have not developed a clear and precise functional definition of neurotransmitter. Neither have they developed a precise description of an excitatory agent or inhibitory agent. Their working definitions depend on the response of an organism to the change in concentration of various pharmaceutical agents, frequently at long physiological distances from where the agent was applied. From these working definitions, they have developed a conceptual definition similar to that of Ganong (referenced in the next section). It is based on the presence of "specialized neuronal mechanisms for storage, release, and postsynaptic action of a particular substance." This definition does not localize these mechanisms with respect to the neuron nor does it specify the substances involved.

Both Fuster (his chapter 3) and Stanfield (page 207) have provided useful lists of materials considered neurotransmitters under the chemical theory of the neuron.

Previously, it has been common to describe any material that appeared to stimulate neural activity as a neurotransmitter. Any material that tended to suppress neural activity was labeled a neuro-inhibitor. While the term neurotransmitter is firmly embedded in the literature at all levels, it does not provide a broad enough framework for research purposes and it is misleading. This work adopts a broader framework based on how the subject chemical impacts the operation of the neurons. These lists are easily re-categorized within the context of the Electrolytic Theory of the Neuron. The resulting framework is summarized in the column of **Figure 3.5.4-1** labeled "New designation." The framework recognizes the electron as the only true (neuron-to-neuron) neurotransmitter and a series of materials as neuro-facilitators, neuro-inhibitors or neuro-affectors.

Materials participating in the stereo-specific electrostenolytic process directly are described as either primary neuro-facilitators or primary neuro-inhibitors depending on whether they drive the reaction to the right or to the left. There are only two materials that can drive the equation to the right, the stereo-specific primary neuro-facilitator, glutamate, and the secondary neuro-facilitator, aspartate. There is only one material known to drive the equation to the left. That is the stereo-specific primary neuro-inhibitor, GABA. Glycine is in a separate class because of its combination of stereo-specificity and its lack of a second carboxyl group. It is able to occupy the site designed for glutamate at the electrostenolytic reaction site. However, its monocarboxylic character leaves it unable to release CO_2 and generate the required free electron. Therefore, its presence tends to stop the electrostenolytic process at a particular molecular level site. Other examples will be discussed below.

The neuro-facilitators can be further divided into primary and secondary classes depending on whether they participate directly in the above equations or act only as necessary enzymes or cofactors. The secondary neuro-facilitators and neuro-inhibitors can be divided into two classes. Class 1 materials directly affect the site of the electrostenolytic process. Class 2 materials affect the ability of other chemicals to reach (or be removed from) those

sites. This framework leads to a much simpler interpretation of the pharmacological results from varying the concentration of one or more of the above materials. **Figure 3.5.4-1** can be compared with a similar, but less specific, listing by McCormick in Shepherd[113].

THEORY	CHEMICAL	ELECTROLYTIC	
Material	**Historic designation**	**New designation**	**Comment**
electron		Neurotransmitter (intrinsic)	can act as "hole"
Glutamate	Neurotransmitter	Primary neuro-facilitator	primary energy source
GABA	Neurotransmitter (frequently)	Primary neuro-inhibitor	pri. reaction product
Aspartate		Alt. primary neuro-facilitator	a dicarboxylic acid
BAPA		Alt. primary neuro-inhibitor	alt. reaction product
Lysine		Primary cardiocyte-facilitator	a amine/carboxylic acid
Isoleucine*		Primary cardiocyte-inhibitor	pri. reaction product
L-Dopa		Class 1 neuro-facilitator	can occupy glutamte site and react (slowly)
Dopamine	Neurotransmitter	Class 1 neuro-inhibitor	can occupy glu. site but cannot react
2-amino-4-phosphono-butrate		Class 1 (or 2) neuro-inhibitor	can occupy glu. site but cannor react
Glycine		Class 1 neuro-inhibitor	may occupy glu. site
Acetylcholine	Neurotransmitter	Neuro-affector	stimulates striate muscle
Nitric Oxide	– –	Neuro-affector	relaxes smooth muscle
Histamine	Neurotransmitter	Neuro-inhibitor	– –
Norepinephrine	Neurotransmitter	Neuro-inhibitor	vasopressor
Serotonin	Neurotransmitter	Neuro-inhibitor	strong vasoconstrictor

Serotonin is 5-hydroxytryptamine. L-Dopa can participate in electrostenolyis, dopamine cannot. L-Dopa can be considered a "sticky" neuro-facilitator. It is slow to react and the reaction product may not leave the site promptly. Vasopressor is synonymous with vasoconstrictor.

Figure 3.5.4-1 A framework for materials impacting neural operations.

The pattern in the above table leads to a set of succinct definitions:

• The designation ***neurotransmitter*** (when referring to the transmission of a signal between conduits of a neural system) is reserved for the *electron* and its alter-ego, the electrolytic *hole*..
•The designation ***primary neuro-facilitator*** is reserved for glutamate. It is one of only two dicarboxylic amino acids that can participate in the electrostenolytic reaction of neurology.

[113]McCormick, D. (1998) Membrane properties and neurotransmitter actions In Shepherd, G. ed. The Synaptic Organization of the Brain, 4th ed. NY: Oxford University Press pg 61

•The designation ***primary neuro-inhibitor*** is reserved for *GABA*. It is the main reactant of the electrostenolytic reaction. The presence of excess GABA slows the normal electrostenolytic reaction. That tends to lower the electrical potential of the conduits of the neurons. The result can be positive or negative depending on the location of the change in potential.
• The ***primary cardiocyte facilitator*** is reserved for lysine.
• The ***primary cardiocyte inhibitor*** is reserved for isoleucine.
• The designation ***Class 1 neuro-facilitator*** or ***Class 1 neuro-inhibitor*** are materials that can significantly impact the operation of the above designations.
• The designation ***neuro-affector*** refers to any material that is employed at the neuro-muscular interface or is normally described as a primary hormone (and release by clearly neural tissue–primarily via the hypophysis (pituitary gland) at the neuro-glandular interface.. Following their release, the hormonal neuro-affectors are typically labeled neuromodulators.
• The designation ***neuro-modulator*** refers to the vast number of chemicals that can affect neurons and other tissue via parametric action at receptors not involved in neuron-to-neuron signaling.

Aspartate acts as a backup for glutamate under certain conditions. It and glutamate are the only two amino acids with negatively charged polar groups (due to their two carboxylic acid groups). It is able to perform in the electrostenolytic process but the reaction product, β-amino propionic acid (BAPA), is not able to be recycled via the glutamate shunt. It must take a more circuitous route through the TCA to regenerate aspartate (or glutamate). Glycine is a simpler amino acid than aspartate and contains only one carboxylic group. It is a class 1 neuro-inhibitor because it can occupy the electrostenolytic site using its one carboxylic ligand but it cannot complete the electrostenolytic process and provide a free electron to the neuron conduit. Many other chemicals can interfere with the homoeostatic conditions supporting the electrostenolytic process (at least a dozen according to McCormick). They are all neuro-inhibitors. A possible exception would be a material that could accelerate the clearance of GABA from the electrostenolytic site. Any material, such as monosodium glutamate that can raise the concentration of the dicarboxyl acid, glutamate, in the area of the electrostenolytic process can be considered a secondary neuro-facilitator. Chemicals that cause constriction of the blood vessels, or otherwise inhibit the diffusion of glycogen to the neurons or CO_2 from the neurons can be considered neuro-inhibitors.

> There is no requirement for any of the above materials (other than the electron) to diffuse into or through the less than 100 nm wide gap junctions involved in neuron-to-neuron signaling. While it is easy to draw caricatures showing such diffusion, it is difficult to implement the caricatures. This very small region is filled with a liquid crystal of semi-metallic water (**Section 1.3.2**) that totally discourages any form of ionic or molecular diffusion. On the other hand, semi-metallic water is an excellent semiconductor of electrons.

3.5.4.1 Reviewing past commentary in the literature

Recently, the Internet has allowed the dissemination of a large variety of generally popular definitions of neurotransmitter. These definitions can be largely ignored within the research community as imprecise and irrelevant (and frequently prepared by undergraduates attempting to rationalize what they are being told pedagogically)..

Prior "neurotransmitter" discussions in the literature have been predominantly conjectural, conceptual and based primarily on the presence of chemicals in the neuron-to-muscle space associated with the end plates . They have totally lacked any discussion of how a change in the potential of the presynaptic axoplasm causes the release of any chemical by the neuron and no documentation has been provided demonstrating the release of any of these chemicals from a vesicle embedded in the axolemma.

Burnstock began modern discussions of the definition of a neurotransmitter as part of a

commentary in 1976[114]. In anticipation of this discussion, he introduced the question of whether a substance was a neurotransmitter or a neuromodulator. He also noted the extraordinary influence of fashionable concepts in science. Burnstock noted the sensitivity of the definition of neurotransmitter to the test protocols and conceptual configurations used by different authors, and vice versa. "The interpretation of the data depends to some extent on the definition of a neurotransmitter."

Burnstock's definition of a neurotransmitter was too broad to bear repeating here. It is largely superceded by the above table and definitions.

Puil has provided an early, massive, well referenced and invaluable paper published in an obscure review[115]. It describes the many roles of glutamate in the neural system, particularly before the heavy emphasis put on its putative neurotransmitter role in the 1970's. He noted that "in spite of the wealth of information concerning its effects and its interaction with other neurotransmitter candidates and drugs, . .there is not yet a great deal of understanding about the mode of action of S-glutamate in the central nervous system." As he also notes, he uses the Caln-Ingold-Prelog system of describing the configuration of a complex hydrocarbon. The notation S-glutamate, which he uses, is identical to L-glutamate.

Puil describes the use of glutamate in the neural system when applied both topically and micro-topically, technically described as microiontophoresis.

In the context of glutamate as a neurotransmitter, it is interesting to note the comment and references of Puil. "It has been known for a long time that intracellular injections of S-glutamate into spinal neurons produce no response" (pg 265). This fact seems unlikely if glutamate was playing the role of a neurotransmitter originating in the axoplasm of a neuron. He closes with "The physiological effects of S-glutamate thus appear to be the result of its interaction with chemical groups (receptors) on the external surface of neurons."

In 1987, McGeer, et. al. referred the reader to a paper more than 20 years old for a general reference on excitatory synaptic action. They then used a generic neuron to discuss the excitation with respect to the observed depolarization (positive going change in voltage) of "intracellularly recorded potentials produced by synaptic excitatory action." They do not differentiate between the depolarization of the axoplasm and any depolarization of an associated dendroplasm (or podaplasm). From this situation, they define "excitatory postsynaptic potentials (EPSPs)." This definition places the excitatory function at the neurite plasma level but its observation at the axoplasm level. While this definition is unique under a two-terminal neuron concept, it becomes awkward when a three-terminal neuron concept is accepted. Under the three-terminal concept, the change in potential applied to the dendroplasm has the same polarity as the resulting change in axoplasm potential. However, the change in potential applied to the podaplasm has a polarity opposite to that of the change in potential of the associated axoplasm. In general, a change induced at the dendrite terminal has the opposite effect of a change at the podite terminal. The definition of an EPSP fails under the three-terminal concept of a neuron.

McGeer, et. al. do address, in one paragraph, the role of a very different synapse, the inhibitory synapse on the Mauthner cell in the fish spinal cord. Although they do not carry their discussion very far, this type of synapse would correspond to excitation of the neuron at the poditic terminal and could be labeled an inhibitory postsynaptic potential (ISPS), with respect to the axoplasm. With respect to the podoplasm, the excitation still causes a positive going change in plasma potential, but a negative-going axoplasm potential.

McGeer, et. al. appear to have defined the EPSP based on earlier work involving the end-plate potential (EPP) of a motor neuron. In a projection type (stage 3) neuron, the role of the poditic terminal may be less important than for the generic neuron. Finding the poditic terminal with the technology of the 1960's was virtually impossible.

The definition of an excitatory agent based on the depolarization of the axoplasm of a neuron is not very useful

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[114]Burnstock, G. (1976) Do some nerve cells release more than one transmitter? *Neurosci* vol 1, pp 239-248

[115]Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res. Rev*. vol. 3, pp 229-332

for most psychophysical researchers. It is also foreign to the typical pharmacologist. They would prefer a definition based on parameters available based on chemical content of a specimen or observed changes in behavior of the subject. Therefore, a more expansive definition is needed that can apply to a wide range of investigations.

Based on the subdivision of the previous section, and dismissing chemical neurotransmitters operating within the synaptic gap, an excitatory agent can be defined. Excitatory agents are those that, in some way, participate directly in the electrostenolytic mechanism that provides power to the neuron **OR** affects the availability of those chemicals required in the above electrostenolytic mechanism. The first class is a small one. The second is endless.

However, he made an interesting observation. "It is also possible for one transmitter to have an excitatory effect on one neuron and an inhibitory effect on another neuron." He offered no explanation of the mechanism(s) supporting this activity.

In 1992, Dowling constructed a different description of neuro-active materials based on his view of their relevant chemical properties[116]. He has provided examples more closely aligned with this work, but employing less precision. He describes neurotransmitters as acetylcholine and a variety of amino acids (L-glutamate, L-aspartate, GABA and glycine). He describes neuromodulators as monoamines and peptides. This latter category does include the monoamine/coarboxylic acid, lysine but actual peptides are missing from the above table and definitions (unless they are broken down by hydrolysis).

Close examination of the stereochemistry of the neurotransmitters according to Dowling in the context of the electrostenolytic process quickly divides his neurotransmitters into the classes defined above. Glycine becomes a class 1 neuro-inhibitor because it occupies a site in the electrostenolytic process designed for glutamate. GABA becomes a primary neuro-inhibitor because it pushes the fundamental electrostenolytic process to the left. L-glutamate becomes a primary neuro-facilitator and L-aspartate becomes an alternate primary neuro-facilitators.

A discussion by Paul is closely aligned with the idea of a primary neuro-facilitator and a primary neuro-inhibitor described in the above table[117]. He says: "Pharmacological studies utilizing drugs which selectively block or augment the actions of GABA or glutamate support the notion that these two neurotransmitters, by virtue of their often opposing excitatory and inhibitory actions, control, to a large degree, the overall excitability of the CNS." The terms neuro-facilitator and neuro-inhibitor can be inserted into this sentence in place of the term two neurotransmitters with excellent results. His subsequent discussions of GABA and glycine as neuro-inhibitors does not recognize their fundamentally different chemistry and resultant roles.

McCormick follows the conventional wisdom (and human predisposition) in separating neuro-active substances into two categories. The first consists of the neurotransmitters, substances that result in rapid post-synaptic response and have a short term impact. The second consists of the neuro-modulators, substances that have a longer lasting duration in their impact on the neural system. McCormick notes that the distinction between these two categories is not always easy. He attempts to relate their action to a variety of receptors within the synaptic gap. However, he only presents a textual discussion. No organization of these materials (labeled neuro-inhibitors here) is offered.

Shepherd has provided a table describing the time courses of the various synaptic events involving his neurotransmitters, facilitators and modulators (3rd Ed, 1994). While he suggests acetylcholine can impact nicotinic receptors in less than a tenth of a millisecond, much

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[116]Dowling, J. (1992) Neurons and Networks: An Introduction to Neuroscience. Cambridge, MA: Harvard University Press pg 141

[117]Paul, S. (1995) GABA and glycine *Chapter 8 In* Bloom, F. & Kupfer, D. *ed*. Psychopharmacology: the Fourth Generation of Progress. NY: Raven Press pg 87

faster than it can affect a muscarinic receptor (ten milliseconds to ten seconds), it is proposed here that the only element achieving tenth millisecond synaptic events is the electron and acetylcholine acts as a chemical neuro-affector supporting event in the ten millisecond range at both nicotinic and muscarinic receptors.

In 1998, Greenfield addressed the current confusion related to the putative chemical synapse. She focused on the confusion about whether a given chemical in a given situation is inhibitive or excitatory[118]. Some of her major themes are; "Why are there so many different neurotransmitters" and "How can familiar transmitters have unpredictable actions?" These questions attack the fundamental understanding of the method of signal transfer across a synapse. Greenfield has elucidated five nominal properties required of a neurotransmitter.

Because of the limited ability of the current technology to measure the progress of micro-mol quantities of chemicals in less than one second intervals, no actual data exists definitively supporting the concept of a chemical synapse.

From the perspective of this work, these authors have not separated the relevant pharmacological agents into the three most important classes. It is proposed that these classes are;

1. those chemicals that act directly as signal transmitters between an axon and a neurite (or vice versa),

2. those chemicals that directly affect the electrostenolytic mechanism at the cell surface and

3. those that indirectly affect the mechanism by affecting the availability of the above agents.

As discussed in **Sections 1.7 and 9.4**, the minute crystal of semi-metallic water present in the extremely narrow synapse area precludes any molecules from passing from the axon side to the neurite side of an actual synapse junction. This physical model of the synapse precludes the conceptual model found in most textbooks (McGeer, et. al. pg 414) The space between the pre- and post synaptic surfaces is too narrow to accommodate any molecule significantly larger than water. The porosity of the semi-metallic water crystal (a liquid crystal closely related to ice) to complex chemicals is essentially zero. Therefore, no chemicals meet the requirements of item 1 above.

The physical impossibility of a large molecule passing from a vesicle of an axon to a receptor site of a neurite within the narrow confines of the semi-metallic water-filled synaptic gap, forces a re-evaluation of the above materials. It means most of the materials defined as neurotransmitters in the literature must be looked upon as facilitators or inhibitors of the electrostenolytic process, items 2 and 3 in the above list (**Section 3.5.4**). *Those materials that only participate in, or affect the electrostenolytic process have been labeled "false neurotransmitters" by McGeer, et. al.* (page 306 & 312).

None of the above investigators were aware of the role of the monoamine/carboxylic acid, lysine in providing a positive potential to the podaplasm of the cardiocytes, when acting in their neural role (**Section 3.4**). Hence, it has never been labeled a neurotransmitter previously. Lysine is the only positively charged amino acid at biological pH levels that can release an NH_2 group while stereo-chemically bonded to a electrostenolytic receptor.

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[118]Greenfield, S. (1998) Future Developments, in Higgins, S. *ed. Essays Biochem.* vol. 33, Chap. 14

3.5.5.2 Agents directly involved in the electrostenolytic process

The agents involved in the basic electrostenolytic process have been identified earlier. There are two: primary agents, glutamate (the pharmacological name for glutamic acid) and GABA and two backup agents, aspartate and BAPA.. Glutamate is converted to GABA with the release of CO_2 and the transfer of an electron across the lemma forming the substrate. The backups operate perform a similar reaction. Within the context of the neural system, all other reactions are incidental to this reaction(s).

In the special case of the cardiocytes, the agent involved in the auxiliary electrostenolytic mechanism leading to a positive potential is lysine. Lysine is converted to isoleucine* with the release of NH2 and the withdrawing of an electron from the podaplasm.

The sites of the electrostenolytic mechanism have been found via electron microscopy. They stand out as zones of high electron density along the surface of the various lemmas of the neuron (see **Sections 9.4, 10.6** and **10.7**). They are generally near but external to the "gap junction," the actual synapse of neurology.

Significantly changing the concentration of either glutamate, aspartate, GABA or BAPA at the site of the electrostenolytic mechanisms is clearly the most effective way to change the performance of the neuron. Steriade, et. al. note this when they point out the role of glutamate (and aspartate) in stimulating neurons[119]. Benson, et. al. also note this when they say "It is well established that GABA is probably the major inhibitory neurotransmitter in the central nervous system. . . .[120]" While these materials can facilitate or inhibit the operation of the neural system, they are not a neurotransmitter found within signaling confines of the synapse.

A similar paragraph can be prepared for the cardiocytes by adding lysine and isoleucine* to the above list.

3.5.5.3 Agents independent of but affecting the electrostenolytic process

Agents, other than glutamate and GABA (alternately aspartate and BAPA), that impact the neurological state of a neuron are frequently described as "false neurotransmitters."[121]

Section 3.5.5.2 leads to a formal restatement of the role of "chemical neurotransmitters" within the neural system. Materials previously labeled neurotransmitters are in fact neuro-facilitators or neuro-inhibitors. They play no direct role in neural signaling. The neuro-facilitators and neuro-inhibitors play an important role in all neurons, whether their output is phasic or tonic. The primary neuro-facilitators are the source of electrical energy to each and every neuron. **Section 3.2.2** shows stereochemistry plays a major role in categorizing the putative neurotransmitters. It also shows how the unique chemical structure of glutamate and aspartate lead them to play a primary role in the electrostenolytic process. They are the only negatively charged amino acids. They are the only amino acids that are dicarboxylic and exhibit a stereochemistry uniquely compatible with the electrostenolytic substrate.

As defined above, the primary electrostenolytic process in neurology is the conversion of glutamate into GABA with the release of CO_2 and the injection of an electron into the plasma within the lemma supporting the process. In this context, glutamate and GABA are the primary neuro-facilitators and neuro-inhibitors respectively. All other materials previously labeled neurotransmitters can be considered secondary neuro-facilitators or neuro-inhibitors within the context developed in **Section 3.5.4**.

Based on the above framework, an excitatory agent independent of the electrostenolytic process, will fall into one of two categories. The short list contains those (class 1 in **Section 3.5.4**) chemicals that expedite the

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[119]Steriade, M. Jones, E. & Llinas, R. (1990) Thalamic oscillations and signaling NY: John Wiley pg 87-88

[120]Benson, D. Isackson, P. Hendry, S. & Jones, E. (1991) Differential gene expression for glutamic acid decarboxylase and Type II calcium-calmodulin-dependent protein kinase - - *J. Neursci*. vol. 11, no. 6, pp 1540-1564

[121]McGeer, P. et. al. (1987) Op. Cit. pg 306 (compare with page 312)

removal of GABA from the immediate proximity of the many electrostenolytic processes. Only a few steps are involved between the formation of GABA and its re-conversion into glutamate or its elimination from the body as urea. The longer list contains all of those (class 2) materials affecting the availability of glutamate at the required locations. Alternately, an inhibitory agent is one that inhibits the removal of GABA from an electrostenolytic site or interferes with the access of glutamate to the site.

3.5.5.3.1 Agents with a positive impact on electrostenolysis

The word putative is used here in consort with McGeer, et. al. They focus on aspartate as a potentially positive agent in the neural system. Aspartate differs from glutamate is having one less CH_2 group. Otherwise, they are structurally identical. While it can participate in the electrostenolytic process, the reaction product is not GABA but a simpler member of its chemical family.

McGeer, et. al. address the subject of excitotoxicity (pp 189-196). They point out that excessive concentrations of glutamate, aspartate and many structurally related amino acids are powerful neural stimulants and they can have destructive effects if administered in sufficient excess.

3.5.5.3.2 Agents with a negative impact on electrostenolysis

Several groups of chemicals that significantly degrade the performance of the neural system at the cellular level are known. Like the positive case, one chemical closely related to GABA is known to have a significant negative impact, glycine. Others in the same chemical class include taurine, proline, serine and β-alanine. The presence of these chemicals near the electrostenolytic substrate probably suppresses the normal electrostenolytic reaction at the site. The effect would be to lower the individual potentials supplied to the plasmas of a neuron. McGeer, et. al. point out that "GABA and, to a lesser extent, glycine probably accounts for most of the inhibitory action in the central nervous system. . . ." (pg 197).

Pharmacologically, members of the choline family were initially found to exert a negative effect on the operation of the neural system. Recent electrophysiological experiments would suggest this chemical effectively occupies the electrostenolytic sites normally occupied by glutamate but does not react to form GABA. However acetycholine is positively charged. An alternate explanation would be that it combines with the negatively charged glutamate in a scavanger action that deprives the neural system of needed glutamate. In either case, this chemical has a major deleterious impact on the neural system. It degrades the voltage supply to the various plasmas significantly. While normally considered a negative agent in neurology, McGeer, et. al. show the overall operational impact of the cholines is not consistent. It is so inconsistent that two subclasses have been identified, those that have a positive impact and those that have a negative impact. (pg 253-260). This finding is consistent with application of the material to either the dendrite or the podite terminals.

An even more powerful neuro-modulatory chemical family is the catecholamines. Historically, they have been looked upon primarily as hormones. These materials are addressed in the following paragraph.

3.5.5.4 The catecholines and other neurological agents related to L-Dopa

The catecholines couple an amine side chain with a catechol ring. In fact, the structural similarity is greater than that. One of the pharmacologically most important catecholines, L-Dopa, has a side chain structure, including part of the catechol ring that is nearly identical to that of glutamate itself. [Consider forming a ring between the β– and γ– carbons of glutamate.] As shown in Section 3.5.2, the structure of this family would suggest they exhibit a glucol arrangement with a d = 2.6 Angstrom. Unless under strain, this glucol arrangement should not affect the electrostenolytic receptor site. Thus, a question remains whether the family acts as a class 1 neuro-inhibitor, or acts at a different receptor site as a class 2 neuro-inhibitor. This question can only be answered through more definitive experiments. The previous literature generally suggests L-Dopa occupies the glutamate receptor site. This action would reduce the electrical potential applied to the various plasmas. Such action could change the firing rate of ganglion cells found in stage 3 projection neurons significantly. The same action would change the quiescent axoplasm potential of tonic neurons.

When L-Dopa participates in the electrostenolytic process, the residue is dopamine. While L-Dopa can act as a neuro-facilitator, its efficiency is apparently less than that of glutamate or

aspartate. Dopamine can act as a class 1 neuro-inhibitor. The presence of these chemicals slows the electrostenolytic reaction rate.

2-amino-4-phosphonobutyrate (23052-81-5), abbreviated either L-AP4 or APB in different communities, has been reported to stop the electrostenolytic reaction in many situations, probably due to occupying the stereo-specific receptor for glutamic acid (glutamate)[122]. However, the results were immediately challenged by DeMarco et al. who state contrary results[123]. The actual situation is probably in between these and depends on a better model. Schiller et al. describe a largely conceptual situation in their abstract. It involves bipolar neurons that are both non-inverting (ON) and inverting (OFF) relative to the input signals. However, their work only explores the non-inverting bipolar neurons. Some of the statements by Schiller et al. to justify their conceptual model are demonstrably in error. However, their results relative to the non-inverting (ON) bipolar neurons are in agreement with this work. The chemical clearly has a structural similarity to glutamic acid and GABA. See **Section 3.5.4**.

L-Dopa has been used medicinally since the 1930's. Its absolute configuration has been known since at least 1913 and its name reflects this history. The Merck index of the 1960's provided three different scientific names for the chemical. Today, it would be described differently still, based on more recent chemical and pharmaceutical knowledge. It would not be described as a phenol at all. Such a material would now be described as a catecholamine, specifically catechol-L-alanine. The importance of this alternate designation relates to many of its properties compared to a phenol. However, even this designation is misleading. Alanine is not a participant in, nor a precursor, of, the electrostenolytic process of neuroscience. It is aspartic acid that is the first member of the family of interest here. Glutamic acid is the second, and most important, member of the family. Of primary interest in neuroscience is the presence of two oxygen atoms on the catecholine ring opposite to the alanine with its own carboxyl group. This material mimics the two carboxyl groups (and the resultant stereochemistry) of glutamic acid and aspartic acid, the primary sources of electrical power in the neural system. It is this stereochemistry that allows L-Dopa to substitute for glutamic acid in the electrostenolytic process.

Like L-Dopa, Dopamine has been given a series of names over the years. Its primary property is its stereochemical similarity to GABA. It is this stereochemistry that makes it an active class 1 neuro-inhibitor.

3.5.5.4.1 The putative role of dopamine in paricrine space of CNS

Dopamine is not found within the brain in significant amounts. Bannon, et. al. estimate "dopamine-containing neurons constitute less than 1 in every $10^5 - 10^6$ neurons in the mammalian brain[124]." However, its medicinal importance is great in controlling neural diseases. The stereo-structure of dopamine suggests that it can occupy the stereo-specific site at the electrostenolytic process designed for glutamate.

The distribution of dopamine, and several relatives, within the paricrine space of several lower species, has been reported by Fuster in his 3rd edition[125]. On page 79 of the fourth edition, he notes, "It has been reasonably argued that dopamine should be considered a neuromodulator rather than a neurotransmitter, either excitatory or inhibitory (Seamans and

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[122]Schiller, P. Sandell, J. & Maunsell, J. (1986) Functions of the ON and OFF channels of the visual system *Nature* vol 322, pp 824-825

[123]Demarco, Jr, P. Bilotta, J. & Powers, M. (1991) DL-2-Amino-4-phosphonobutyric acid does not eliminate "ON" responses in the visual system of goldfish *Proc Nati Acad Sci* USA vol 88, pp 3787-3791

[124]Bannon, M. Granneman, J. & Kapatos, G. (1995) The dopamine transporter *Chapter 16 In* Bloom, F. & Kupfer, D. *ed*. Psychopharmacology: the Fourth Generation of Progress. NY: Raven Press pg 179

[125]Fuster, J. (1988) The Prefrontal Cortex, 3rd Ed. NY: Lippincott-Raven Chapter 3 *Also* in chapter 3 of 4th Ed, 2008.

Yang, 2004)."

Baldessarini has identified the source and primary targets of dopamine as of 1979 in **Figure 3.5.4-2**[126].

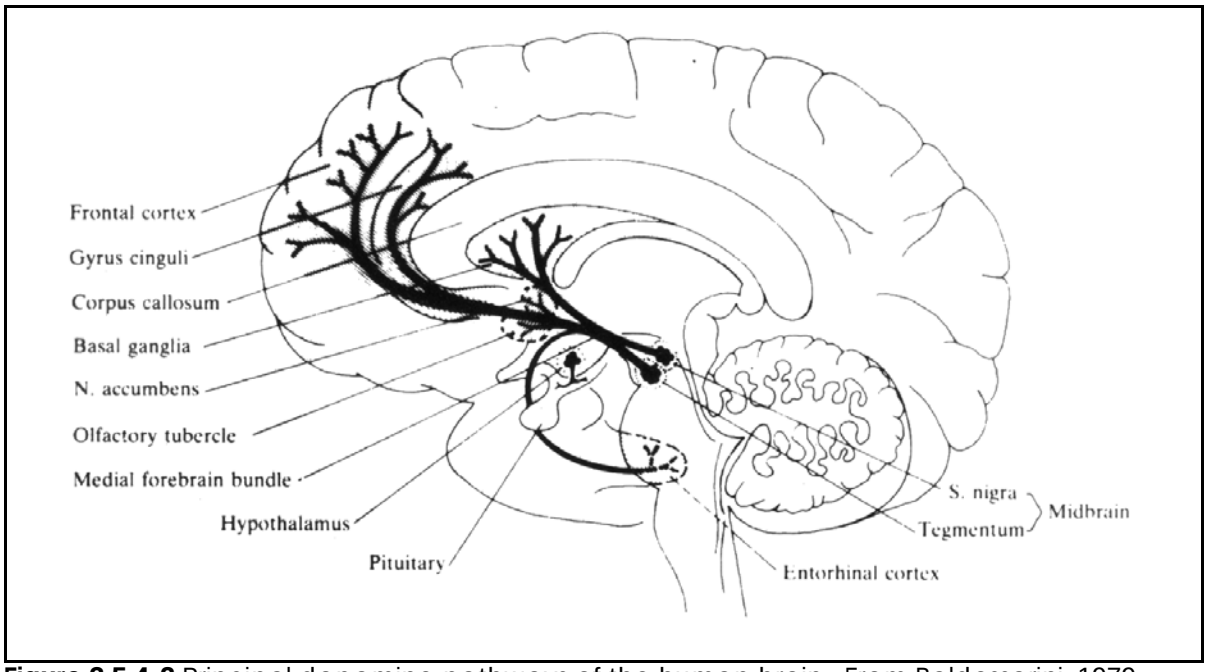

Figure 3.5.4-2 Principal dopamine pathways of the human brain. From Baldessarini, 1979.

A precursor to dopamine that is found in trace amounts in insects is octopamine, with only one oxygen attached to the resonant ring of the arene.

3.5.5.5 The putative role of glutamic acid decarboxylase

Paul discusses the very early (1950) studies of the role of GABA in neural activity. He described the role of an enzyme called glutamic acid decarboxylase (GAD) in the brain of mouse. It was closely associated with a cofactor, pyridoxal 5' -phosphate (PLP). It is not clear whether GAD was actually isolated or only postulated during these studies. It is quite possible that GAD was postulated to act as the substrate actually provided by the cell membrane in electrostenolysis.

With the elucidation of the electrostenolytic process in neuroscience, the requirement for, and action of, a GAD is essentially replaced by the electrostenolytic process performing the same decarboxylation process.

3.5.5.6 The limited role of nicotinic and muscarine receptors, curare, atropine etc

McGehee & Role provided a comprehensive review of the nicotinic acetylcholine receptors in 1995. "How can the well-known behavioral, cognitive, and addictive effects of nicotine be reconciled with the paucity of evidence for CNS synapses where the transmission is mediated by nicotinic receptors?" In conclusion, they note, "Although there is still little evidence for classical nicotinic synaptic transmission in the CNS, we have a new appreciation for probable

[126]Baldessarini, R. (1979) The pathophysiological basis of tardive dyskinesia *Trends Neurosci* Volume 2, pp 133–135

presynaptic effects."

If there is little evidence of nicotinic synaptic transmission in the CNS, which comprises 95% of the neurons in the human neural system, nicotinic synaptic transmission must be classified as a trivial mechanism, with its use (if any) associated primarily with stage 7 neuro-affectors (See **Sections 1.1** & **1.2** for stage designations).

Dani & Bertrand reviewed the subject of cholinergic synapses in considerable detail in 2007, but had little to say about nicotinic acetylcholine synapses within the CNS[127]. They stress the role of nicotinic acetylcholine in non-synaptic paracrine ("volume cholinergic") action within the CNS. They also note a paucity of nicotinic cholinergic synapses within the brain. "Although fast, direct nicotinic synaptic transmission drives neuromuscular junctions and autonomic ganglion synaptic transmission, only rare cases of fast nicotinic transmission have been reported in the mammalian brain." Neuromuscular junctions are the defining form of stage 7 neural elements. They also note the modulatory role, rather than direct role, of nicotinic acetylcholine within the CNS. "Modulation of neurotransmitter release by presynaptic nAChRs is the most prevalent and well-studied nicotinic role in the CNS." Their review focuses on two perspectives. First, the potential chemistry of the neurons and synaptic junctions involving nicotine and/or acetylcholine. Second, behavioral observations following pharmacological intervention.

Dani & Bertrand close by taking a diametrically opposite position than McGehee & Role, and stress the modulatory (non-synaptic) role of nicotinic receptors. "Nicotinic receptors are widely expressed throughout the CNS, influencing electrical events in nearly every area of the mammalian brain. They enhance neurotransmitter release, modify circuit excitability, and influence synaptic plasticity.

Sutor & Zolles have also reviewed the role of these pharmacological agents but primarily from a clinical perspective. "Within the mammalian central nervous system (CNS), acetylcholine (ACh) acts as a neurotransmitter that modulates neuronal activity via two subtypes of receptors: (1) the metabotropic muscarinic acetylcholine receptors (mAChRs) and (2) the ionotropic neuronal nicotinic AChRs (nAChRs)." As noted in **Section 3.5.3**, the terms ionotropic and metabotropic remain ill-defined at this time and should be ignored in the above context.

The roles of curare and its antidote atropine have frequently been associated with muscarine and nicotinic receptors but mostly from a clinical perspective. It is best to ignore all of the associations mentioned in this section until laboratory results are available to provide a formal framework in this area.

3.5.5 A graphic clarifying the neuro-modulator & neuro-inhibitor roles

A goal of this work is to rationalize the field of neuro-affectors and modulators. It first separates the primary and secondary neuro-facilitators/inhibitors from the discussion. These are chemicals that are ***not*** released by neuron but are the critically important elements of the electrostenolytic process. After establishing the unique role of the electron in neuron-to-neuron signaling operations (at the synaptic gap junction), it provides an expanded framework adequate to delineate the information acquired in previous laboratory investigations. It modifies the view of McCormick and proposes a more detailed and specific set of neuro-inhibitor categories than Dowling. **Figure 3.5.5-1** provides a framework for the description of agents involved in processes originated by or affecting the neural system.

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[127]Dani, J. & Bertrand, D. (2007) Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system *Annu Rev Pharmacol Toxicol* vol 47, pp 699–729

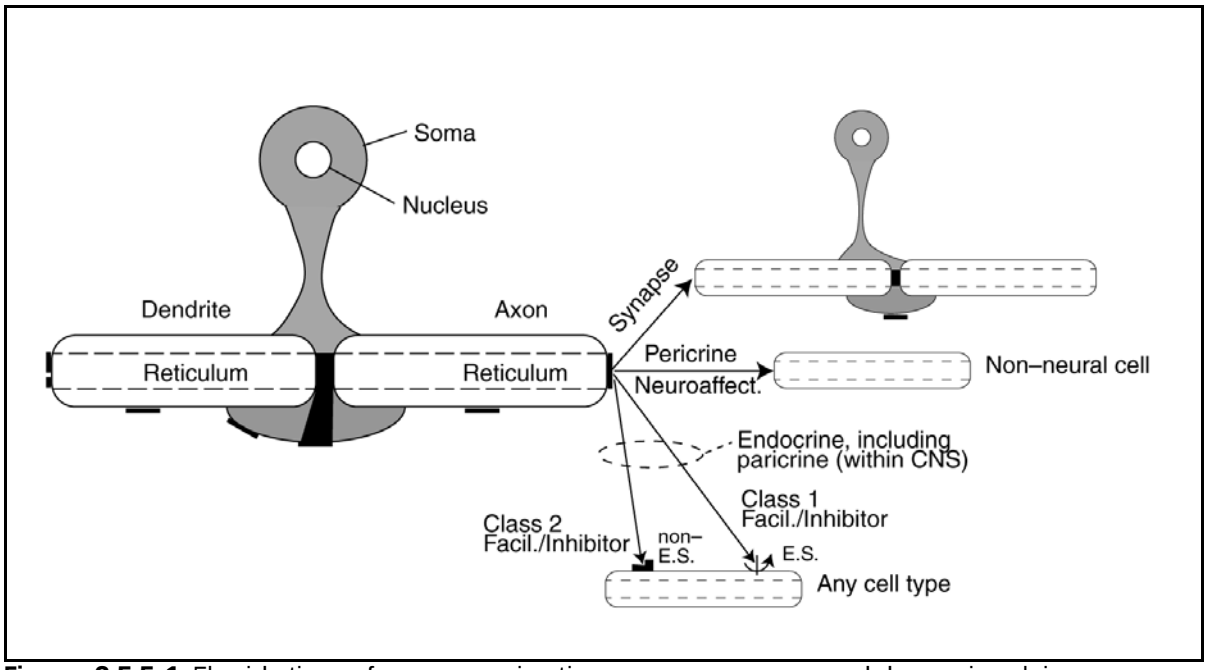

Figure 3.5.5-1 Elucidation of communications processes sourced by or involving neurons. Pericrine action is primarily between neurons and muscle cells. The endocrine and paricrine actions are considered parametric signaling (not related to the direct signaling between cells).

After separating the synaptic interface as totally electrolytic in character, it describes a series of distinct neuro-affectations. The most highly studied in the neural context is the direct pericrine neuro-affectation of muscle. After that class, a variety of endocrine affectations have been defined that involve interference, whether positive or negative, with the normal operation of the electrostenolytic processes and placed in a Class 1. These include the well known L-dopa and dopamine. They interfere via the normal stereochemical configuration of the electrostenolytic receptor and normally exhibit a characteristic dipole potential. A separate Class 2 is defined as those neuro-affectors that affect non-electrostenolytic receptor sites on cell surfaces. Like the Class 1 neuro-affectors, these chemicals typically involve a stereochemical interaction with a receptor and exhibit a dipole potential.

After accounting for the Class 1 & Class 2 neuro-affectors, it is appropriate to define two additional classes involving more indirect actions.

Class 3 neuro-affectors, documented primarily as neuro-inhibitors, include those materials changing the chemical diffusion parameters of the interneuron matrix (or the walls of the vascular channels). Class 4 neuro-inhibitors interfere with the electrical conductivity of the interneuron matrix.

Referring to the above discussion of Paul, glycine (a mono carboxylic amino acid) is a class 1 neuro-inhibitor because it occupies the stereochemical position designed to receive glutamate in the electrostenolytic process. By occupying this position, to the exclusion of glutamate, it inhibits the glutamate-GABA electrostenolytic process.

3.5.6 Re-framing the pharmacology of the neural system

No adequate framework has evolved under the chemical ideology to explain the detailed operation of a wide range of putative neurotransmitters. On the other hand, the Electrolytic Theory of the Neuron provides a simple and unique framework for explaining the pharmacological operation of these materials. Under the Electrolytic Theory, the largely conceptual neurotransmitters of the chemical ideology take their proper chemical place as neuro-facilitators, neuro-inhibitors, neuromodulators and neuroaffectors of the system but do

not participate in neural signaling. Although this assertion flies in the face of many (highly ornate) caricatures in the recent literature, the results of electron microscopy do not support the role of any chemicals in neural signaling. They show areas of high electron density in the very locations expected by the Electrolytic Theory (Search Vardi in **Chapter 5**).

The unique and detailed mechanisms related to the amino acids (glutamate, aspartate and lysine) provided under the electrolytic theory are beautiful in their simplicity (**Sections 3.2.2** & **3.5.4**). These mechanisms are completely compatible with the recent language of Stephenson & Strange[128], but they require a different interpretation of the location of various "neurotransmitter" receptors. The receptors are found outside the synaptic gap. With only the most minor semantic changes, their words are quite compatible with the theory presented in **Chapter 3**. "From biochemical studies it became apparent that neurotransmitter *(primary neuro-facilitator*) receptors are integral membrane proteins with binding sites for the neurotransmitter; these binding sites are available extracellularly (frequently adjacent to, *but outside, the synaptic gap*), and the receptor also has the ability to signal to the inside of the cell." An open question remains concerning the "integral membrane protein." No protein or protein mechanism has been identified except conceptually. A more satisfactory situation replaces the term "integral membrane protein" with the polar portion of a lipoid integral to the underlying asymmetrical (type 2) BLM.

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Interference in the metabolism of glutamate to GABA (and the backup metabolism of aspartate to glycine) is a primary means of achieving anesthesia through pharmacological purposes. Pharmacology is beyond the scope of this work. However, it is useful to discuss the potential means by which interference with the metabolic processes can be achieved.

The metabolism of the neuro-facilitator lysine to the neuro-inhibitor iso-leucine, as found in the auxiliary electrostenolytic process of the heart has not been documented previously..

3.5.6.1 Background related to the sensitivities of the neuron

Another action would be to sequester the glutamate and aspartate within the neural matrix.]

There are multiple sensitivities of the neural system to interference or intended intervention. Because of the blood-brain barrier, many of these interferences, especially anesthesia, can best be examined by treating the CNS and the PNS separately. Because of the variability in sensitivity of different portions of the neurons, it is also important during investigations to specify what portion of the neuron is being treated or is otherwise involved. It is particularly important to identify the site of topical applications of chemicals to the neurons *in-vitro*.

Direct interference with the signaling current passing through the synapses and the Nodes of Ranvier is unlikely. The Activa base forming the extremely thin liquid crystalline layer of semi-metallic water between the pre and post synaptic lemma is virtually impervious to large pharmaceutical molecules, unless they are able to destroy the liquid crystalline character of the base.

Significant interference with the axon receptors of stage 3 neurons will generally result in the complete (and sudden) shutdown of signaling by those neuron. Any pharmaceutical that can reduce the amplitude of the action potentials of the ganglion encoding neurons (or the subsequent Nodes of Ranvier of stage 3) by a factor of two can cause complete paralysis of the neural command system (stages 6 & 7) because the Nodes of Ranvier will not be excited. Similarly, interference with the dendritic receptor sites of stage 3 ganglion neurons will also cause significant changes in the threshold level, and the probability of action potentials generation.

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[128]Stephenson, F. & Strange, P. (1993) Receptors for neurotransmitters, *Chapter 2 in* Shinitzky, M. Biomembranes. NY: Balaban Publishers

Alternately, interference with the electrostenolytic reduction process at the axon receptors and the dendritic receptors of purely analog neurons of non stage 3 neurons, will generally cause a graded response leading to complete shutdown of the signaling path at Activa cutoff. A significant change in the axoplasm potential of the analog neurons of stage 1 & 2 will also cause significant impairment. Such changes generally will cause the active diode of the orthodromic synapse to become non-conductive. A similar situation will occur within the CNS (stages 4 & 5) if the pharmaceutical can cross the blood-brain barrier.

Pharmaceutical anesthetics can also interfere with the porosity of the neural matrix to glutamate and aspartate, can interfere with the operation of the electrostenolytic mechanism by blocking access of glutamate and aspartate, can sequester glutamate and aspartate within the neural matrix, can change the impedance of a variety of tissue within the neurons, etc.

Another action would be to sequester the glutamate and aspartate within the neural matrix.

3.5.6.2 Background related to the ambiguous -ergic suffix

The extension –ergix is frequently found in the clinical literature of medicine and psychiatry. The confusion in that literature concerning the -ergic properties of various chemicals speaks for itself. The following historical review is supplemented by discussions in **Section 16.2.1.3** of this work.

Cucchiaro, et. al. attempt to extend the specific nature of these -ergic processes by stating; "That is, cholinergic inputs to interneurons and perigeniculate cells seem to hyperpolarize them."[129] They then reflect the inadequacy of the overall -ergic concept, based on a two-terminal concept of a neuron. In a long sentence, including many references, they end with "by operating through different cholinergic postsynaptic receptors that can *either* hyperpolarize or depolarize the cell. [Emphasis added]" As the discussion proceeds, they introduce the concept of disinhibition. This convolution is apparently distinct from excitation.

Sherman & Guillery have attempted to clarify the use of GABA-ergic, within the chemical neurotransmitter context, with less than the desired clarity[130]. To minimize the confusion, they suggest that; "Transmitters should no longer be classified as excitatory or inhibitory, because it is known that the same neurotransmitter can be both excitatory and inhibitory depending on the post synaptic receptor." They then focus on two putative post synaptic receptors, $GABA_A$ & $GABA_B$. Their claim is that $GABA_A$ is ionotropic and its action inhibits the host cell, while $GABA_B$ is metabotropic and it hyperpolarizes the cell (unstated but apparently the axoplasm of the cell). Their definitions of ionotrpic and metabotropic appear to lack precision as to their actual function.

It is proposed that the above "different cholinergic postsynaptic receptors" of Cucchiaro, et. al. and the post synaptic receptors, $GABA_A$ & $GABA_B$, of Sherman & Guillery are distinctly different physical inputs to the neuron itself (based on the three-terminal concept of an Activa containing neuron). The dendritic input is non inverting and the poditic input is inverting. Excitation, in the form of acetylcholine, applied to one of them will cause hyperpolarization of the axoplasm while excitation of the other one will cause depolarization. See **Sections 2.2.4.3** & **3.2.2.3.4**.

Puil has provided a detailed report on the response of neurons to a wide variety of excitatory and inhibitory pharmacological agents in his Section 4.2.1. However, his Section 3.2 must be read with care since it assumes a two-terminal neuron. His discussion frequently reflects on the inconsistency of polarization or hyperpolarization. The acceptance of a three-terminal neuron with both an inverting and a non-inverting input and three identifiable plasmas solves

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[129]Cucchiaro, J. Uhlrich, D. & Sherman, S. (1993) Ultrastructure of synapses from the pretectum in the A-Laminae of the cat's lateral geniculate nucleus. J. Comp. Neurobiol. vol. 334, pp 618-630

[130]Sherman, M. & Guillery, R. (1996) Functional organization of thalamocortical relays *J. Neurophysiol*. vol. 96, no. 3, pp 1367-1395

these problems.

Pin & Duvoisin have provided an extensive review (26 pages) ostensibly of the neurotransmitters with a focus on the metabotropic receptor sites[131]. The title of the paper is much broader than the goal of the paper. "In this review, we will first describe the mGluR family as defined by the cloned receptors, in terms of diversity, transduction, structure function relationship, and pharmacology." The work is totally pharmacologically based and lacks a physiological foundation (except for the exogenous application of their materials to a variety of neural substrates). The paper covers a very broad area and necessarily incorporates the expression "putatively" quite frequently.

They do note, "Because molecular cloning has preceded pharmacological characterization in the identification of novel mGluRs, it has provided the basis for a simple nomenclature of mGluRs: mGluRs are numbered following the order in which their cDNAs have been cloned, to date: mGluR1 through mGluR8. Moreover, because most of this work has been done in a single laboratory, the numbering scheme is consistent and the same number has not been used for different receptors, sadly a source of confusion for other receptor families."

The opening premise of Pin & Duvoisin is not supported here without clarification. "Most of the excitatory synapses in the central nervous system use glutamate (Glu) as a chemical messenger." As developed in this section, glutamate is a unique neuro-facilitator through its electrostenolytic function based on its unique negatively charged (acidic) amino acid group. This property is shared with only one other amino acid, aspartic acid (which is a backup for glutamate in the electrostenolytic process).

Fuster has provided a guide to the literature of neurotransmitters based on the chemical neuron theory (the conventional wisdom)[132]. The material is focused on the frontal lobe of the cerebral cortex and is tied to the role of neurotransmitters in relation to the "action potential." His figure 3.2 goes farther than most other authors in defining six different -ergic forms that may involve as many as thirty different neurotransmitter materials. These are presented in caricature form suggesting six different types of synapses. Fuster has provided a discussion that hints at an underlying neurosecretory system that can influence the effectiveness of various neuro-facilitators and neuro-inhibitors. It is suggested that this system (or systems) originates in the brainstem. As Fuster notes, these materials have been studied only empirically. No theoretical studies are reported or referenced. No discussion of the stereochemistry of the materials is offered. Except the above figure, the presentation of Fuster is in prose. This presentation style is susceptible to misunderstanding. The following are a few examples.

1. He makes several definitive statements on page 58. "GABA is . . . the most abundant of all neurotransmitters thus far identified in the central nervous system. The brain content of GABA is between 200 and 1,000 times greater than that of any of the four transmitters reviewed so far." The four are presumably norepinephrine, dopamine, serotonin and acetylcholine. Unfortunately, he did not address the role of glutamate to the same degree in the discussion. McIlwain & Bachelard ([**Figure 3.2.3-1**]) suggest that glutamate is 50% higher in concentration than GABA. Glutamate is clearly a neurotransmitter, according to both Fuster and many others.

2. He states that neurotransmitters are produced within the body of the nerve cell for transport along the axon to the terminal synaptic vesicles (pg 43). In another context, he says several neurotransmitter distribution pathways originate in the brainstem (pg 45). He also discusses the variation in concentration of different neurotransmitters within different portions of the cerebral cortex. The discussion suggests there may be one or more neurosecretory signal paths between the brainstem and the prefrontal cortex that control the concentration

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[131]Pin, J. & Duvoisin, R. (1995) Neurotransmitter receptors I: The Metabotropic Glutamate Receptors *Neuropharmacology* vol 34(1), pp l-26

[132]Fuster, J. (1998) The Prefrontal Cortex, 3rd Ed. NY: Lippincott-Raven, Chapter 3

of different neuro-facilitators and neuro-inhibitors. This suggestion, along with the experiments of McIlwain & Bachelard, support the conclusion that the various neuro-facilitators and neuro-inhibitors may be fabricated outside of the neurons themselves. This is particularly true of the vasoconstrictors and other secondary facilitators and inhibitors. It also appears to be true of lactate, a precursor of glutamate (**Section 3.5.4**).

3. He describes "Dopamine is also a neurotransmitter in its own right; accordingly, there are in the brain dopamine-specific terminals and receptors. Dopaminergic systems, like norenipherinergic systems, originate in the brainstem." These statements appear to conflict with his view that "neurotransmitters are produced within the body of the nerve cell. . . ." (Page 43). As shown in **Section 3.5.4**, dopamine is a class 1 neuro-inhibitor because of its ability to occupy an electrostenolytic site.

3.5.6.2.1 Characterizing GABA-ergic, cholin-ergic and similar reactions

A major problem with the above discussions and categories is the lack of a precise definition of each type of -ergic material and the differences between the types. The chemical theory of the neuron does not provide a framework in this area and is not supported here (**Section 1.1.2**). Instead, a framework of neuro-facilitators and neuro-inhibitors will be described that explains the theoretical action of each of these materials. This description is based on the Electrolytic Theory of the Neuron (**Section 1.1.3**). These explanations are consistent with the observed pharmacological effects of these materials. The organization of these materials into a functional framework is provided in **Section 3.5.4**.

The -ergic properties of a chemical can be addressed in two distinct arenas. The first describes the results of topical application of the chemical to an individual neuron. The second describes the results of global application of a chemical to the organism, usually via injection into the bloodstream.

To frame the discussion of topical application, consider first the Node of Ranvier as shown in **Section 2.6.3**. At each Node, the electrostenolytic processes associated with the pre-nodal, nodal and post nodal elements are in very close proximity. These morphological elements are closely identified with the input, base and output terminals of the Activa at the heart of the Node. Consider the topical application of GABA to each of these elements. The result is an increase in the concentration of GABA at these sites. Such an increase has a retarding effect on the normal electrostenolytic reaction. When applied to the post-nodal element, GABA tends to reduce the collector potential of the Activa. This tends to reduce the amplitude of the action potential generated, and this reduction reduces the probability that the next Node will be excited sufficiently to regenerate the action potential. Regarding the propagation of the neural signal, the result is clearly inhibitory. If GABA is applied topically to the pre-nodal element, the result is generally similar but for a different reason. By lowering the negative potential at the non-inverting input of the Activa, the probability that the Activa will regenerate any action potential received from the previous Node is reduced. Thus, this application is also inhibitory. However, the topical application of GABA to the inverting input to the Activa has the opposite effect. Lowering this negative potential increases the forward bias between the emitter and base of the Activa. This action increases the likelihood that any action potential received from the preceding Node will be regenerated. Thus, this application of GABA is excitatory.

The above discussion used probabilities to describe the effect on signal propagation related to action potentials. When discussing tonic neurons (the vast majority of neurons), the effects are deterministic but slightly different. The topical application of small amounts of GABA to the site of electrostenolytics of the axon will have little effect on signal amplitude. Application of GABA in excessive amounts will cause the Activa to shut down for lack of reverse bias between the axon and the poditic terminal. Similarly, topical application of small amounts of GABA to the poditic electrostenolytic site will cause a reduction in negative potential at this site. This change in bias will cause an increase in axon potential (an increase in the signal amplitude relative to the quiescent condition). The effect is therefore excitatory. A similar application to the dendritic electrostenolytic site will have an inhibitory effect on the output at the axon. The application of large amounts of GABA to the dendritic or poditic sites will tend to change the biases on the Activa sufficiently to cause shutdown of the circuit. GABA is the prototypical neuro-inhibitor.

The effect of other pharmacological agents is similar. If the topical application of the agent increases the measured parameter relative to the neuron, it is considered excitatory (whatever the ultimate result on the complete neural entity). If the topical application results in a decrease in the measured parameter, the agent is considered inhibitory (regardless of the ultimate result on the complete neural entity).

Once initiated, the actions described above tend to propagate through the remainder of the system until a stage 3 stellate circuit is reached. The output of a stellate circuit is applied to an engine consisting of thousands to millions of neurons performing Boolean Logic and generating many individual output signals. Whether these individual outputs reflect the original character of the excitatory (or positive) or inhibitory (or negative) input is impossible to say.

When the concentration of GABA within neural tissue is increased globally, the result is indeterminate in three ways. It is indeterminate with respect to its effect on a single neuron and it is indeterminate with regard to multiple neurons in series. The effect on the output of an engine consisting of many neurons is similarly indeterminate. This is the source of the problem in using the expression GABA-ergic in pharmacology. A global application may cause multiple observable events. As a caricature, the observed effect following global application of GABA may be a slowing of the heart rate accompanied by an opening of the iris and a tingling feeling in the left toe. What the investigator reports depends on what characteristic(s) he has chosen to observe.

The effect of topical application of the neuro-facilitator glutamate tends to be the opposite of GABA since it drives the individual electrostenolytic processes toward completion. Aspartate, in its role as a secondary neuro-facilitator, acts similarly. The roles of other class 1 neuro-facilitators and neuro-inhibitors can be described similarly because they act to disturb the electrostenolytic process by occupying stereo-specific sites on the substrate. The role of class 2 neuro-facilitators and neuro-inhibitors are more difficult to predict because they tend to change the diffusion coefficients of the inter-neural matrix (INM) and the walls of the capillaries. These actions affect the concentrations of many individual materials within the INM.

The roles of other Class 1 and Class 2 neuro-facilitators and neuro-inhibitors are more difficult to predict. [Their initial definitions appear in **Section 3.5.4**]

The effect of various neuro-facilitators and neuro-inhibitors, when applied topically, depends on where they are applied and in what concentrations. In this regard, each active region of the neuron must be looked at separately. This is particularly important regarding long axons containing Nodes of Ranvier. Besides each Synapse and each Activa placed within the soma of a neuron, each of these Nodes represents a separate active circuit. Exploring tonic and phasic neurons separately, regarding their sensitivity to pharmacological changes, is also important.

In summary, the effect of a given chemical, whether a glutamate or other pharmacological agent, on a neural circuit depends on where it is applied topically. If it is applied globally to a neuron, the impact depends on at least three factors. First, the relative concentrations applied to different electrostenolytic areas of the plasma wall. Second, the relative porosity of the local environment to the topical agent. Third, the ability of reaction byproducts to exit the immediate area of electrostenolytics. Finally, the toxicity of neuro-facilitators and neuro-inhibitors suggests excessive dosages can lead to neural shutdown and coma in the subject.

3.5.6.2.2 GABA-ergic is a clinical, imprecise, designation

The effect of an individual neuro-facilitator or neuro-inhibitor is highly dependent on how it is applied and what outcomes are observed. While a designation such as GABA-ergic can be used in a stylized clinical setting, it is imprecise and largely meaningless in a scientific setting (**Section 16.2.1.3**). The same conclusion can be drawn concerning many other

pharmaceuticals[133]. Their action can only be defined precisely when topically applied to a specific portion of a specific neuron. When ingested, or injected, their effect tends to be global (involving millions of neurons. Their effect can not generally be specified precisely and many side effects are to be expected.

3.5.6.3 A tabular framework for neuro--pharmaceuticals

Von Bolen described the neural environment from a pharmaceutical perspective in 2006. **Figure 3.5.6-1** provides an alternative description based on this work. This framework is open ended and can be extended indefinitely. There is an undefined role for the opioids and endorphins within this framework.

[133]Baker, M. & Wood, J. (2001) Op. Cit.

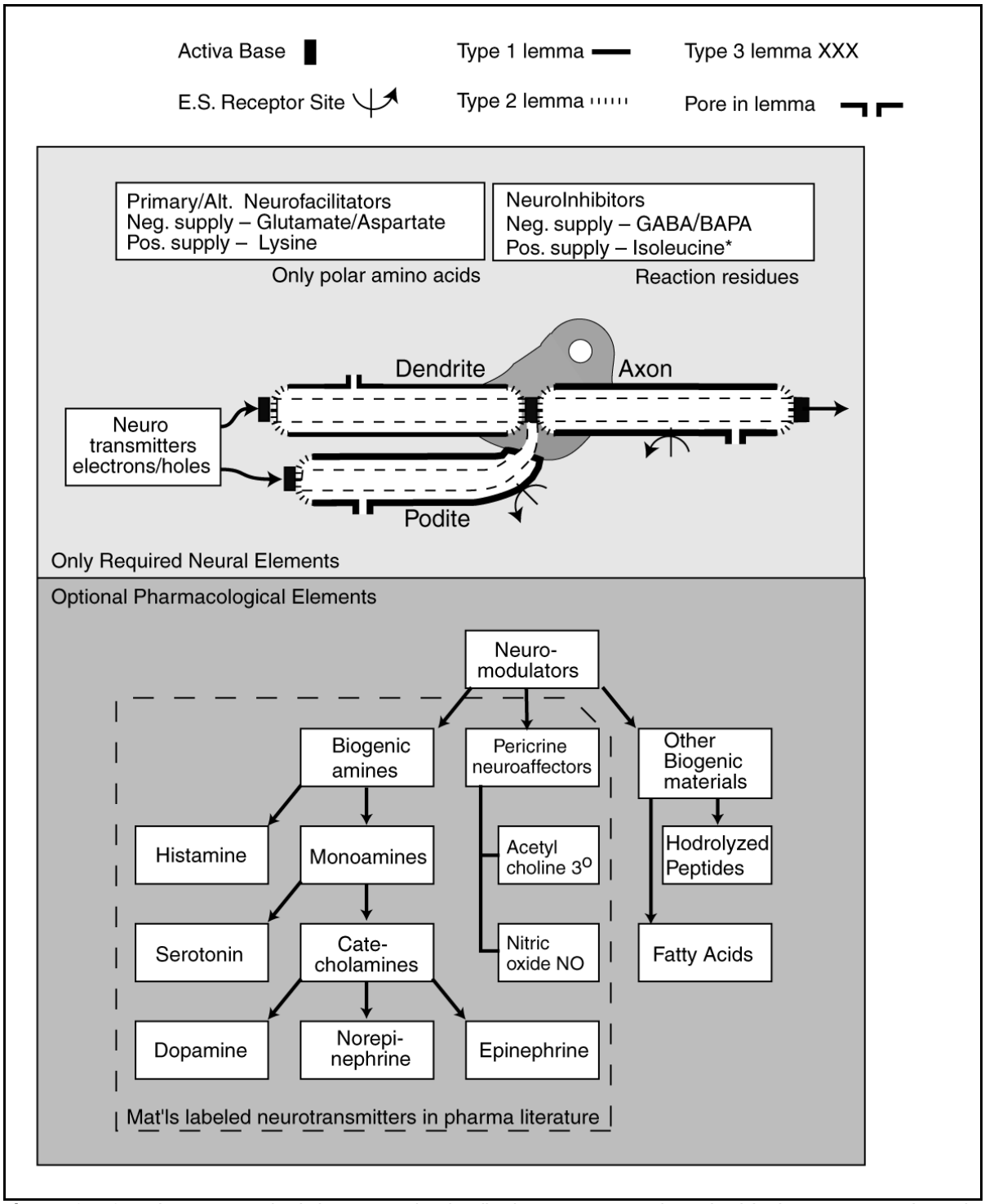

Figure 3.5.6-1 The exogenic (pharmacological) elements associated with the neuron. The role of the endogenic neuro-affectors is not addressed in this table. The role of the opioids and endorphins have not been defined in the context of this table. Compare to von Bolen, 2006. See text.

The above figure does not address the neuro-affectors. They have been introduced in **Section 3.5.4** and are discussed in detail in **Chapter 16**. The neuro-affectors include NO and the hormones. The terminology associated with the biogenic peptides and fatty acids is still evolving.
There are a large number of pharmaceutical agents that are antagonistic to the materials in the figure that are not addressed here.

3.5.6.3.1 The considerable opportunity to interfere with neuron operation

As noted in **Sections 2.2.2** & **3.1.1**, the fully elaborated neuron requires a considerable number of chemicals to pass through their lemma. As a result, they are susceptible to a great variety of potential pharmacological interferences. These interferences do not affect neuro signaling directly but indirectly (also described as parametrically), by destabilizing the normal operation of the neuron as a complex cell. As a result, these destabilizing pharmacologicals are considered modulators of neuron activity.

An important point to note that many of the pharmaceutical modulators of neural activity are themselves endogenic neuro-affectors released by other neurons. Acetylcholine appears to be a primary example of an agent that is released by neuro-affectors and affects a wide variety of neural activities over pericrine distances.

McGehee & Role have commented[134], "The last decade has revealed an astounding degree of physiological and structural diversity in neurotransmitter-activated receptors." Their position is consistent with this work if the term neurotransmitter is replaced with neuro-affector.

3.5.7 Need to determine the dipole potential of many chemicals

While the stereochemical properties of many agents affecting the neural system have been studied, their dipole potential has not. This parameter, while requiring different measurement techniques than the dipole moment, can provide an ordering of many neuro-affectors and neuromodulators not currently available. Such measurements should be a high priority task within the laboratory activity of the neuroscience community.

1.8 CHAPTER SUMMARY

This chapter has presented the neuron as viewed from the perspective of "Modern Physics." Modern Physics introduces the fields of quantum-mechanical physics, semiconductor physics, the liquid-crystalline state of matter and the static and dynamic areas of conventional electricity to the field of neurobiology. Based on these disciplines, this chapter has presented an electrolytic theory of the neural system as an alternate to the previous ionic permeability theory. The additional understanding provided by the new theory is impressive. The electrolytic theory shows that;

+ it is important to define the individual regions of the external membranes associated with the neuron much more precisely than ever before in order to understand the function of each differentiated region of the membrane.

+ the neuron is a specialized neuro-secretory cell of the animal. Neurons are grouped into signaling paths in support of the overall sensory and motor functions of the animal.

+ the fundamental neuron consists of a series of electrical conduits supported by a variety of metabolic processes grouped around the nucleus.

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[134]McGehee, D. & Role, L. (1995) Physiological diversity of nicotinic acetylcholine receptors expressed by vertebrate neurons *Annu Rev Physiol* vol 57, pp521-546

+ the nucleus plays no role in the signaling function of a neuron.

+ each conduit of the neuron represents a closed membrane filled with a heterogeneous electrolyte.

+ the functional performance of the fundamental neuron can be explained in terms of an active electrolytic semiconductor device called an Activa. It is formed by the precise juxtaposition of two conduits within a neuron or at the junction of two neurons. In the latter case, the Activa is known under the morphological name of a synapse.

+ The membrane of a conduit of a neuron, including the axolemma, is not an "excitable" structure. It is a passive structure consisting of a highly insulating bilayer of phosphoglyceride material. The membrane may consist of two symmetrical bilayers in which case it is an excellent insulator impervious to virtually all matter, including molecules, atoms, ions and electrical charges such as electrons and holes. The membrane may exhibit regions of asymmetrical bilayers in which case it shows a significant permeability to electrons and/or holes but remains essentially impervious to molecules, atoms and ions. In this case, it acts as a very high impedance but imperfect insulator when biased with the inner surface negative relative to the outer surface.

+ the membrane of a conduit may also exhibit a region that can be made permeable to neutral molecules, and possibly to neutral ion pairs, under specific circumstances.

+ the electrical characteristics of a conduit are dominated by the electrostenolytic and transistor processes related to it.

+ the charge injected into a conduit by transistor action need not become associated with an atom to form an ion. It may exist as a free electron on the interior surface of the membrane, as in any capacitor.

+ the overall electrolytic potentials and currents associated with a conduit and its surrounding matrix are defined in terms of a variable field equation and the principles of conventional electrostatics. The proper application of the variable field equation requires recognition of both the transistor interface at the Activa and one or more electrostenolytic interfaces on the surface of the membrane.

+ the Activa formed within a fundamental neuron is a typical three-terminal semiconductor device employing the principles of electrolytics within a liquid-crystalline environment.

+ the Activa can perform as a two terminal device (third terminal is identifiable but electrically unconnected) when it is stimulated by non-electrical means.

+ the power source for each conduit of a neuron is an electrostenolytic process on the surface of the conduit membrane employing a glutamate cycle which is reversible.

Based on the analysis, the following additional conclusions can be drawn. Much to the expected surprise of some readers, these conclusions are compatible with the position of Hodgkin and Huxley on page 541 of their final paper of 1952[135].

+ there is no requirement for ions to traverse the exterior membrane of a conduit associated with a neuron for the purpose of signaling.

+ the ions within the conduit are there primarily to provide a low impedance electrical path as far as signaling is concerned.

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[135]Hodgkin, A. & Huxley, A. (1952) A quantitative description of membrane current and its applicatin to conduction and excitation in nerve. *J. Physiol.* Vol 117, pp. 500-544

+ there is no requirement that the total ionic charge within the electrolyte confined by an insulating membrane be equal to the total charge on the surface of that same membrane.

+ the experiments of the 1950's did not demonstrate a direct relationship between the measured changes in interior plasma and the transit of ions through the membrane of the axon.

+ no theoretical foundation has been found for the differentiation of the putative current through the axolemma wall into an inrushing and an outrushing current.

+ no theoretical foundation has been found for the putative separation of the total current through the axolemma of a neuron in response to a putative action potential into two separate currents associated with the transfer of positive ions through that same axolemma.

+ no theoretical foundation has been found for the "certain simple assumptions" used to separate the above putative currents into currents associated with a specific type of positive ion. The independence principle cannot be supported.

Finally, a new representation of the plasmalemma of a cell can be defined that greatly aids in the discussion of neuron function. The plasmalemma can be divided into three primary types of membrane, each optimized for a different functional role.

The type 1 plasmalemma consists of a molecularly symmetrical continuous liquid crystalline bilayer that is impervious to transverse molecular and electron flow (it is a very good insulator). This region is essentially inert with respect to cell operations.

The type 2 plasmalemma consists of a molecularly asymmetrical continuous liquid crystalline bilayer that is impervious to transverse molecular but acts as an electrical diode with respect to electron flow . It is the primary participant in both the signaling and electrical biasing of the cell.

The type 3 plasmalemma consists of a liquid crystalline bilayer with many embedded proteins providing a transport path through the membrane. To avoid disturbing the electrical balance of the cell, this type of membrane transports electrically neutral (although frequently polarized) molecules through the cell wall. While some of these molecules may go into solution within the cell, the resulting ions are generally immobilized by the gelatinous nature of the plasma.

It is likely that much of the type 3 membrane associated with an axon is found buried within the neuron. There it would support the transfer of complex molecules from the region of the nucleus to the axoplasm. Some type 3 membrane may be exposed to the neural matrix to facilitate the transfer of lactate from adjacent glia cells to the axon.

Table of Contents 1 August 2016

Chapter 3 List of Figures 8/1/16

(Active) SUBJECT INDEX (using advanced indexing option)