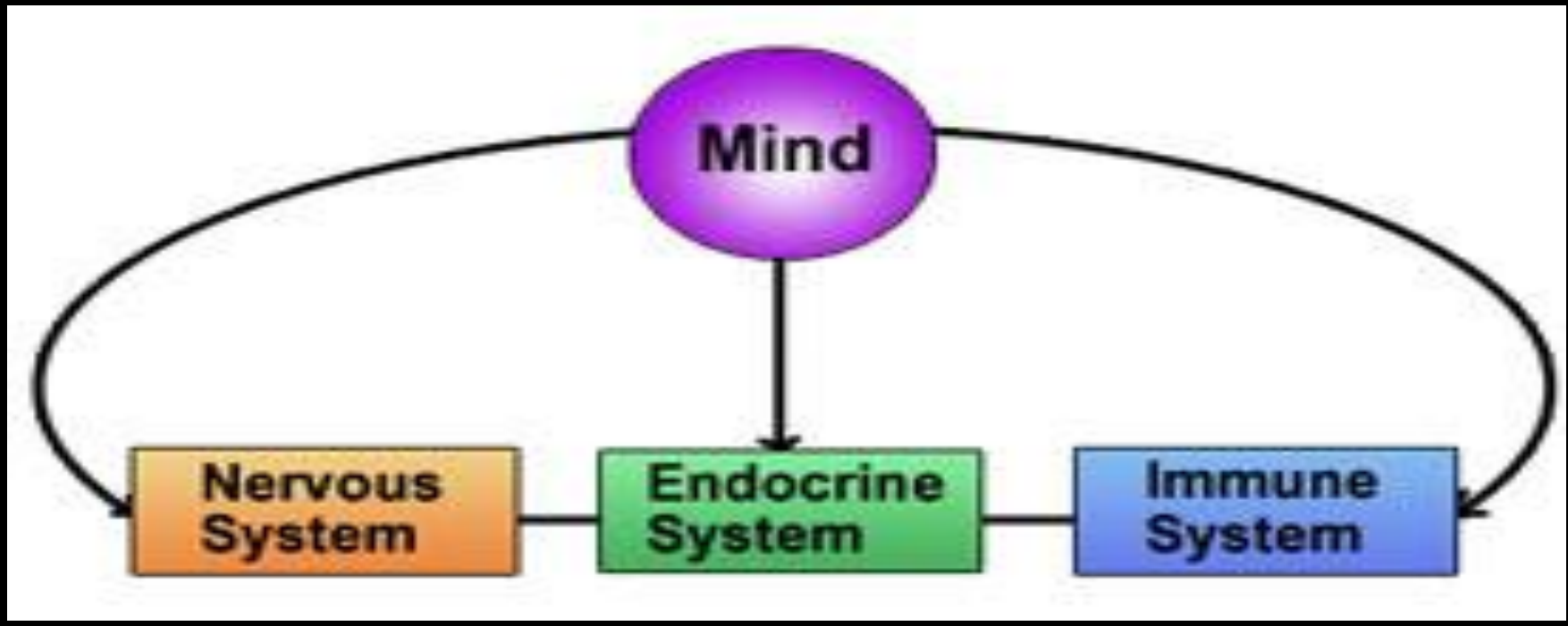
PSYCHONEUROIMMUNOLOGY



Evidence for Nervous – Immune system Interactions

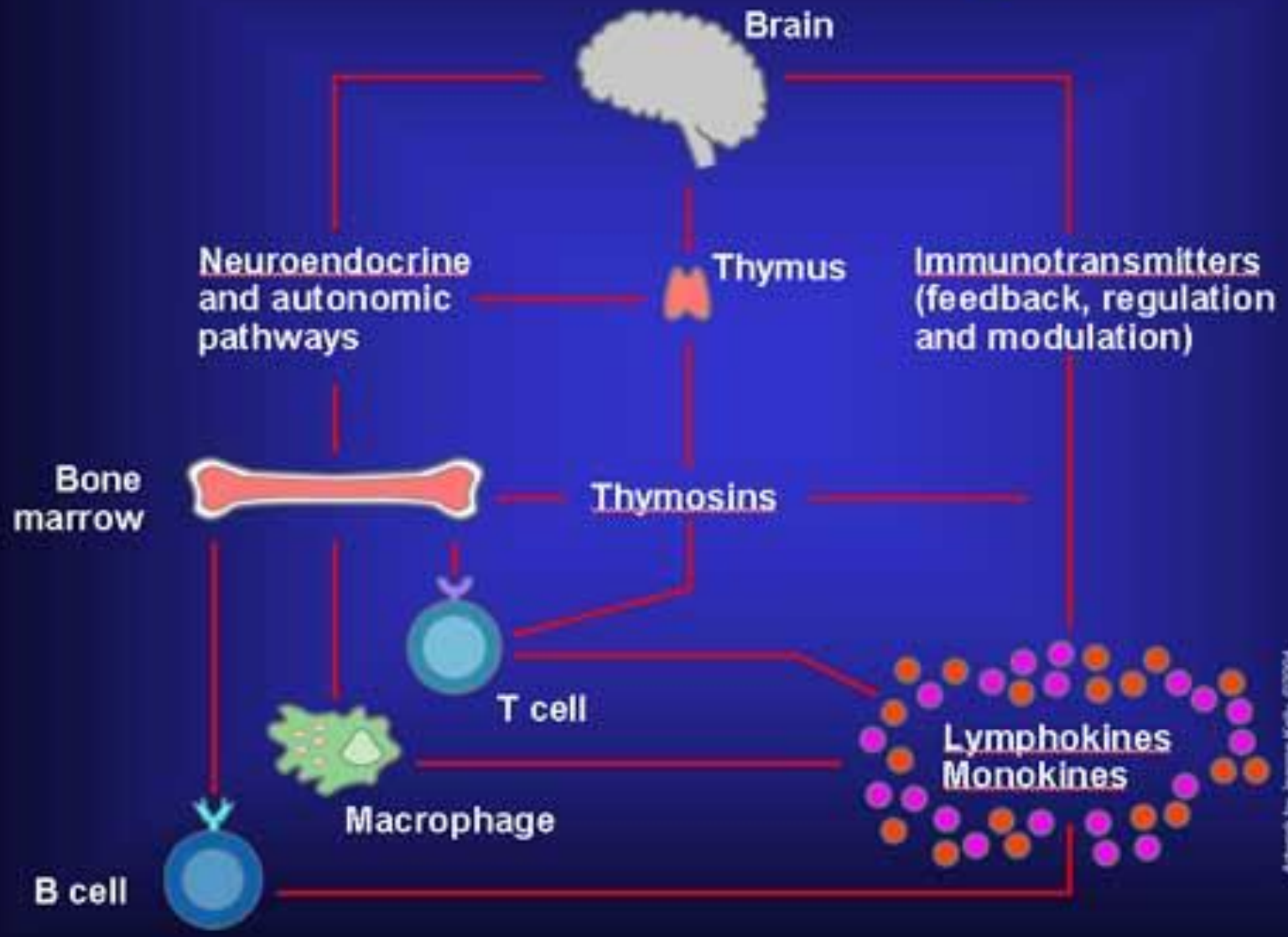
- Expression of receptors on immune cells.
- Autonomic nervous system and the lymphoid tissue.
- Conditioning of the immune response.
- Stress affects the immune response.
- Immune system affects neurotransmitter function, receptor density, regional brain blood flow and behavior.

Neurotransmitters involved

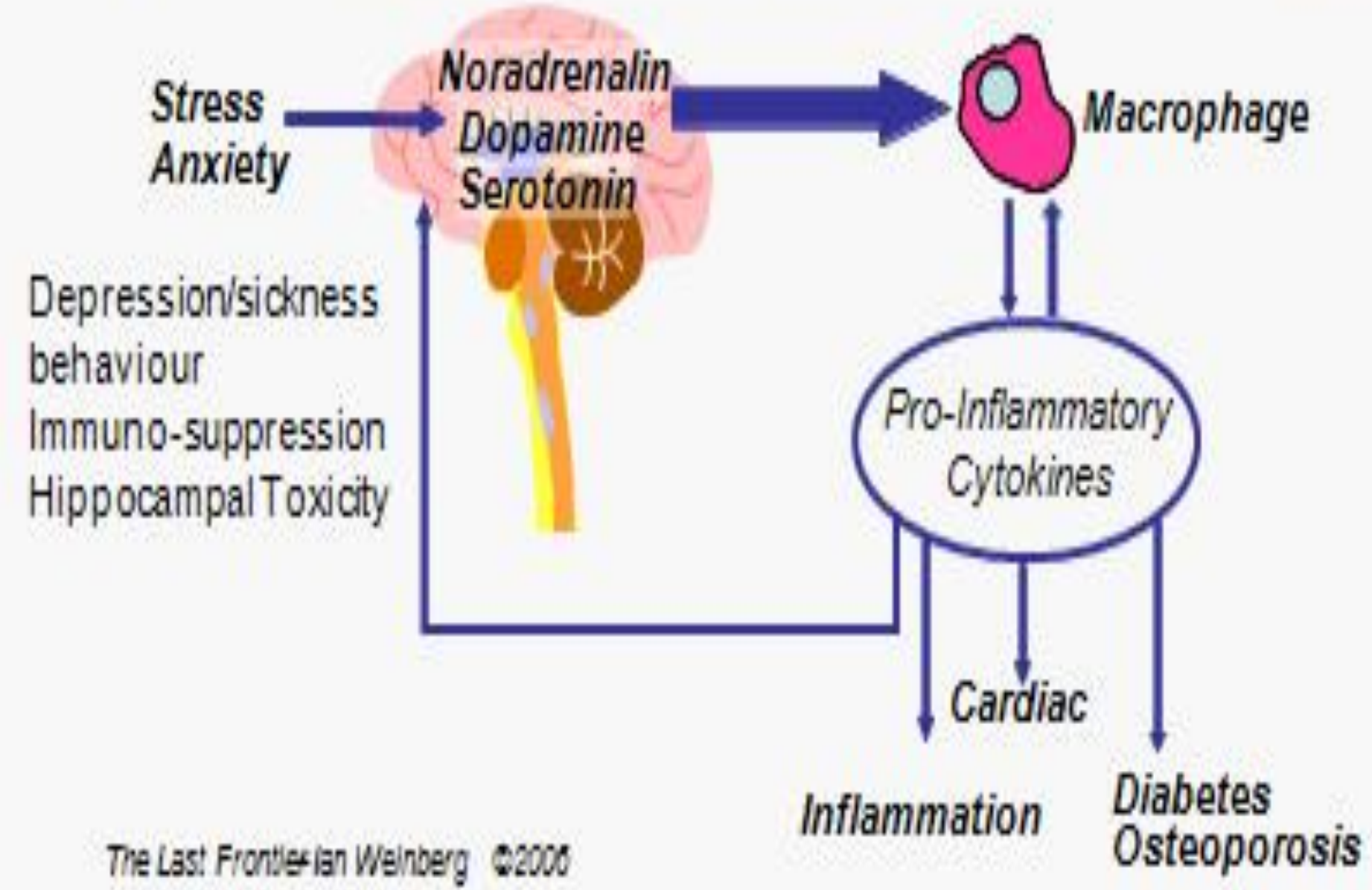
- Nor-epinephrine.
- Serotonin.
- Opioids.
- Substance P.
- ACTH
- CRH.
- VIP.
- MSH.

- Dopamine.
- Acetylcholine.
- Histamine.
- AVP.
- Oxytocin.
- Neuropeptide Y
- Somatostatin.
- IGF-1

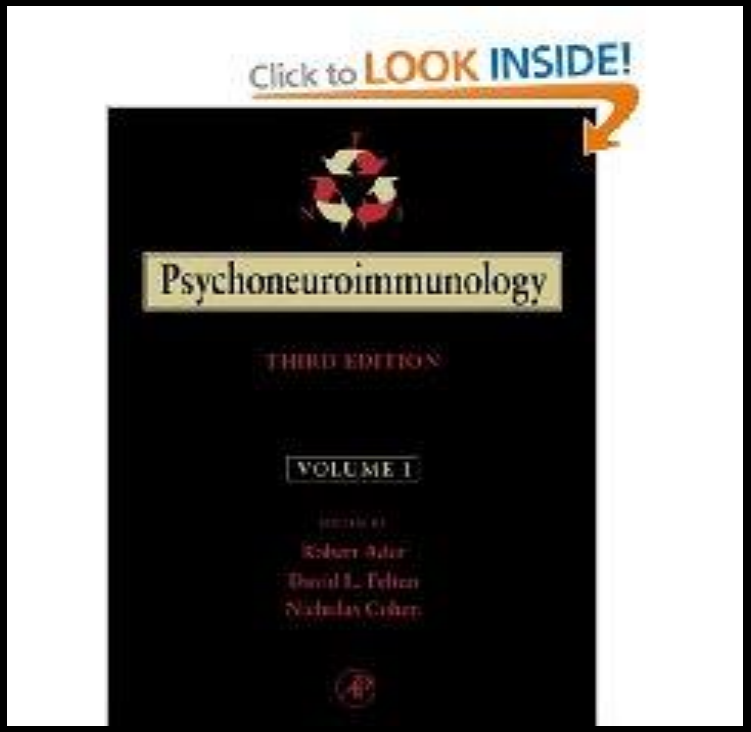
The Immune System and the Nervous System



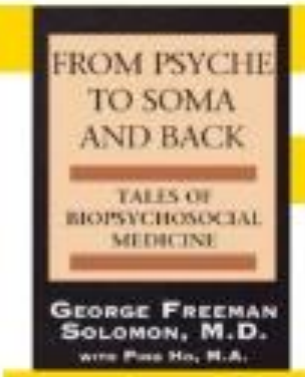
Chemical dynamics of Psychoneuroimmunology



- Robert Ader 1970
- Father of psychoneuro-immunology.



History



1931 - 2001

George Freeman Solomon

1964 -
coined the term
"psychoimmunology"

published a landmark paper:
"Emotions, immunity, and disease: a speculative theoretical integration."

Freeman et al., Phillips et al., Vaughan et al. - mid XXth century studies of psychiatric patients:

→ immune alterations in **psychotic patients**, including numbers of lymphocytes and poorer antibody response to pertussis vaccination, compared with **non-psychiatric control subjects**

Freeman H, Elmadjian F. The relationship between blood sugar and lymphocyte levels in normal and psychotic subjects. Psychosom Med 1947; 9: 226–33.
Phillips L, Elmadjian F. A Rorschach tension score and the diurnal lymphocyte curve in psychotic subjects. Psychosom Med 1947; 9: 364–71
Vaughan WTJ, Sullivan JC, Elmadjian F. Immunity and schizophrenia. Psychosom Med 1949; 11: 327–33.

Ader - Cohen - Felten

authors of book

Psychoneuroimmunology

1981

underlying premise that

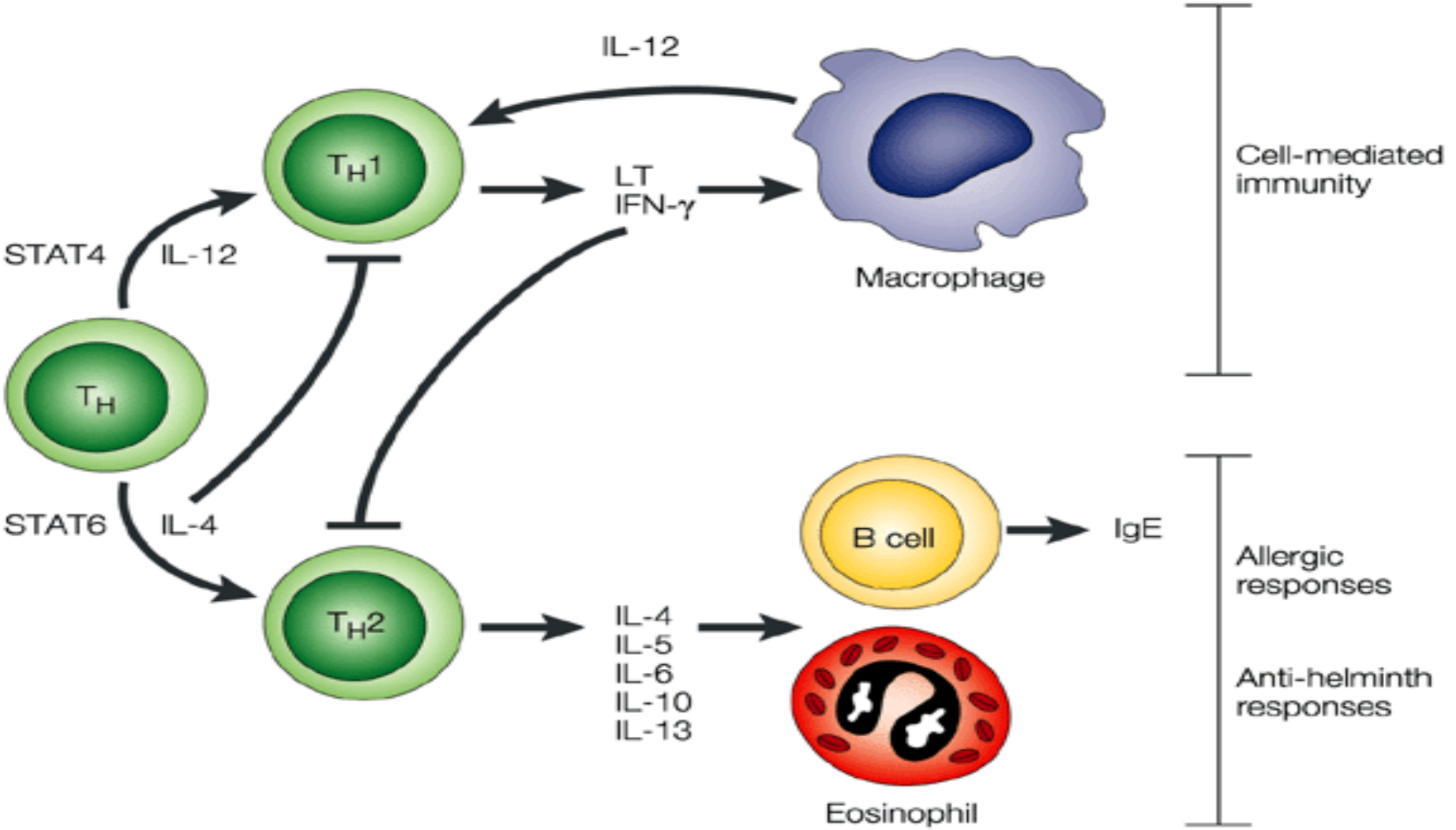
the brain and immune system
represent
a single, integrated system of defense.

Psychoneuroimmunology

- **Google search**
  349 000 results in 0,37 sec
- **Pubmed**
  1261 articles
- **the last decade**
  the no. of scientific papers using the term 'PSYCHONEUROIMMUNOLOGY' has more than doubled.

Naming of Cytokines

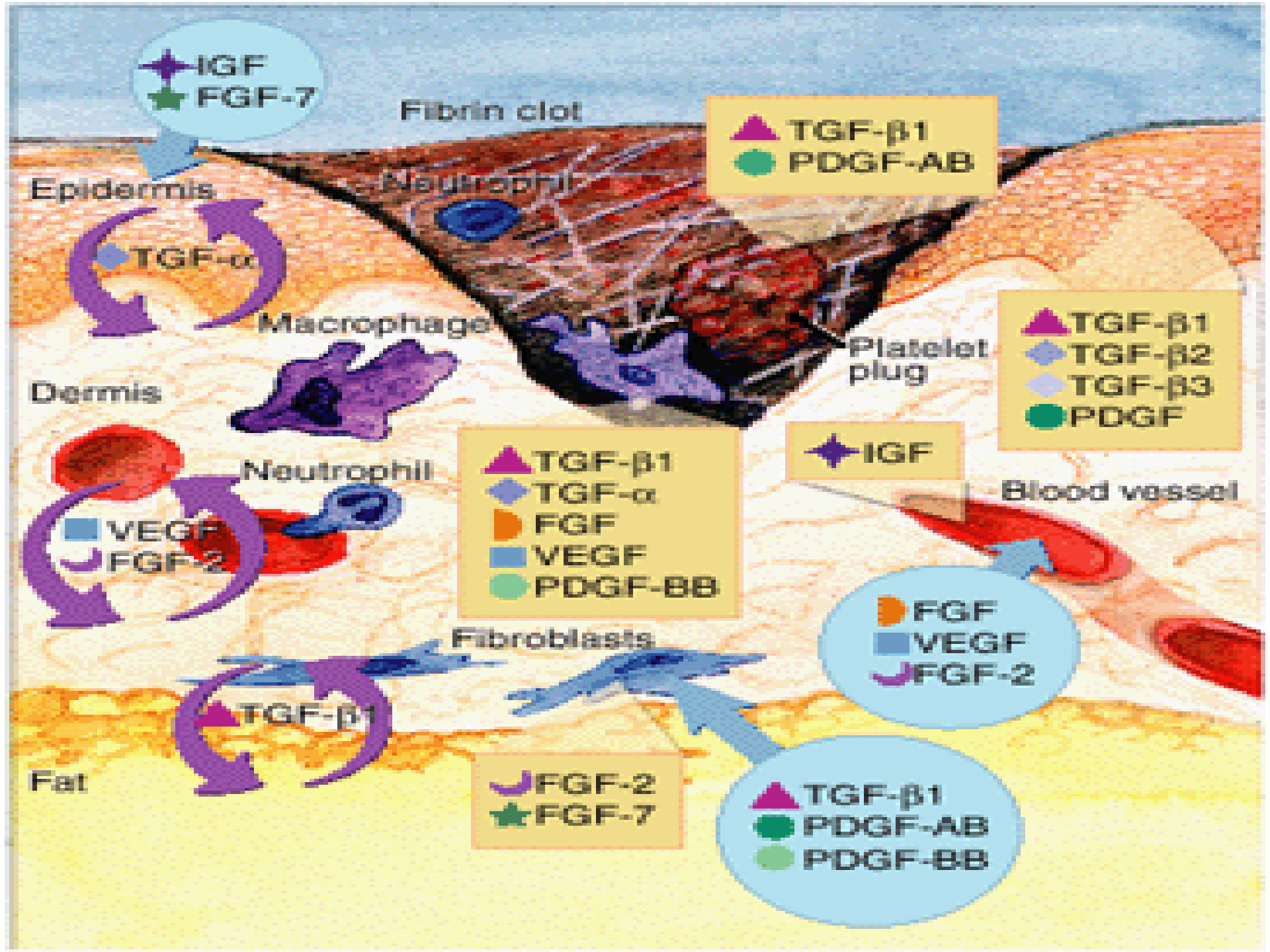
- 1. **Monokines** - produced by mononuclear phagocytes (monocytes)
- 2. **Lymphokine**s - produced by activated T cells, primarily helper T cells
- 3. **Interleukins** - cytokines made by one leukocyte and acting on other leukocytes
  4.**Chemokines-**cytokines with chemotactic activities


IL-12
T_H1
LT
IFN-γ
Macrophage
Cell-mediated immunity
STAT4
IL-12
T_H
STAT6
IL-4
B cell
IgE
T_H2
IL-4
IL-5
IL-6
IL-10
IL-13
Allergic responses
Anti-helminth responses
Eosinophil

Negative States

Bereavement	Decreased lymphocyte proliferation.
Pessimistic states	Decreased lymphocyte reactivity; decreased T-cell effectiveness.
Academic stress	Decreased NK cell activity; decreased T-cells; decrease in certain immune chemicals; increased susceptibility to herpes virus; decreased immunoglobulin A; increased blood levels of Epstein-Barr virus.
Depression	Decreased T-cells; decreased number and function of lymphocytes; decreased NK cells.
Loneliness	Decreased NK (Natural Killer Cell) activity.
Chronic stress	Decreased T-cells; decreased NK cells; decreased B-cells; increased levels of Epstein-Barr virus.
Divorce/separation poor marital quality	Decreased lymphocyte function; increased blood levels of Epstein-Barr virus; decreased T-cell effectiveness.
Expressed need for power and control	Decreased NK activity; decreased lymphocytes.
Negative behavior during discussions of marital problems	Decreased NK activity; decreased macrophages; increased blood levels of Epstein-Barr virus; increase in certain T-cells; decreased immunity by mitogen tests.

Cytokine	Cell source	Target	Actions
Proinflammatory Cytokines			
IL-1	Macrophage Dendritic cell	Lymphocytes Endothelial cell CNS Liver	Enhances responses Activates Fever, sickness behavior Synthesis and release of acute-phase proteins
IL-6	Macrophage Dendritic cell Endothelium Th2 cell	Liver B cell	Synthesis and release of acute-phase proteins Proliferation
TNF-alpha	Macrophage Dendritic cell Th1 cell	Endothelial cell Neutrophil Hypothalamus Liver	Activates vascular endothelium – increased permeability and stimulates adhesion molecules Activates Fever Synthesis and release of acute-phase proteins
Anti-inflammatory Cytokines			
IL-10	Macrophage Th2	Macrophage Dendritic cell	Inhibits IL-12 production Inhibits pro-inflammatory cytokine synthesis
Il-12	Macrophage Dendritic cell	CD4+T helper cell NK cell	Th1 differentiation IFN-gamma synthesis
Cytokines Involved in the Acquired Immune Response			
IL-2	T cell	T cell NK Cell B cell	Proliferation Activation and proliferation Proliferation
IL-4	Th2 cell Mast cell	T cell B cell Macrophage	Th2 cell development/proliferation Isotype switch to IgE Inhibit IFN-gamma activation
IFN-gamma	Th1 cell Cytotoxic T cell NK cell	T cell B cell Macrophage	Th1 cell development Isotype switch to IgG Activation


IGF
FGF-7
Fibrin clot
TGF-β1
PDGF-AB
Epidermis
Neutrophil
TGF-α
Macrophage
Platelet plug
TGF-β1
TGF-β2
TGF-β3
PDGF
Dermis
TGF-β1
TGF-α
FGF
VEGF
PDGF-BB
IGF
Neutrophil
Blood vessel
VEGF
FGF-2
FGF
VEGF
FGF-2
Fibroblasts
TGF-β1
Fat
FGF-2
FGF-7
TGF-β1
PDGF-AB
PDGF-BB

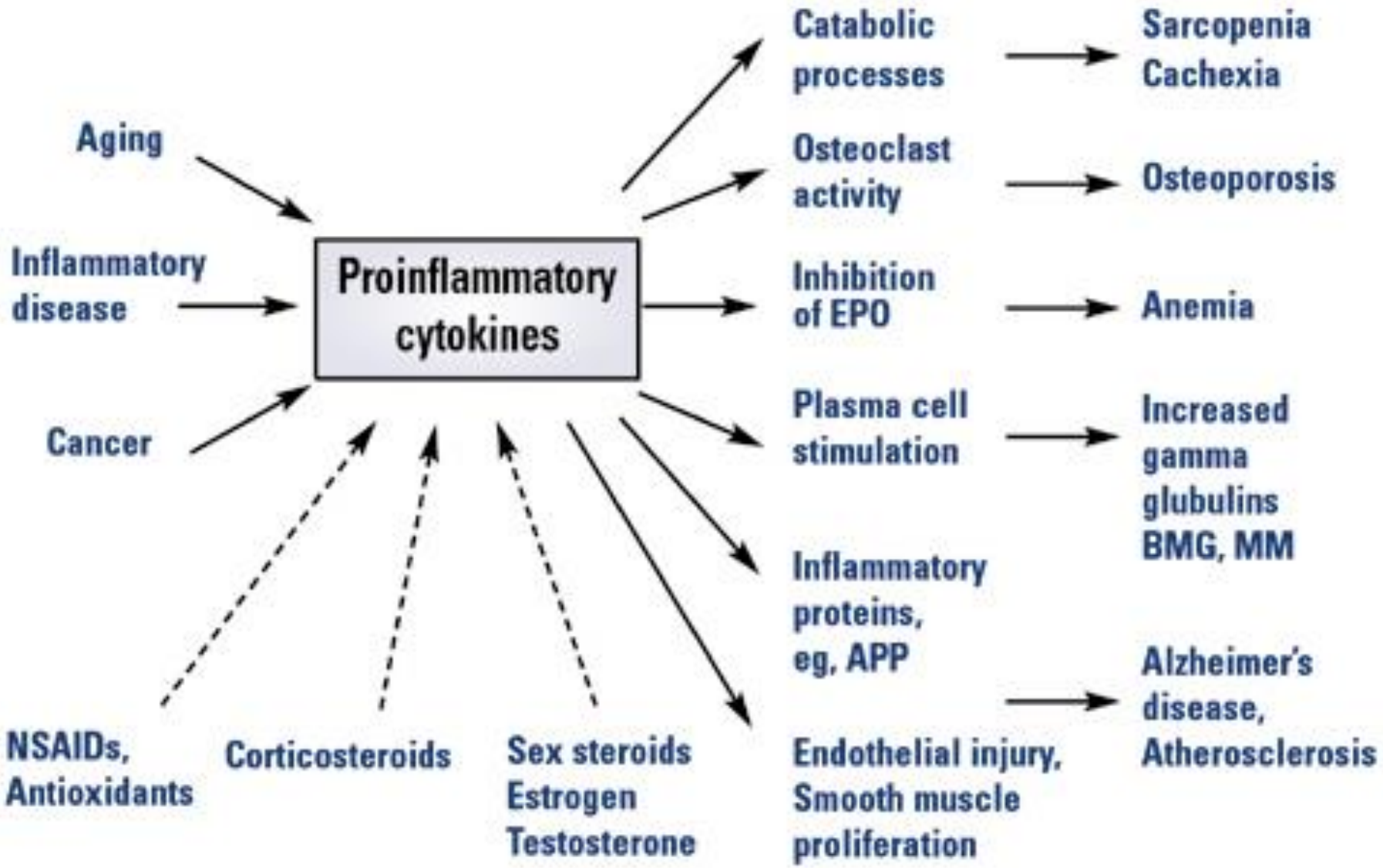


Fig 7. Role of proinflammatory cytokines in degenerative diseases and aging.

Neurodegeneration Hypothesis of Depression

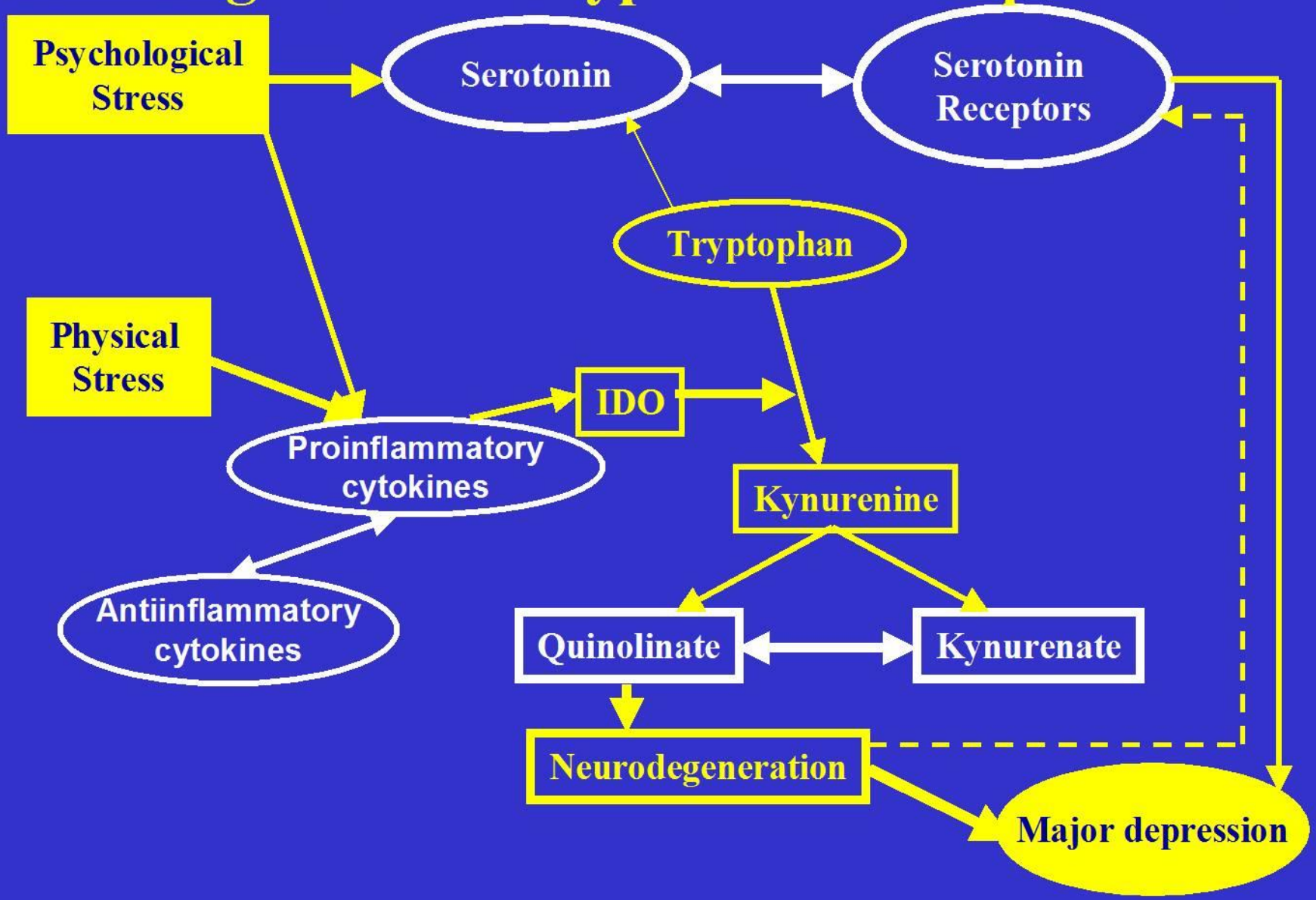
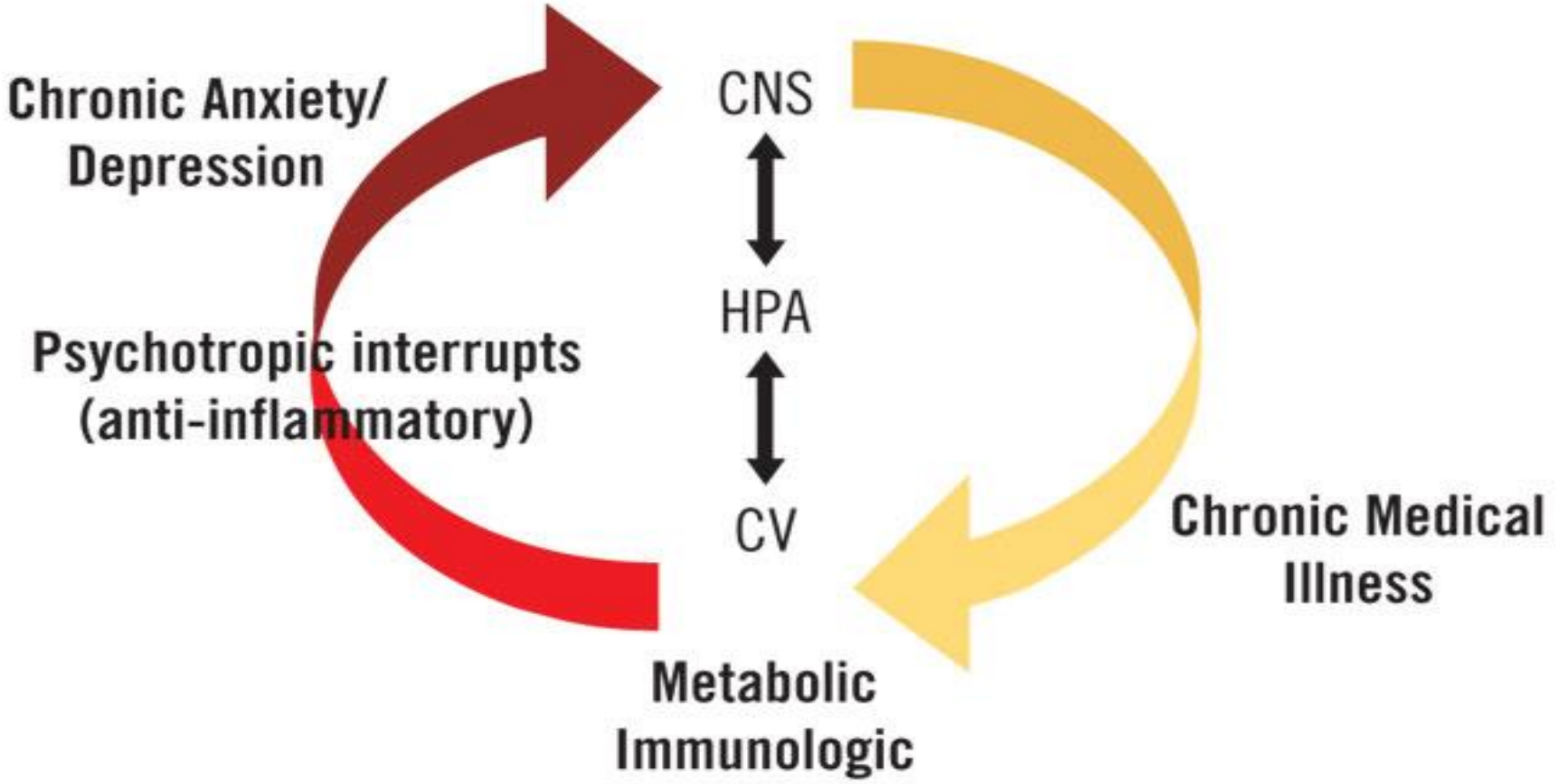


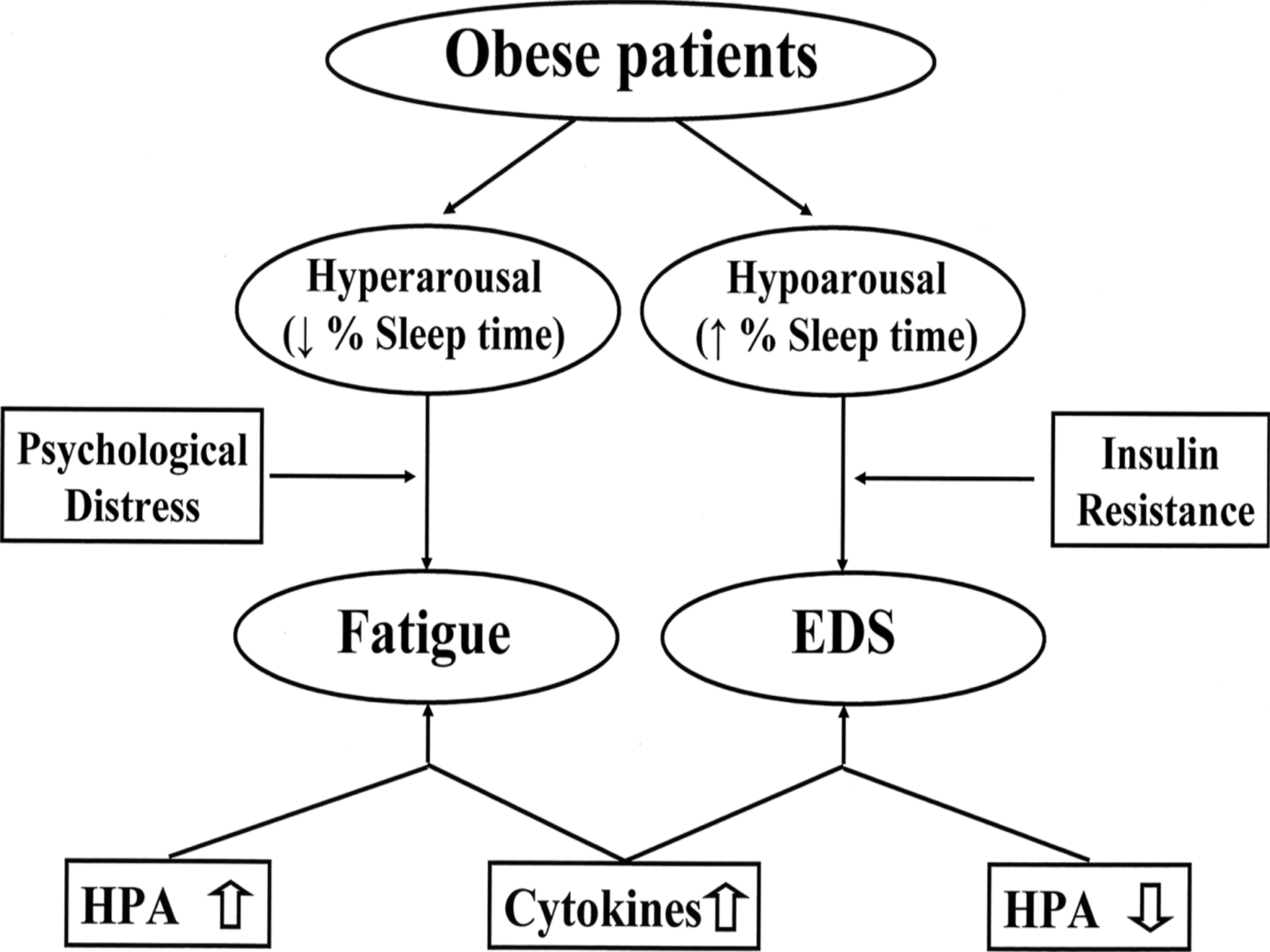
FIGURE 3

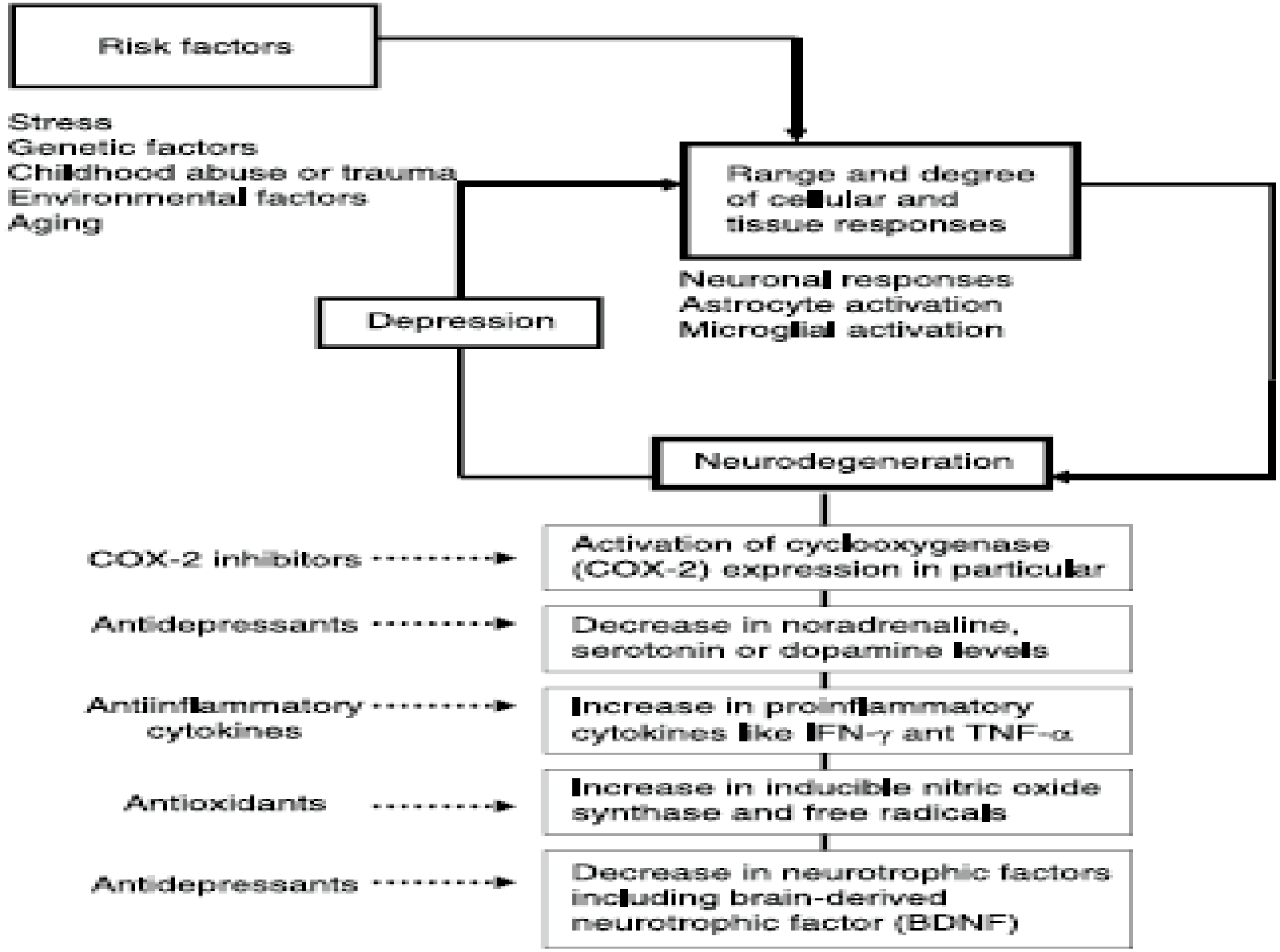
MEDICAL ILLNESS ↔ ANXIETY/DEPRESSION PRO-INFLAMMATORY CHRONICITY CYCLE[33,36]



CNS=central nervous system; HPA=hypothalamic pituitary adrenal axis; CV=cardiovascular.

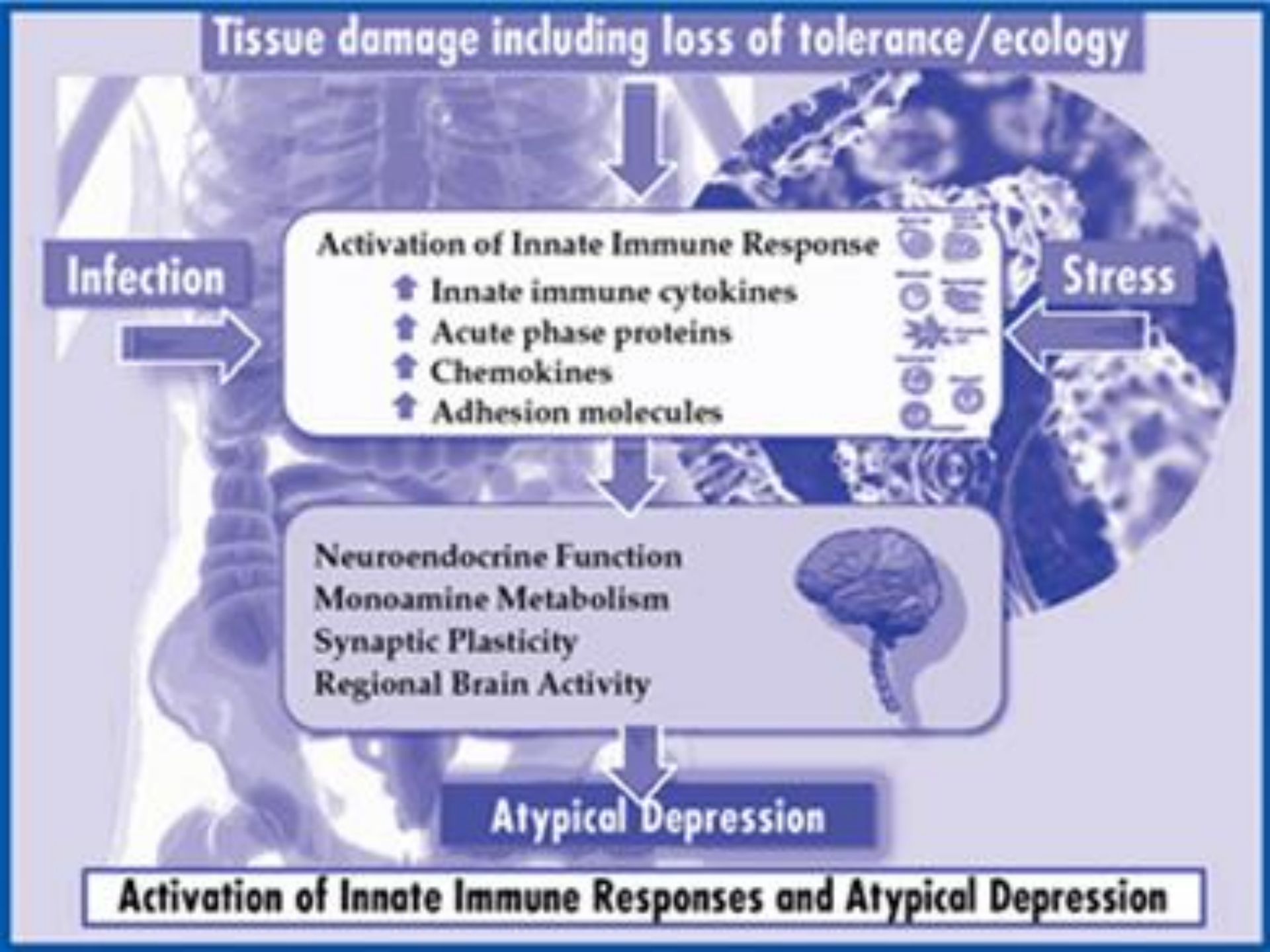
Goddard ER, Barth KS, Lydiard RB. *Primary Psychiatry*. Vol 14, No 4. 2007.


Obese patients
Hyperarousal
(↓ % Sleep time)
Hypoarousal
(↑ % Sleep time)
Psychological
Distress
Insulin
Resistance
Fatigue
EDS
HPA ⇧
Cytokines⇧
HPA ⇩


Risk factors
Stress
Genetic factors
Childhood abuse or trauma
Environmental factors
Aging
Range and degree of cellular and tissue responses
Neuronal responses
Astrocyte activation
Microglial activation
Depression
Neurodegeneration
COX-2 inhibitors
Activation of cyclooxygenase (COX-2) expression in particular
Antidepressants
Decrease in noradrenaline, serotonin or dopamine levels
Antiinflammatory cytokines
Increase in proinflammatory cytokines like IFN-γ ant TNF-α
Antioxidants
Increase in inducible nitric oxide synthase and free radicals
Antidepressants
Decrease in neurotrophic factors including brain-derived neurotrophic factor (BDNF)

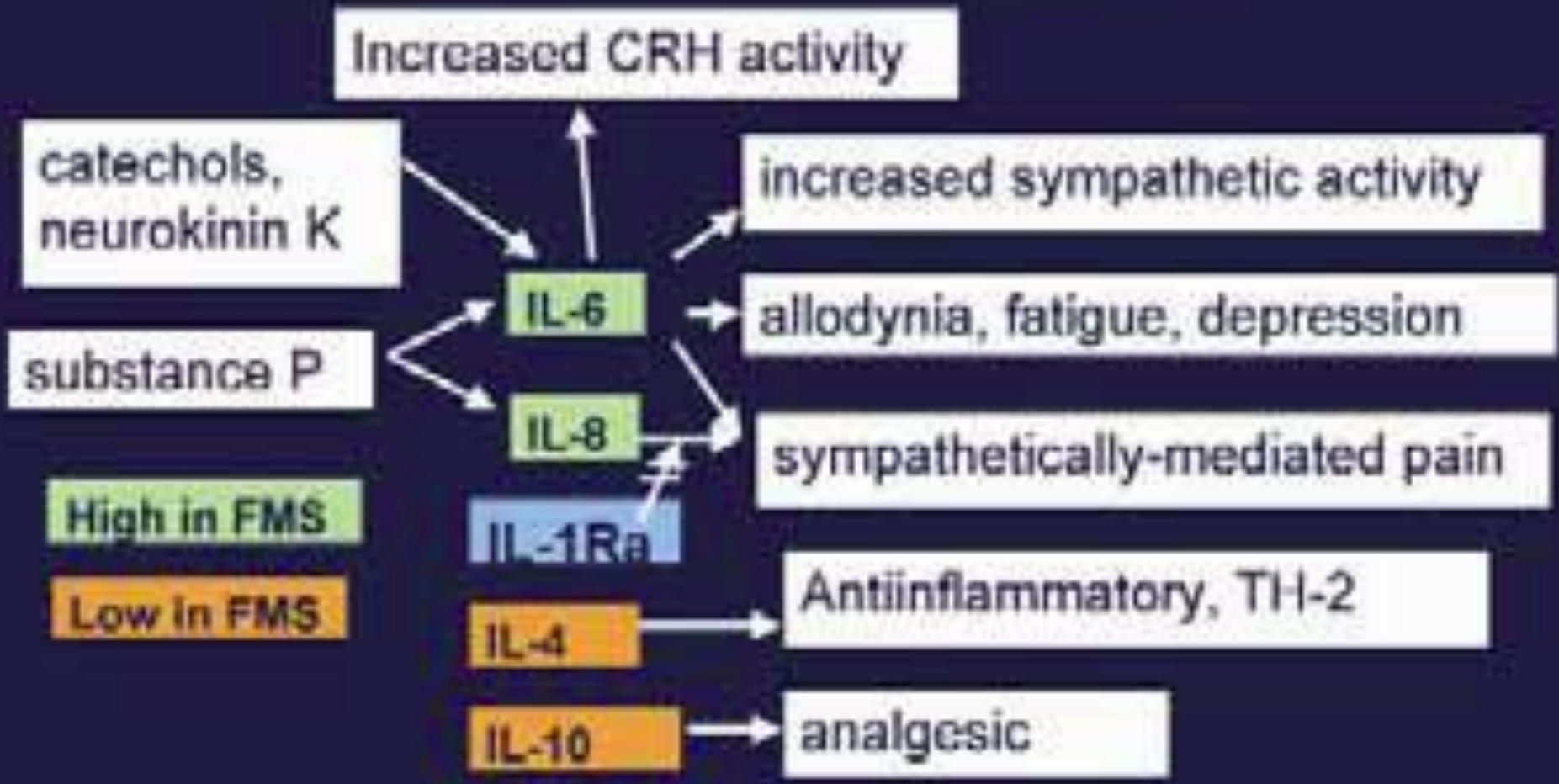
Some affects of the inflammatory cytokines on neural function and pathology

Effect	Cytoline	Reference
oligodendrocyte cytotoxicity and demyelination	TNF-α	Selmaj et al. (1991)
increased neurite outgrowth and decreased neuronal cell survival	IL-6	Alstiel and Sperber (1991)
stimulation of the synthesis of the β-amyloid precursor protein	IL-1, IL-6	Goldgaber et al. (1989), Alstiel and Sperber (1991)
delusions, hallucinations, paranoia, agitation, anorexia, fatigue and severe cognitive charges	IL-2	Denicoff et al. (1987)
astrocyte proliferation	TNF-α, IL-6	Barna et al. (1990), Selmaj et al. (1990)
reduction of extracellular acetylcholine in the hippocampus	IL-1β	Rada et al. (1991)
increases the secretion of glucocorticoids via the HPA axis	IL-1, IL-2, IL-6, TNF-α	Herrnus and Sweep (1990)



Activation of Innate Immune Responses and Atypical Depression

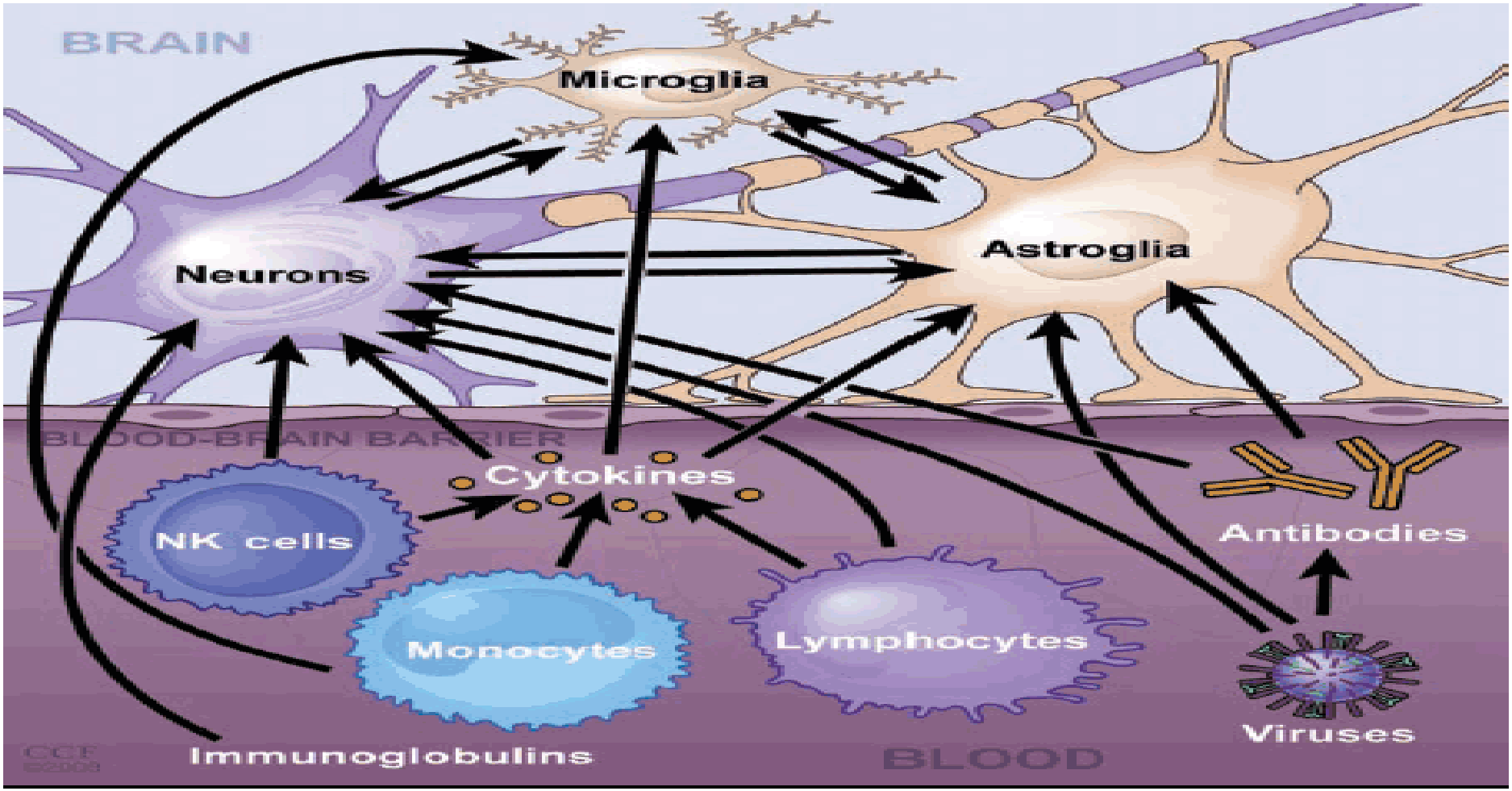
Fibromyalgia Cytokine Hypothesis



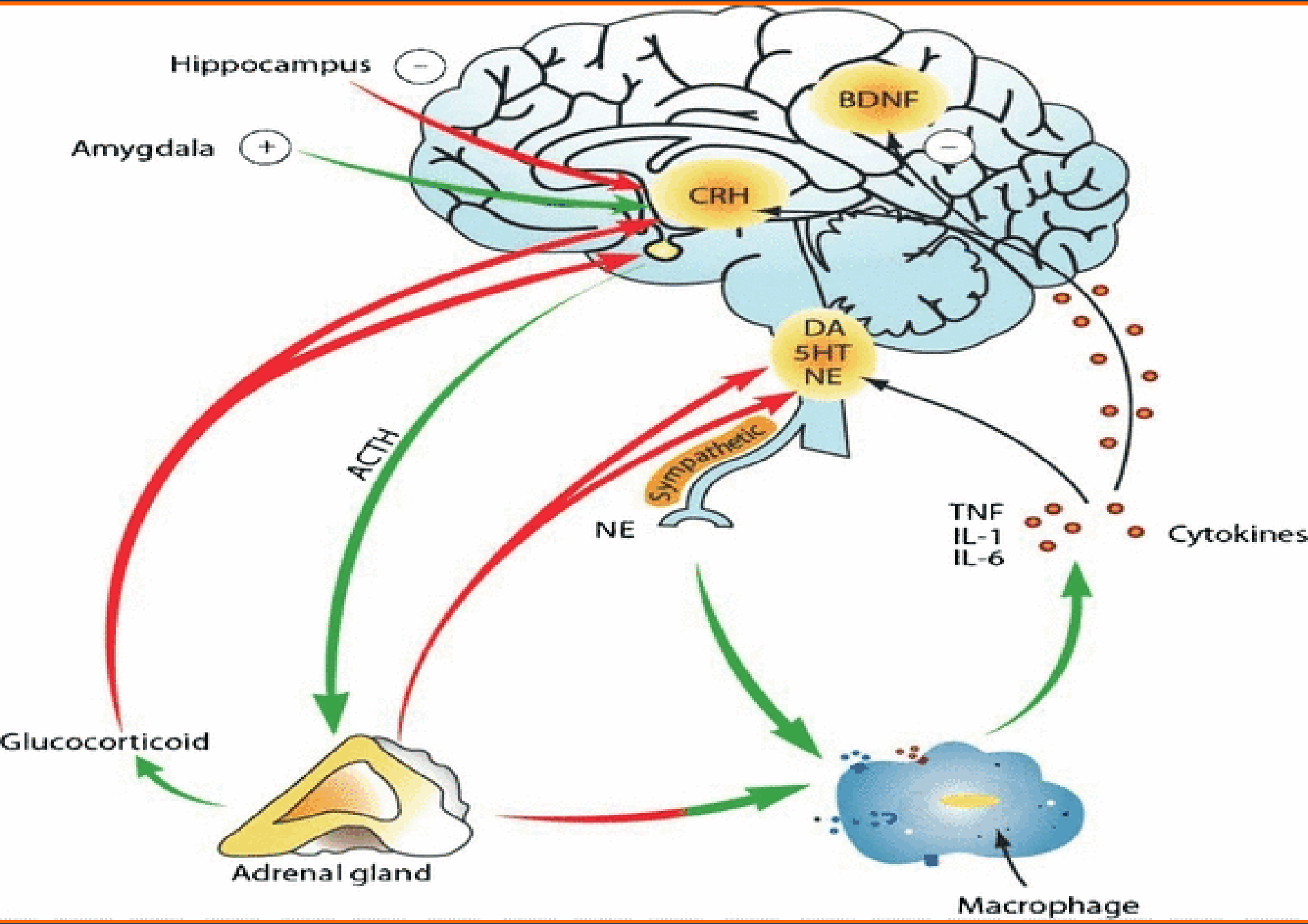
Adapted from Wallace D.J. et al. Rheumatol 40: 743, 2001

Figure 1

Interaction between the immune system and schizophrenia



Different immune reactions directly influence neuronal proliferation, differentiation, migration, and apoptosis. Microglia become activated after stress, trauma, or infection. They react with tissue repair or induction of immune responses: phagocytosis, secretion of cytokines, neuronal growth factors, and antigen presentation. Microglial activation may sustain chronic brain inflammation.[2]
NK, natural killer.



General Model

Etiology: Multiple convergent factors
(e.g., DNA, gene expression, viruses, toxins, nutrition, birth injury, psychological experiences)

↓

Pathophysiology: Brain development from conception to early adulthood
(e.g., neuron formation, migration, synaptogenesis, pruning, apoptosis, activity dependent changes)

↓

Anatomic and functional disruption in neural connectivity and communication

↓

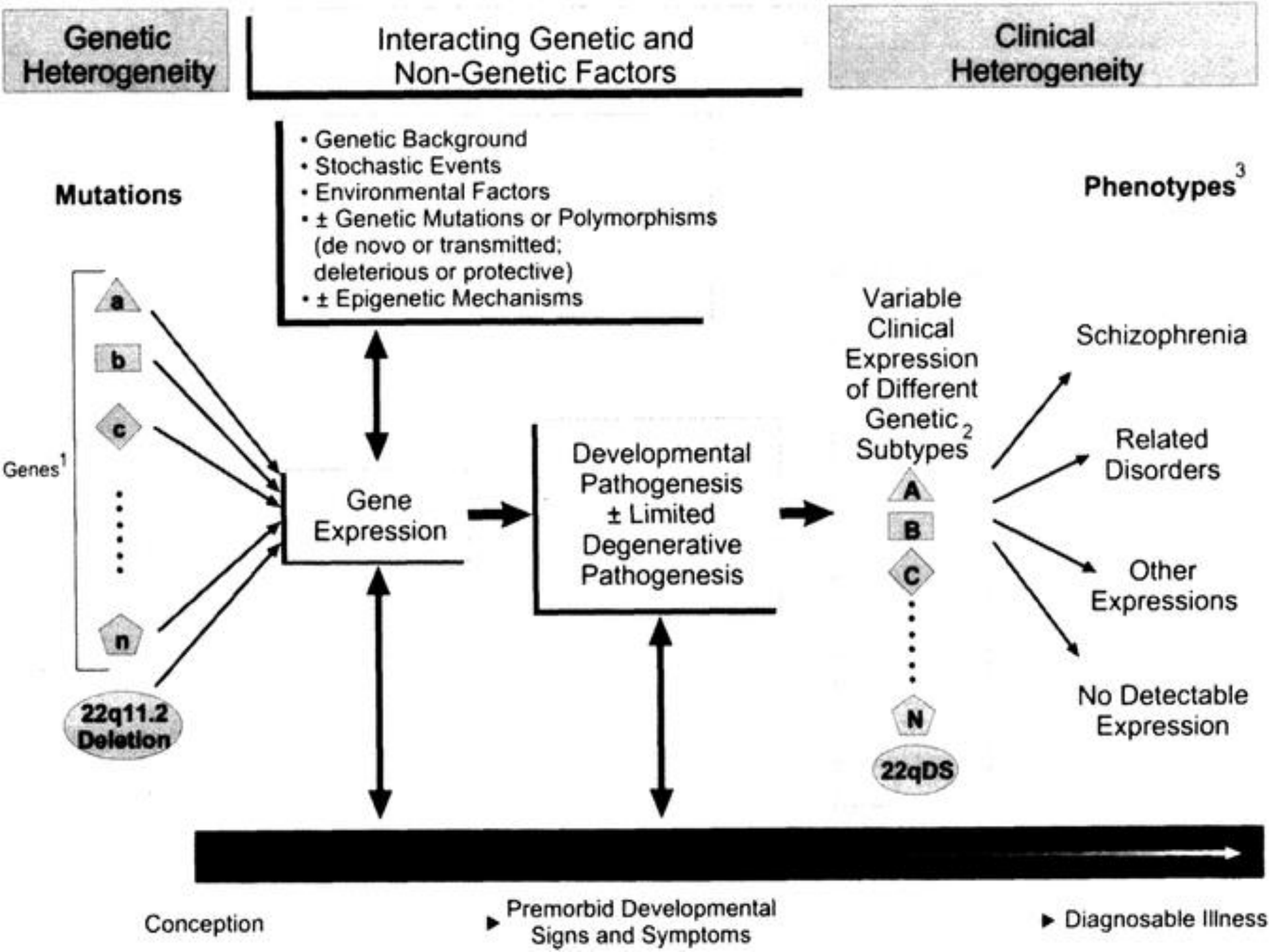
Impairment in a fundamental cognitive process

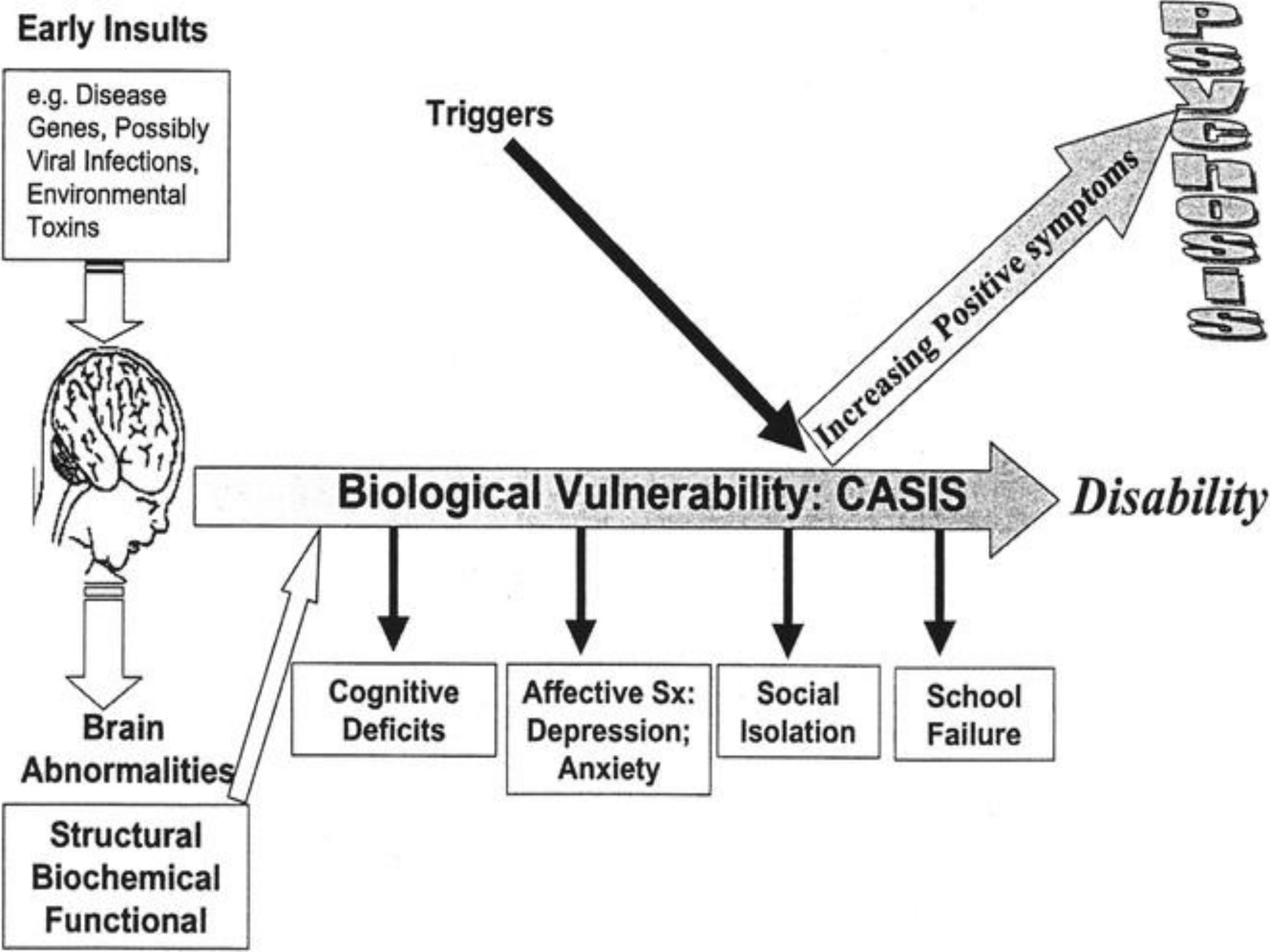
↓

Phenomenology: Impairment in one or more second-order cognitive processes
(e.g., attention, memory, language, emotion)

↓

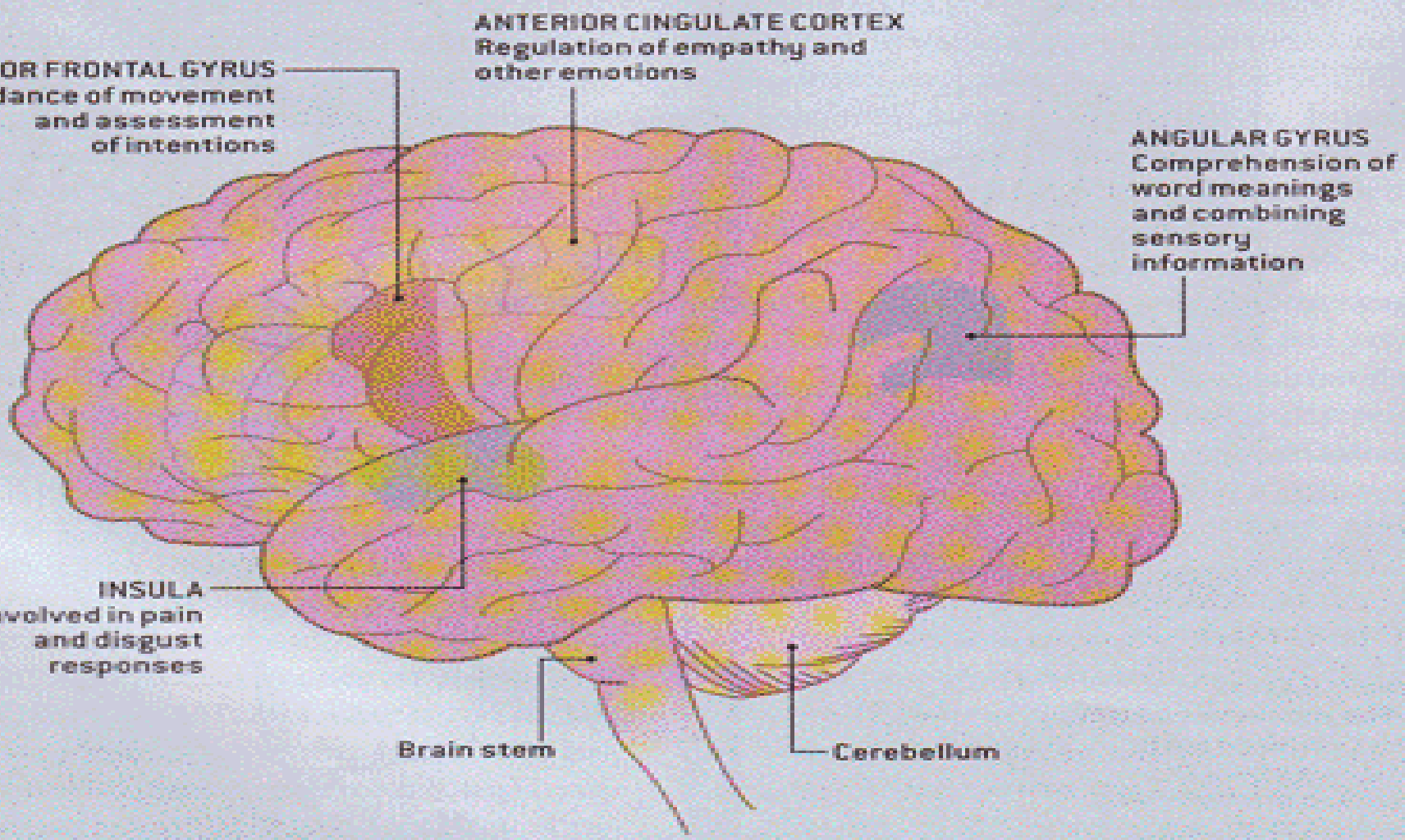
Phenomenology: Symptoms of schizophrenia
(e.g., hallucinations, delusions, negative symptoms, disorganized speech)


Genetic Heterogeneity
Interacting Genetic and Non-Genetic Factors
Clinical Heterogeneity
• Genetic Background
• Stochastic Events
• Environmental Factors
• ± Genetic Mutations or Polymorphisms (de novo or transmitted; deleterious or protective)
• ± Epigenetic Mechanisms
Mutations
Phenotypes[3]
Genes[1]
a
b
c
n
22q11.2 Deletion
Gene Expression
Developmental Pathogenesis ± Limited Degenerative Pathogenesis
Variable Clinical Expression of Different Genetic Subtypes[2]
A
B
C
N
22qDS
Schizophrenia
Related Disorders
Other Expressions
No Detectable Expression
Conception
Premorbid Developmental Signs and Symptoms
Diagnosable Illness

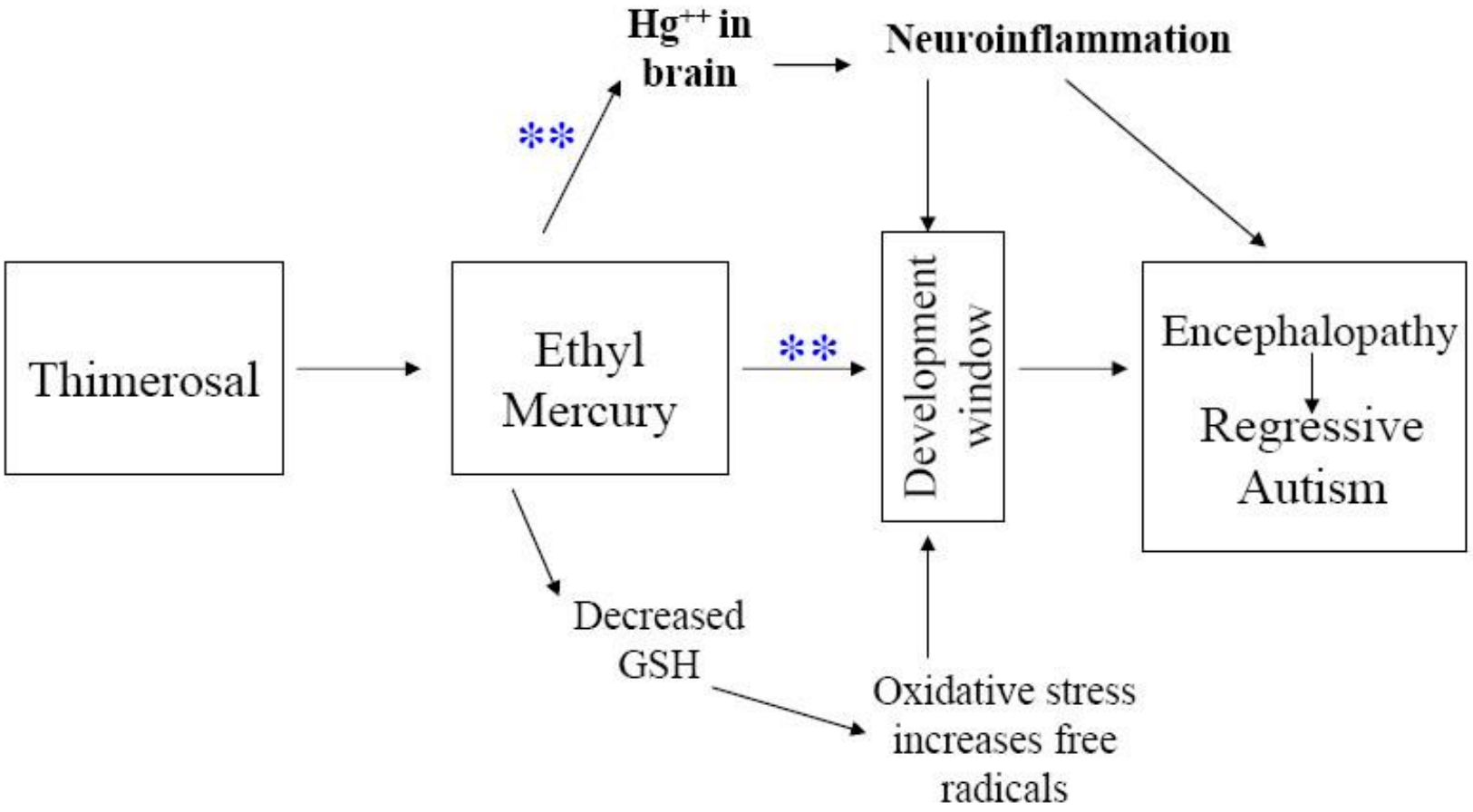

Early Insults
e.g. Disease Genes, Possibly Viral Infections, Environmental Toxins
Triggers
Increasing Positive symptoms
Psychosis
Biological Vulnerability: CASIS
Disability
Brain Abnormalities
Structural Biochemical Functional
Cognitive Deficits
Affective Sx: Depression; Anxiety
Social Isolation
School Failure

THE ANATOMY OF AUTISM

People with autism show reduced mirror neuron activity in the inferior frontal gyrus, a part of the brain's premotor cortex, perhaps explaining their inability to assess the intentions of others. Dysfunctions of mirror neurons in the insula and anterior cingulate cortex may cause related symptoms, such as the absence of empathy, and deficits in the angular gyrus may result in language difficulties. People with autism also have structural changes in the cerebellum and brain stem.



Plausible Paths for Ethyl Mercury Toxicity



**Hypersusceptibility?

Aposhian

Hypothalamus

Mammillary body

Median eminence

Optic chiasm

Infundibulum

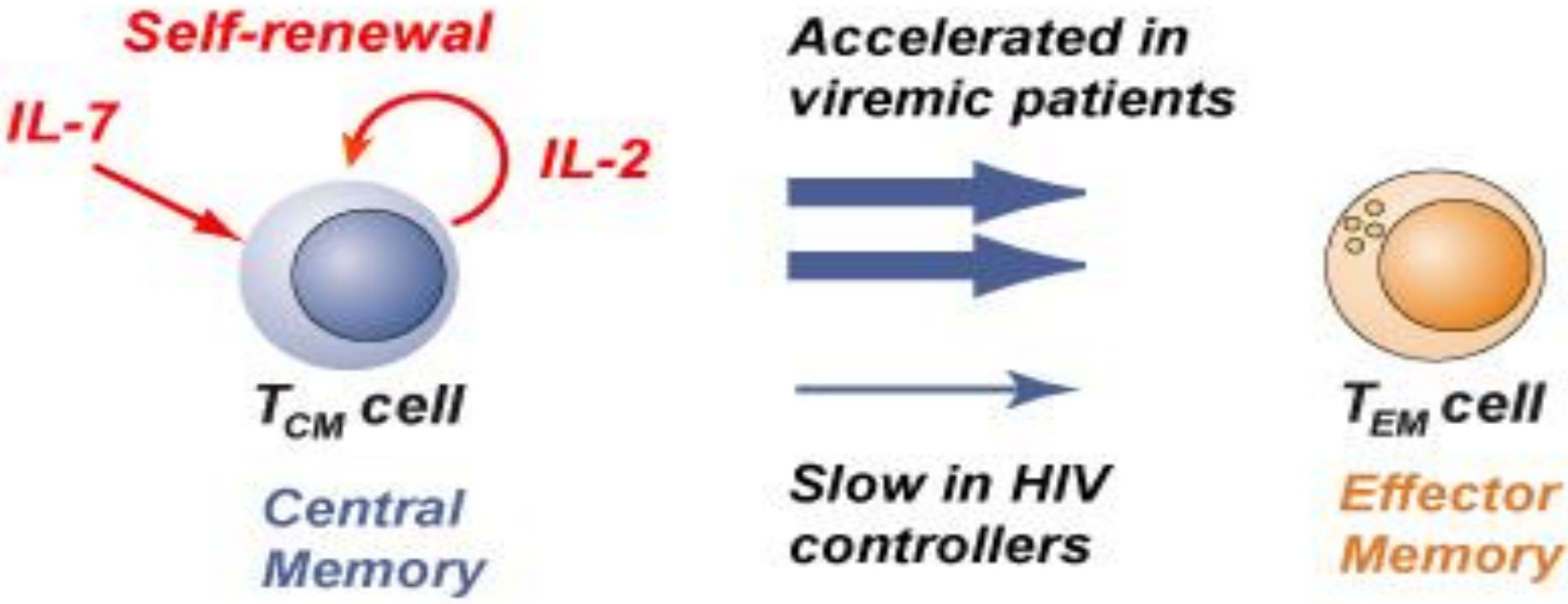
Anterior pituitary

- Pars tuberalis
- Pars intermedia
- Pars distalis

Posterior pituitary

- Infundibular stalk
- Pars nervosa

Hypophyseal fossa in sella turcica of sphenoid bone



Key role of central memory (CM) CD4+ T cells cells in HIV pathogenesis: The differentiation of CM to effector memory CD4+ T cells is accelerated in viremic patients, leading to the exhaustion of the CM pool. In contrast, CM CD4+ T cells are preserved in HIV controllers, allowing the persistence of an efficient antiviral response in the long term.

Metabolic Syndrome

Cytokine Imbalance

TNF

Pro-inflammatory

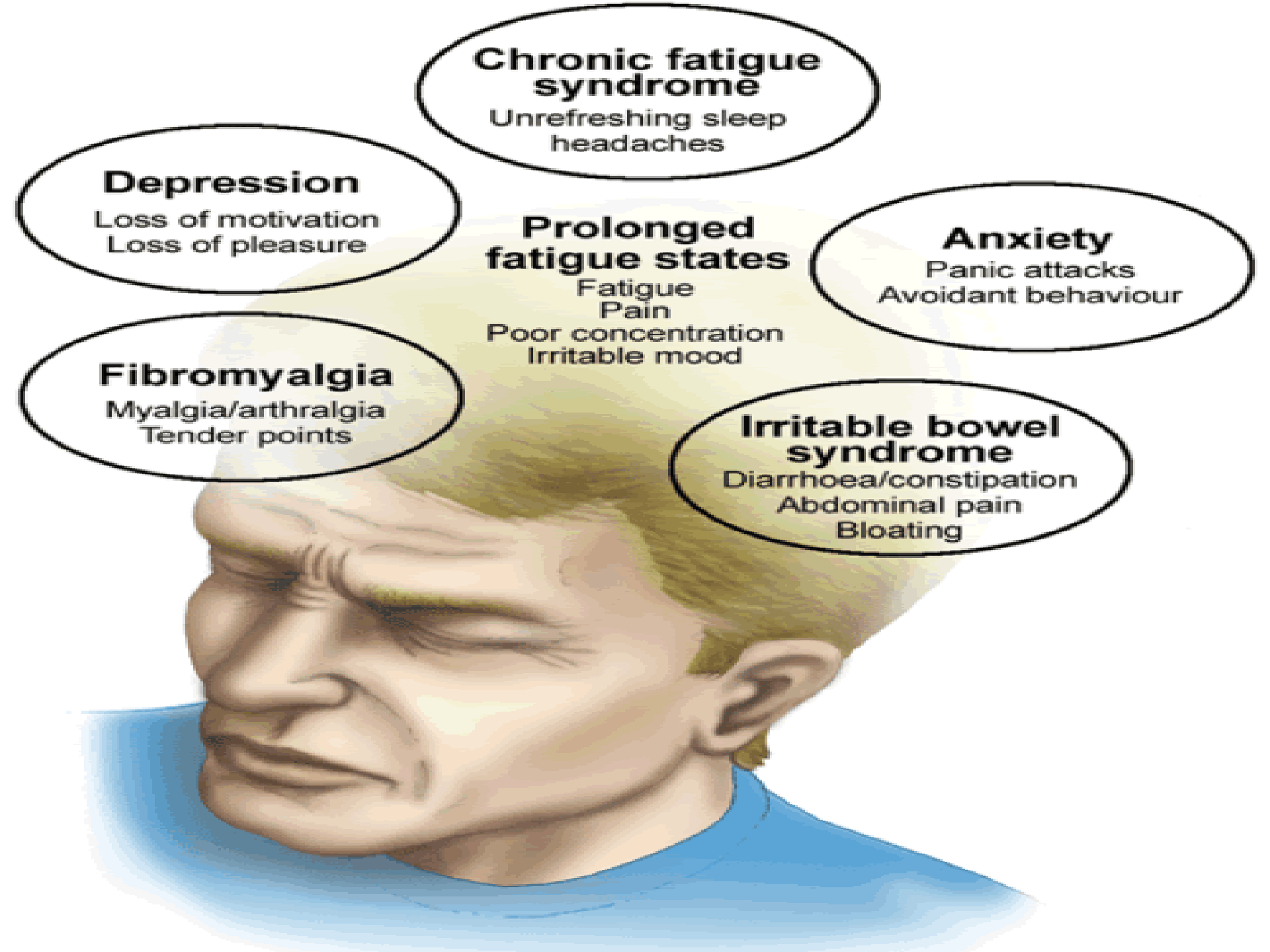
- Pro-apoptotic
- Recruits WBC's
- Promotes insulin resistance

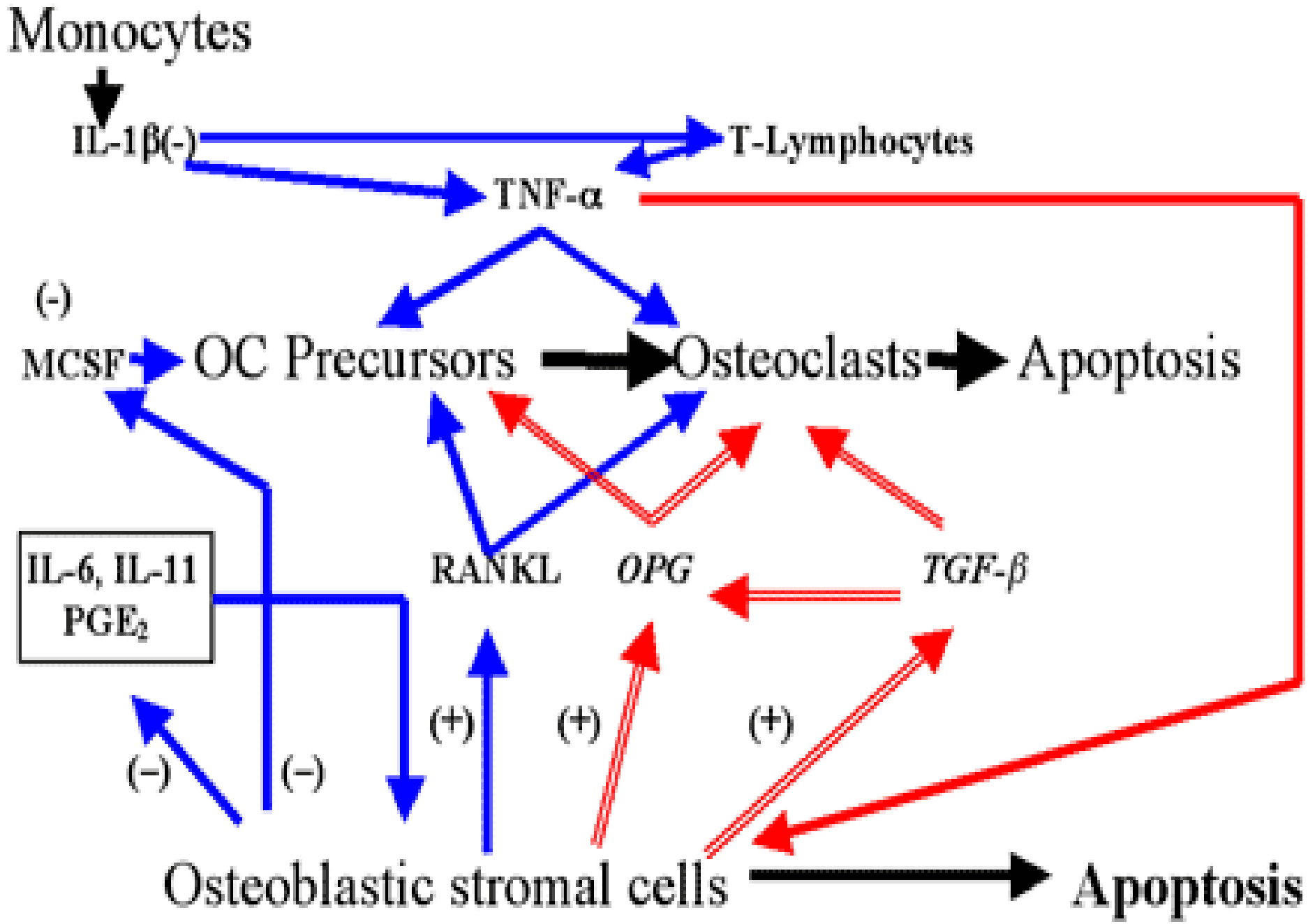
Adiponectin

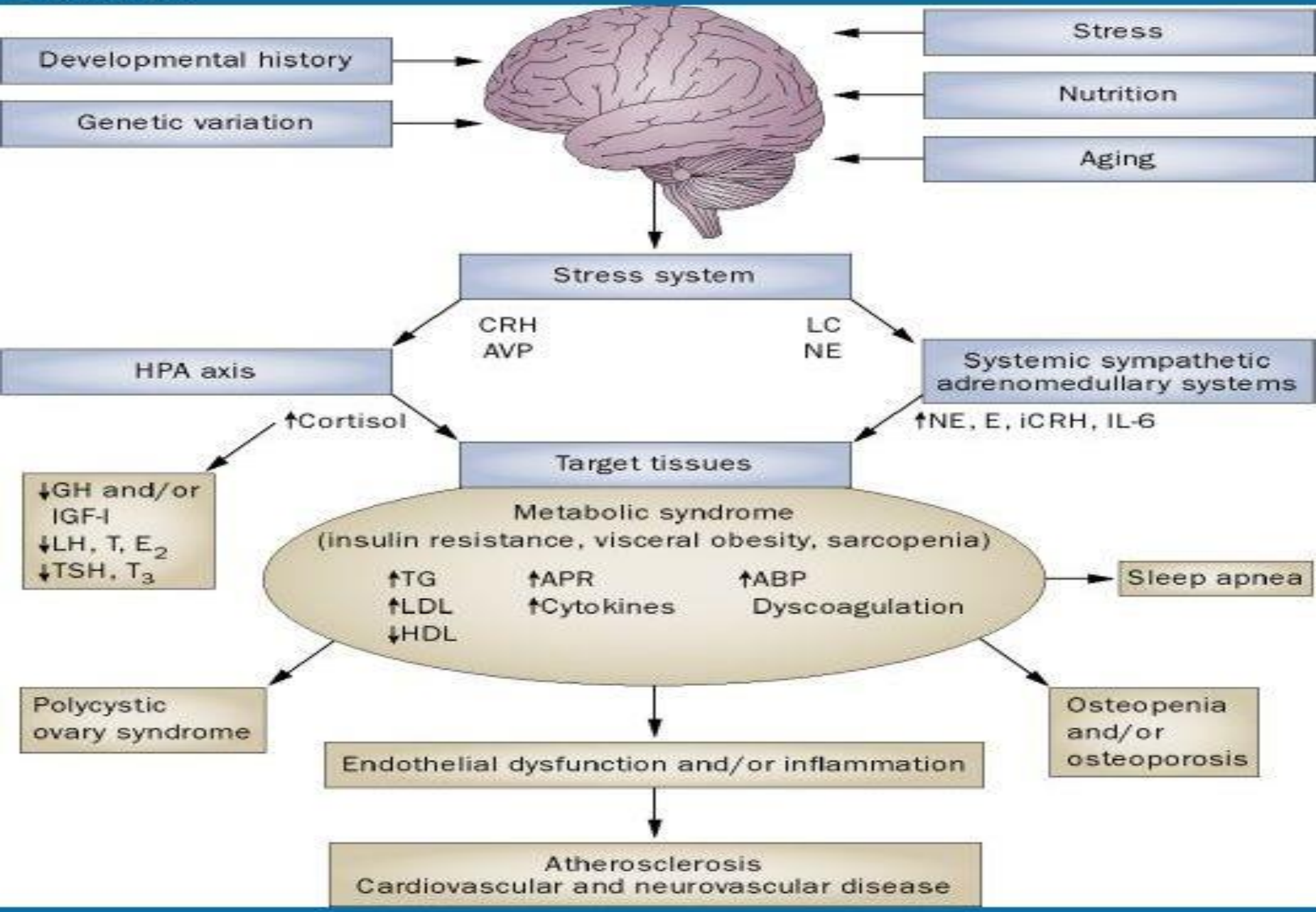
Anti-inflammatory

- Inhibits FA uptake
- Stimulates FA oxidation & lipid export
- Enhances insulin sensitivity

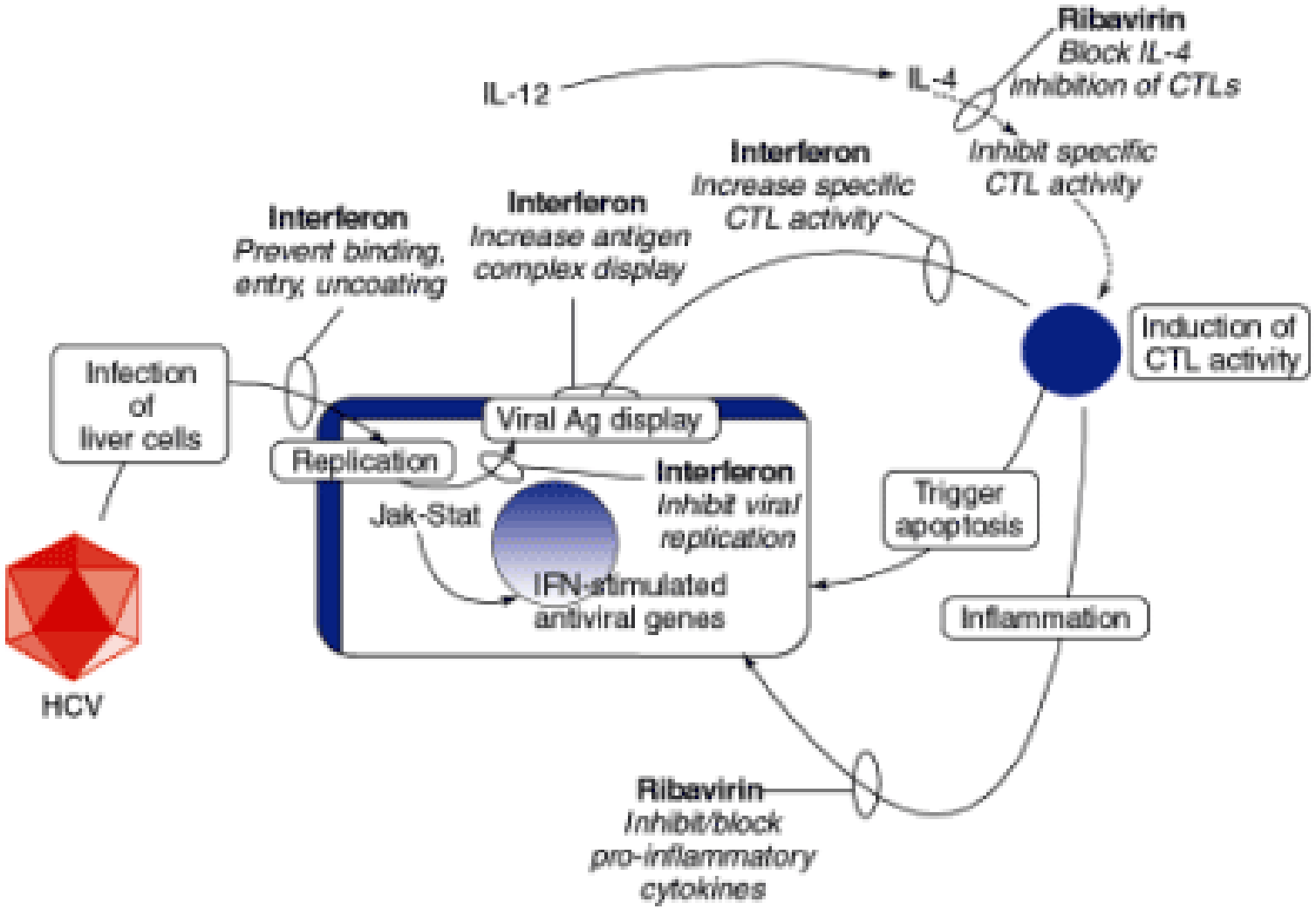
Steatosis (NAFL) + cell death + inflammation (NASH) & insulin resistance


Chronic fatigue syndrome
Unrefreshing sleep
headaches
Depression
Loss of motivation
Loss of pleasure
Prolonged fatigue states
Fatigue
Pain
Poor concentration
Irritable mood
Anxiety
Panic attacks
Avoidant behaviour
Fibromyalgia
Myalgia/arthralgia
Tender points
Irritable bowel syndrome
Diarrhoea/constipation
Abdominal pain
Bloating

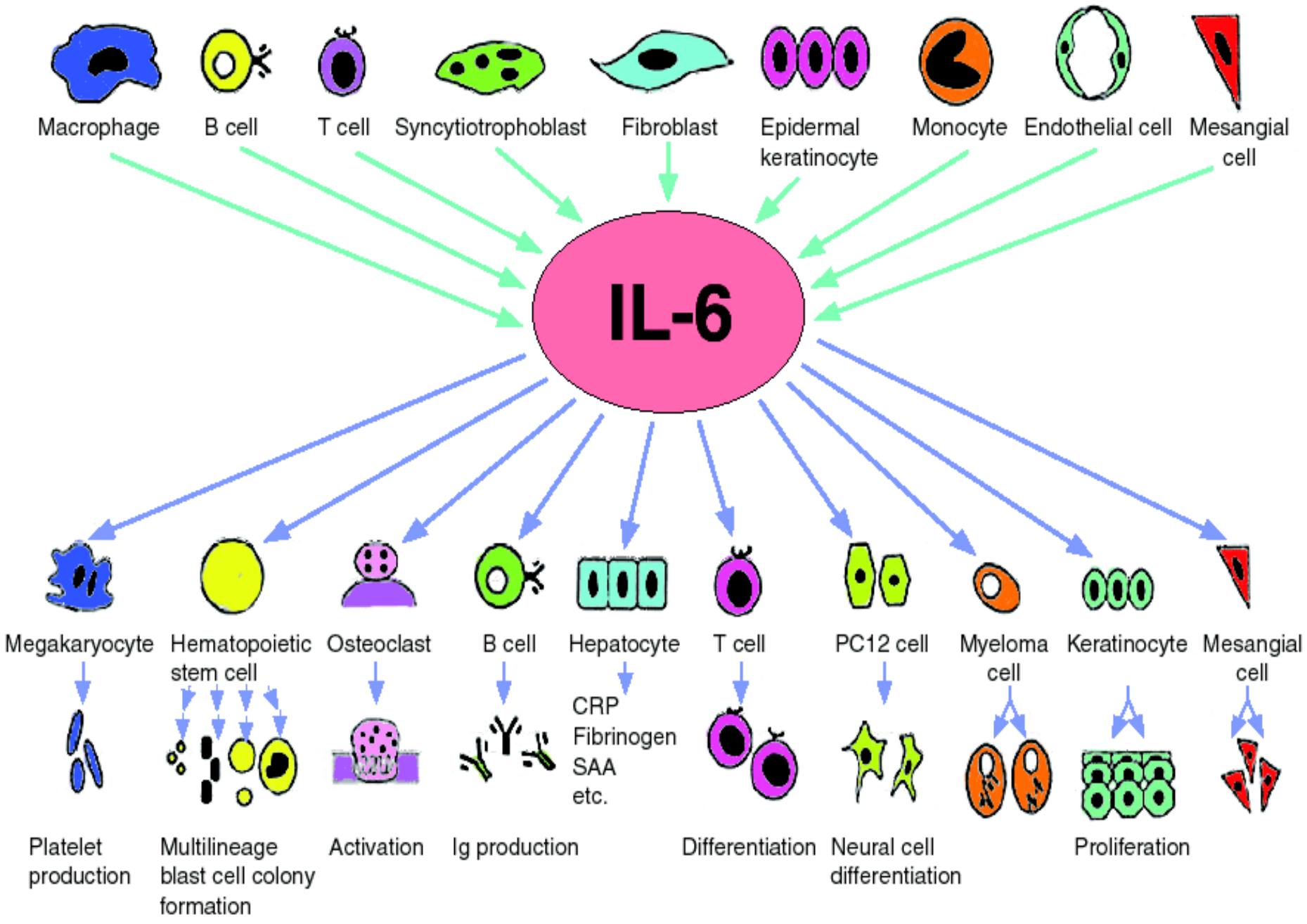

Monocytes
IL-1β(-)
T-Lymphocytes
TNF-α
(-)
MCSF
OC Precursors
Osteoclasts
Apoptosis
IL-6, IL-11
PGE2
RANKL
OPG
TGF-β
(+)
(+)
(+)
(–)
(–)
Osteoblastic stromal cells
Apoptosis

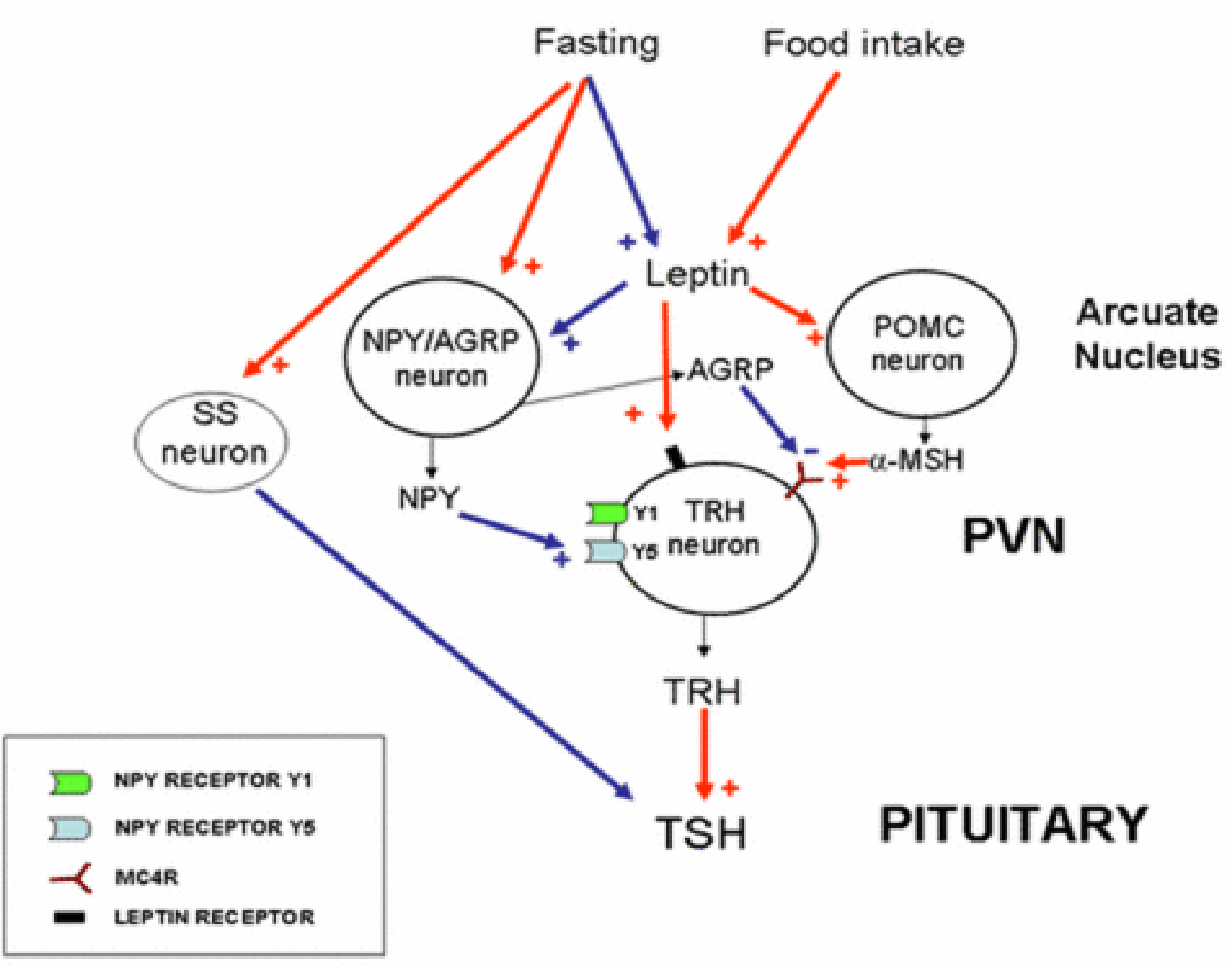


Proposed Mechanism of Interferon and Ribavirin on Liver Injury In Chronic HCV Infection



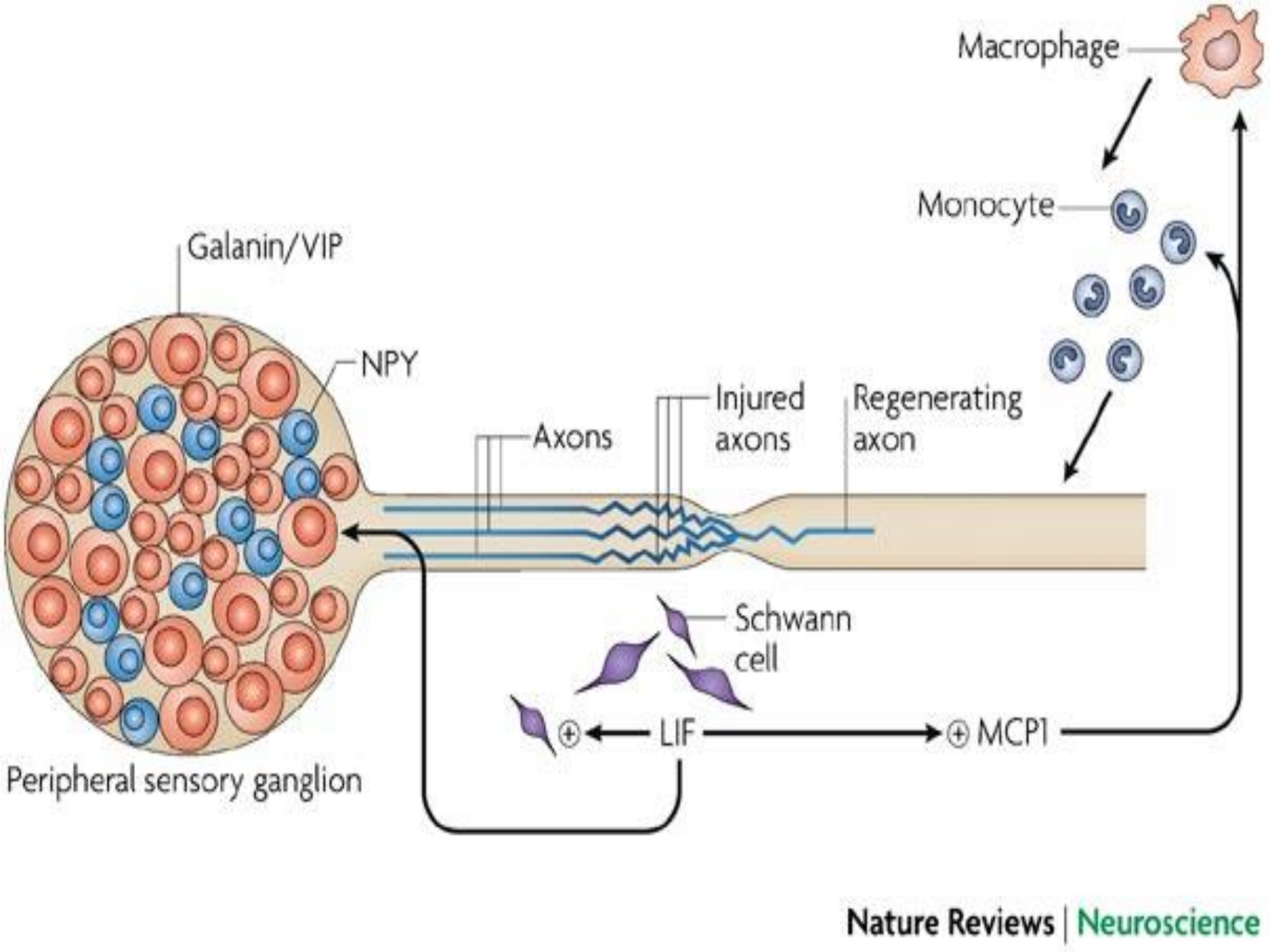
Davis GL. *Semin Liver Dis*. 1999;19(suppl 1):49-55. Reprinted with permission.

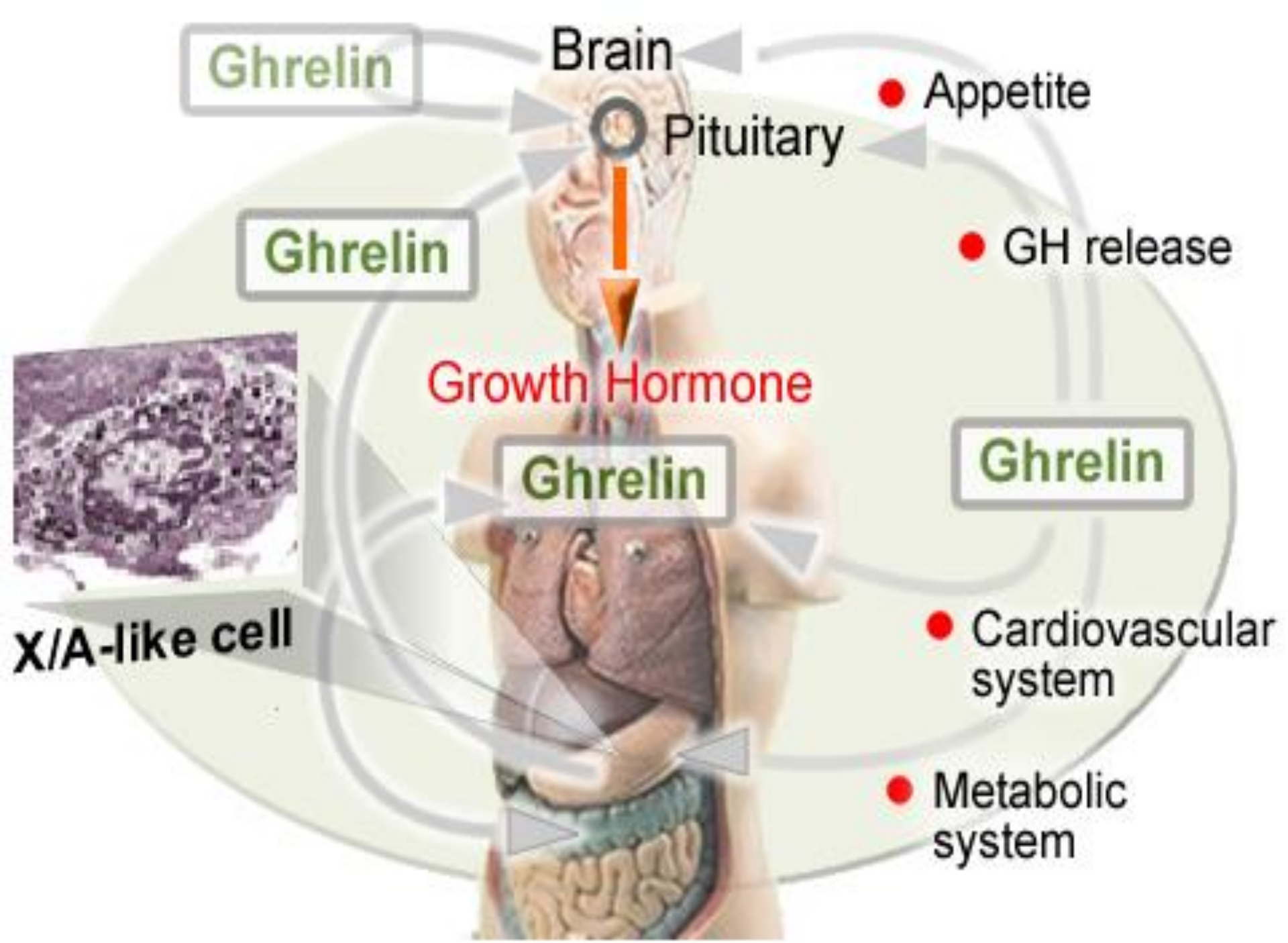


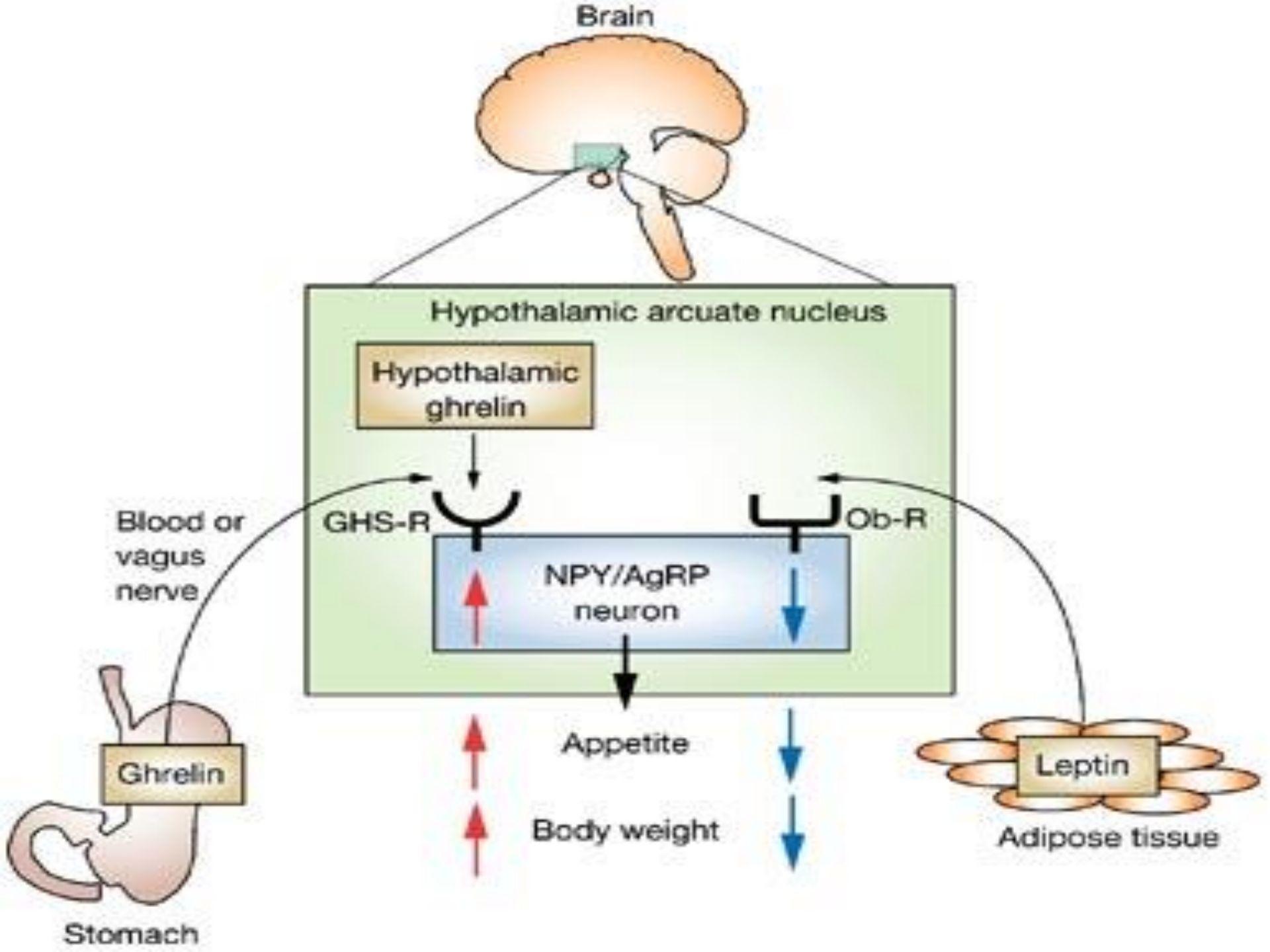

Fasting
Food intake
Leptin
NPY/AGRP neuron
POMC neuron
Arcuate Nucleus
AGRP
SS neuron
α-MSH
NPY
Y1
Y5
TRH neuron
PVN
TRH
TSH
PITUITARY
NPY RECEPTOR Y1
NPY RECEPTOR Y5
MC4R
LEPTIN RECEPTOR

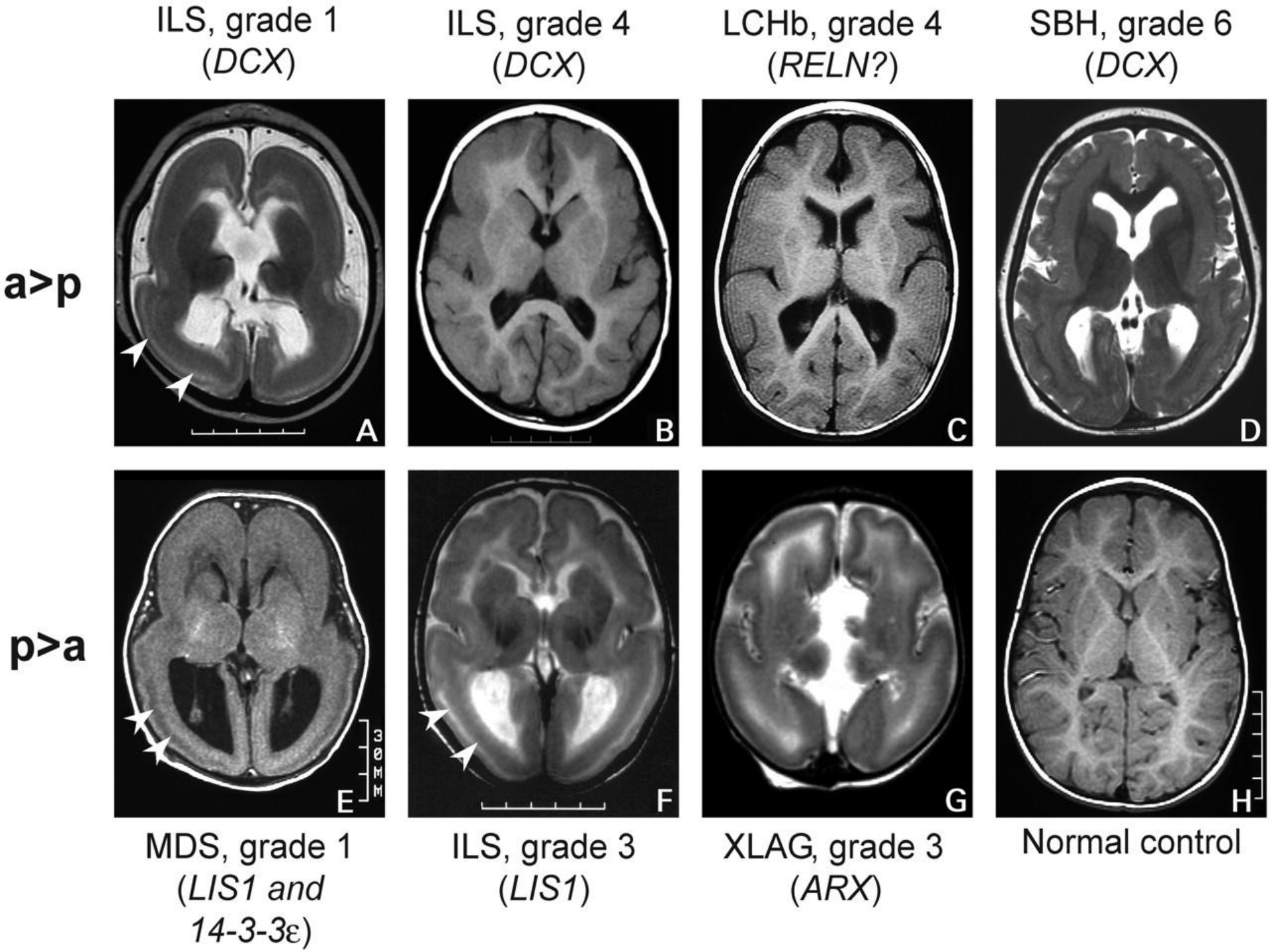
THE INTERLEUKINS

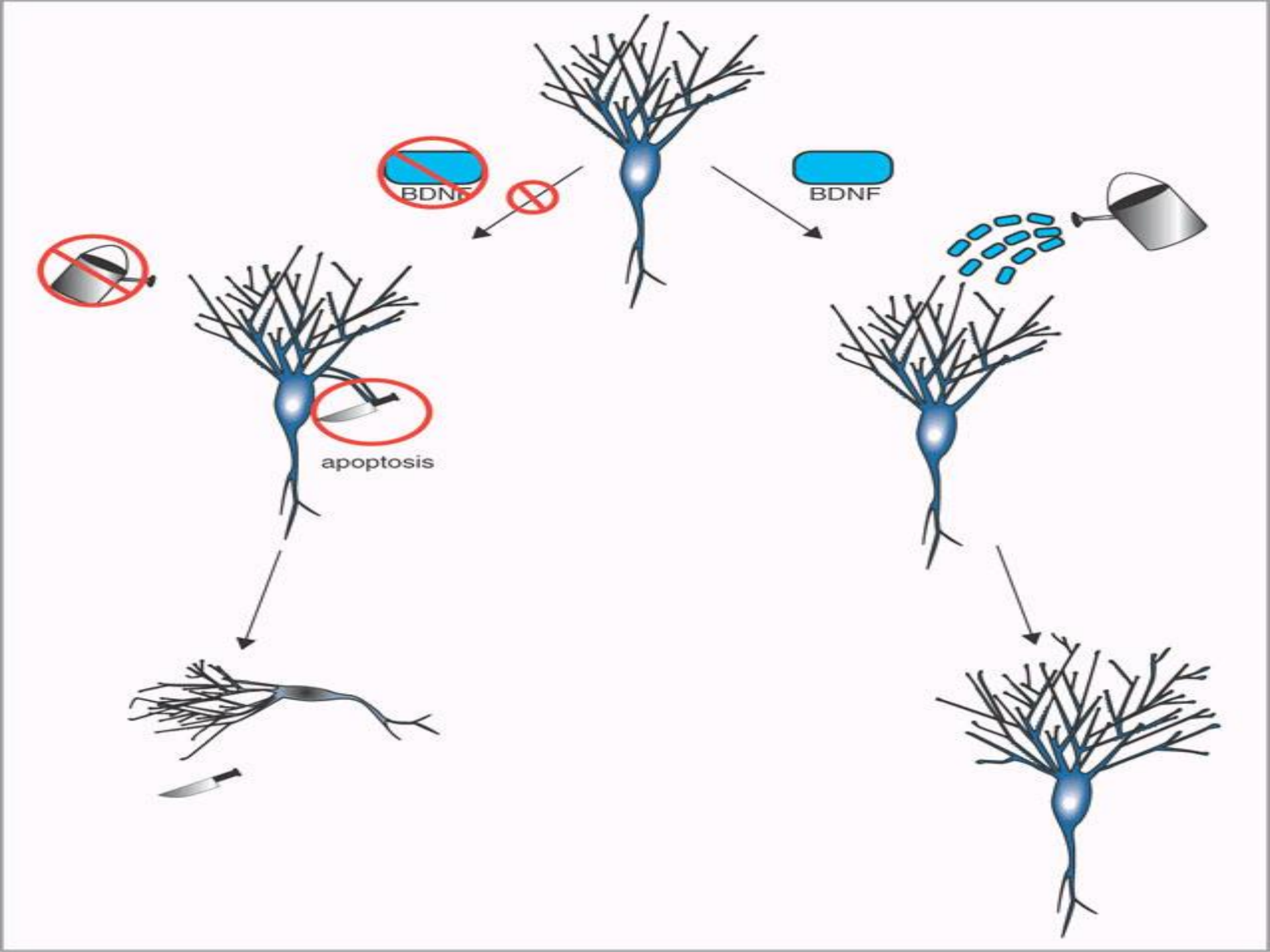
Cardiovascular diabetologic clustering

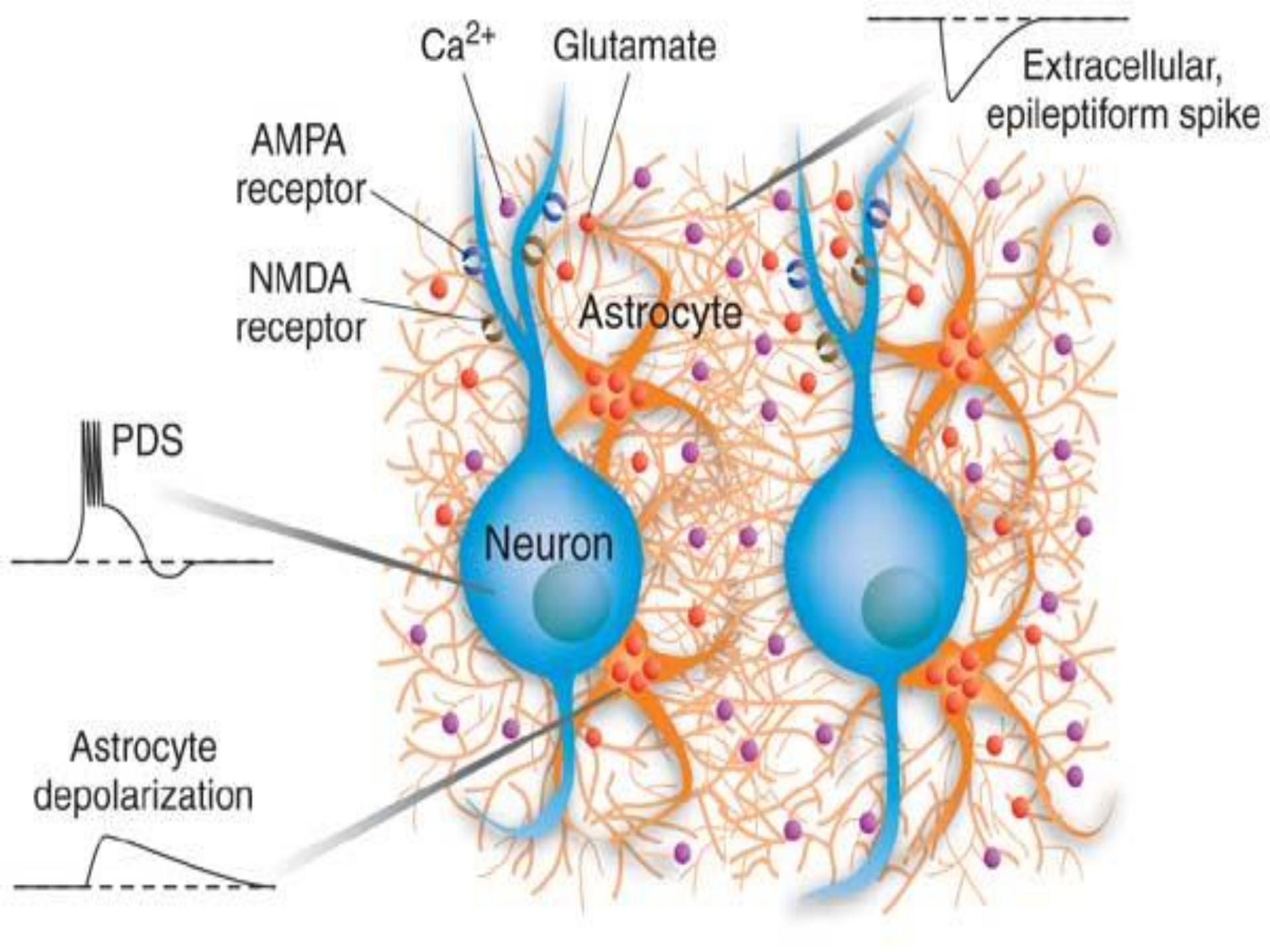

Macrophage
Monocyte
Galanin/VIP
NPY
Axons
Injured axons
Regenerating axon
Schwann cell
LIF
MCP1
Peripheral sensory ganglion

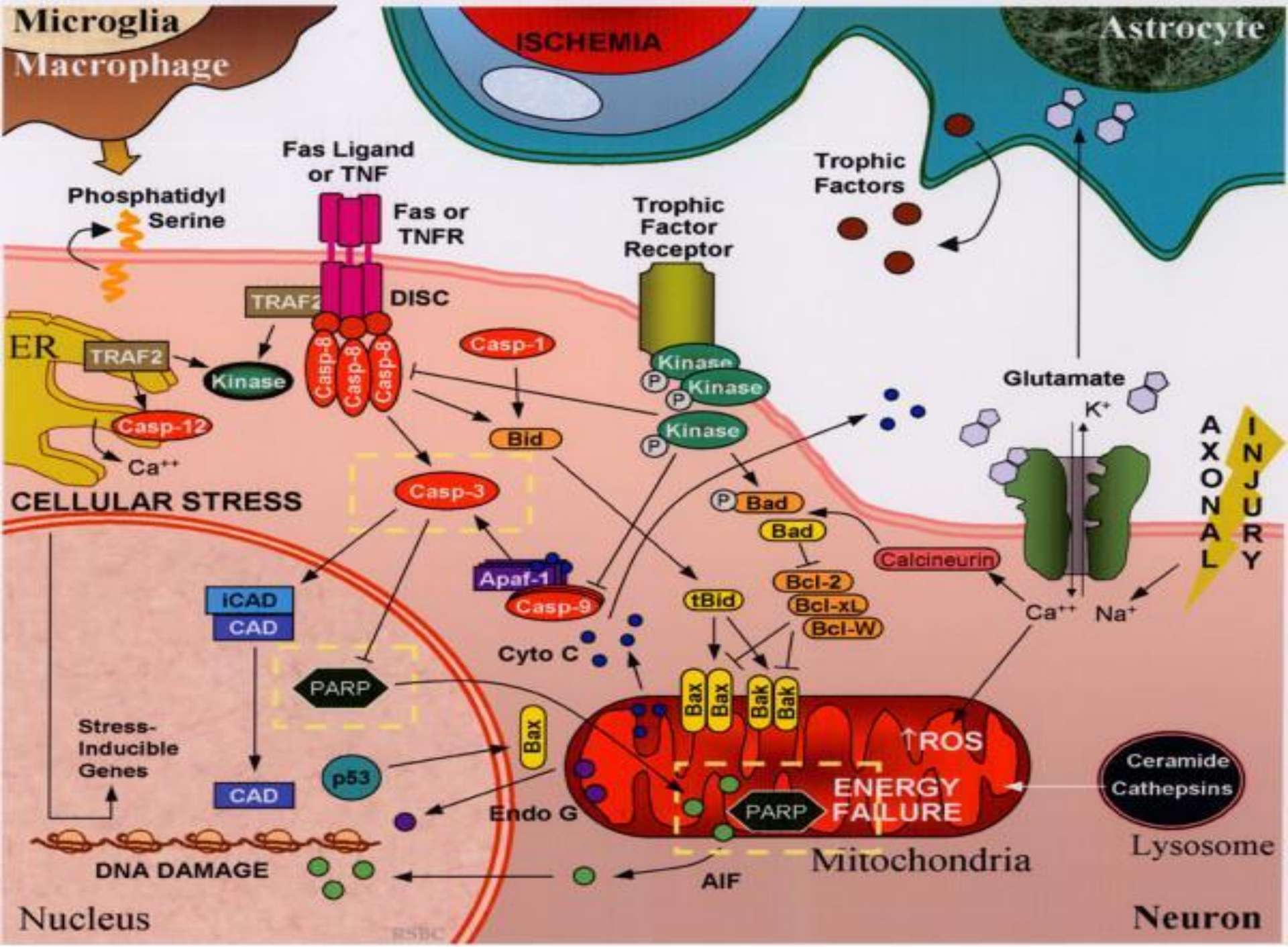

Ghrelin
Brain
Appetite
Pituitary
Ghrelin
GH release
Growth Hormone
Ghrelin
Ghrelin
X/A-like cell
Cardiovascular system
Metabolic system


Brain
Hypothalamic arcuate nucleus
Hypothalamic ghrelin
GHS-R
Ob-R
NPY/AgRP neuron
Blood or vagus nerve
Ghrelin
Stomach
Appetite
Body weight
Leptin
Adipose tissue


ILS, grade 1
(DCX)
ILS, grade 4
(DCX)
LCHb, grade 4
(RELN?)
SBH, grade 6
(DCX)
a>p
A
B
C
D
p>a
E
F
G
H
MDS, grade 1
(LIS1 and
14-3-3ε)
ILS, grade 3
(LIS1)
XLAG, grade 3
(ARX)
Normal control


BDNF
BDNF
apoptosis


Ca^{2+}
Glutamate
Extracellular,
epileptiform spike
AMPA
receptor
NMDA
receptor
Astrocyte
PDS
Neuron
Astrocyte
depolarization



Critical Care

Synaptogenesis in Prefrontal Cortex and the Development of Executive Functions

Age 6

age at which inattentive symptoms of ADHD become noticeable

Age 14-60

Birth

planning skills emerge; ability to sustain attention on one task but not perseverate; recognition memory; formation of abstract concepts

executive functioning emerges

rapid expansion of executive functions

working memory emerges

preschool: little ability to sustain attention on task; easily distracted by irrelevant stimuli

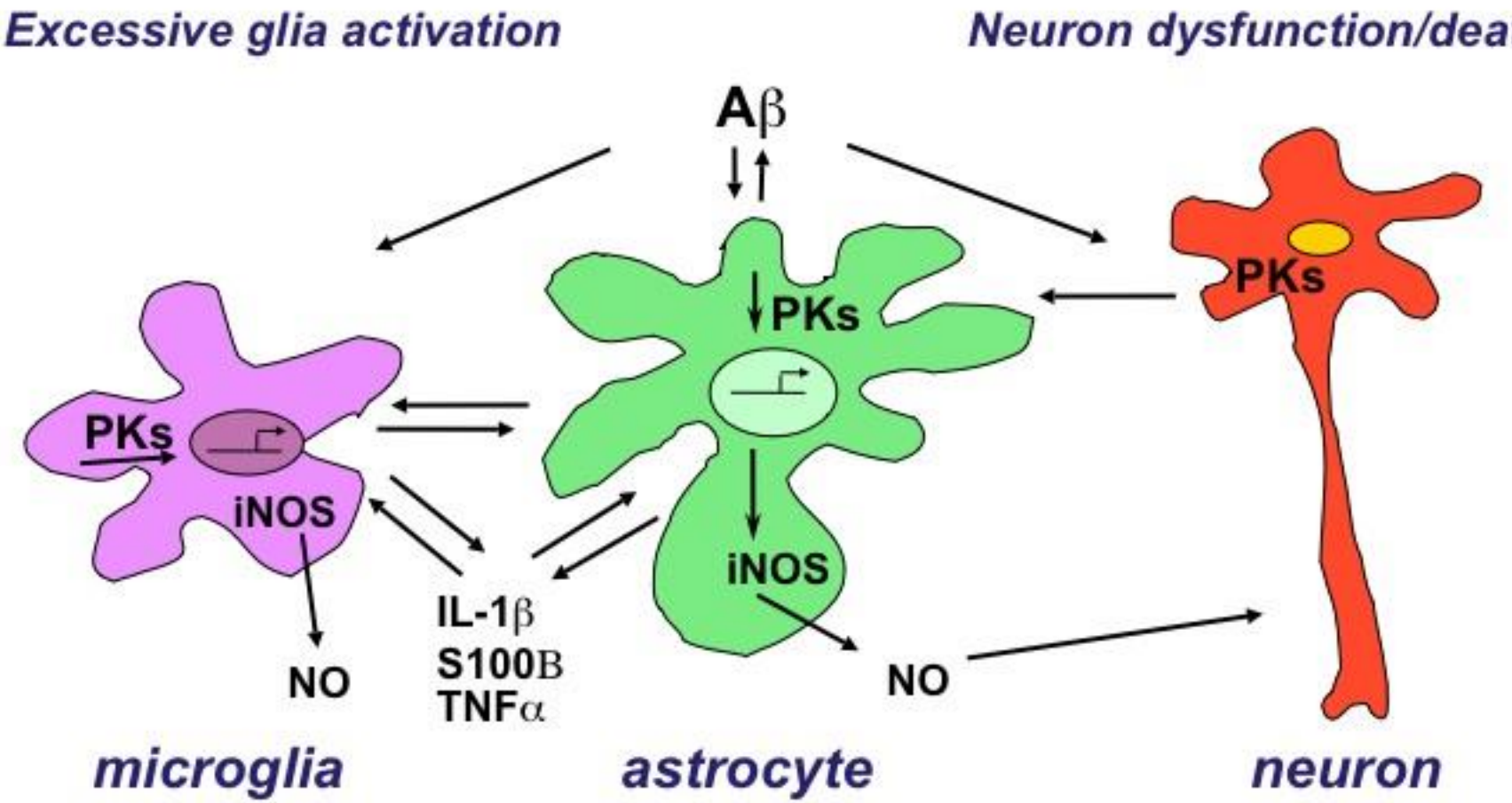
attending to one task while ignoring irrelevant stimuli; cognitive flexibility and inhibition; verbal memory performance

number of synapses in PFC

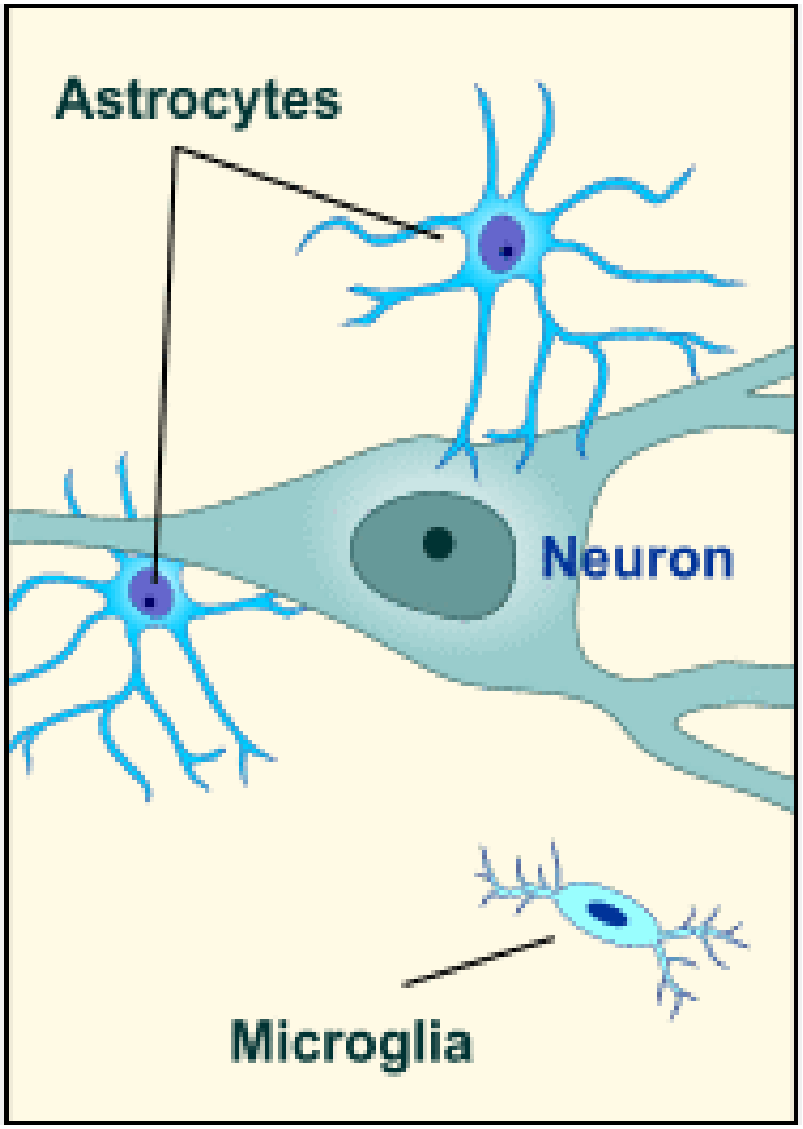
newborn 1yr 5yr 10 15 20 40 60 80 100

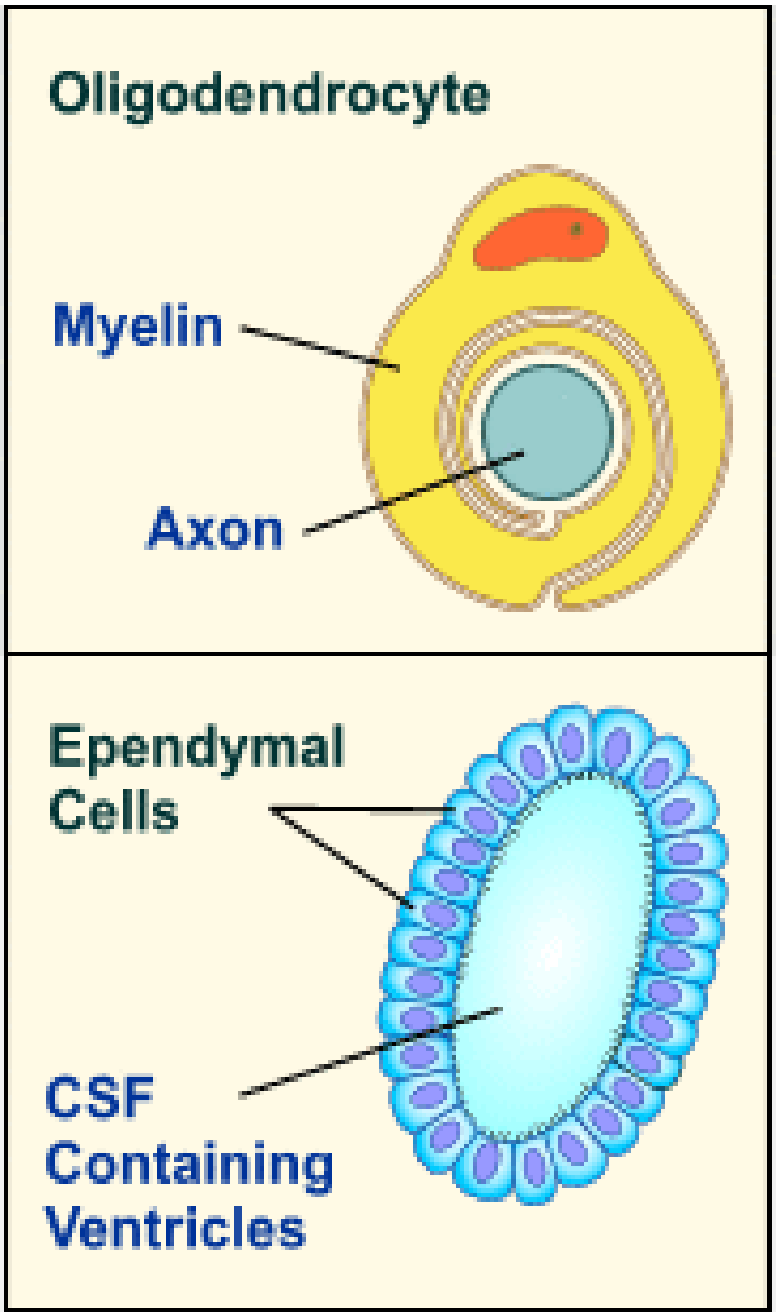
years

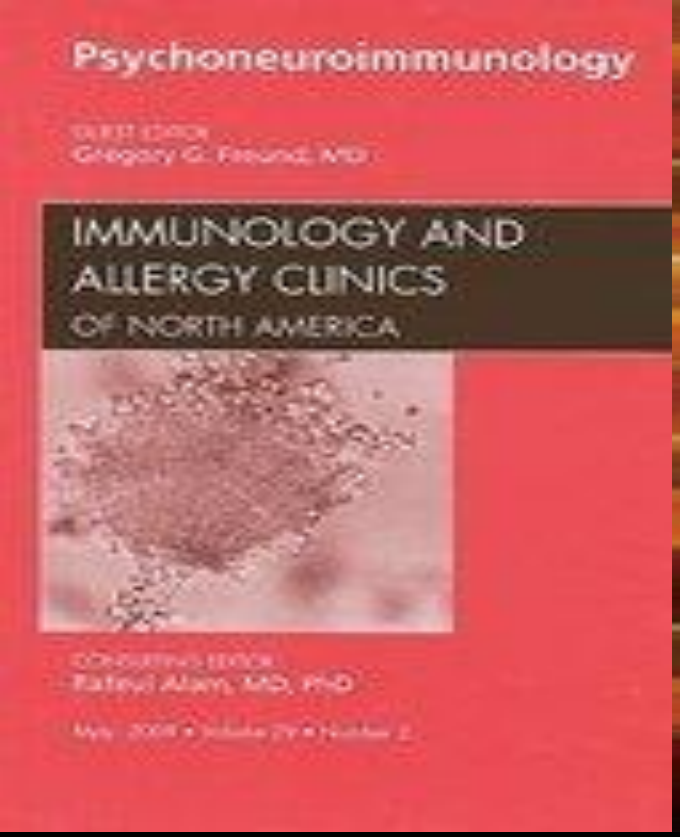
The Neuroinflammatory Cycle as a Therapeutic Target

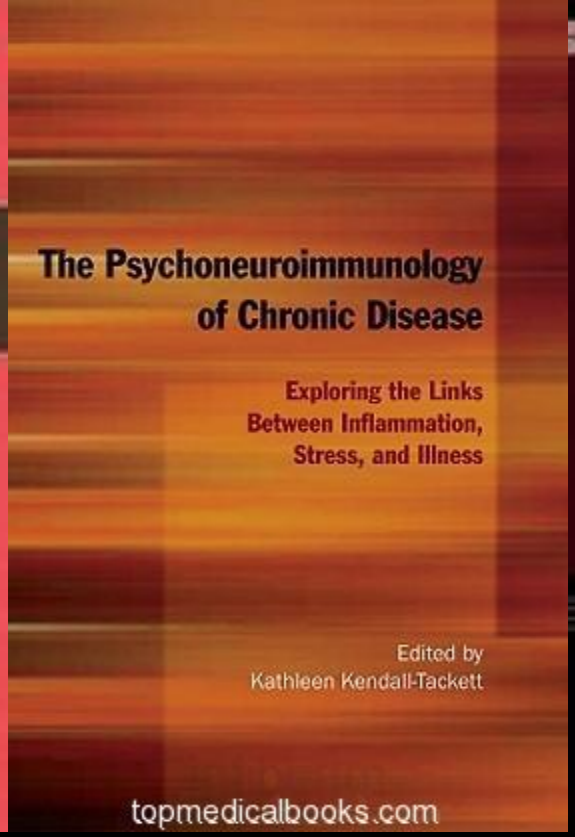


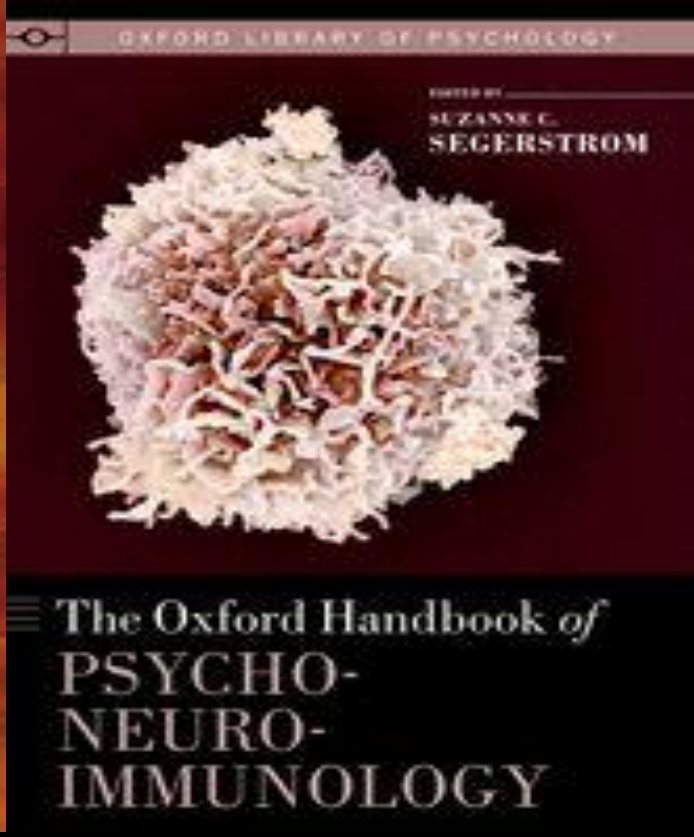
Pro-inflammatory cytokines: IL-1β, S100B, TNFα;
Aβ= beta-amyloid1-42 peptide; PKs = protein kinases;
iNOS= inducible nitric oxide synthase; NO= nitric oxide


Astrocytes
Neuron
Microglia


Oligodendrocyte
Myelin
Axon
Ependymal Cells
CSF Containing Ventricles







Thank you

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