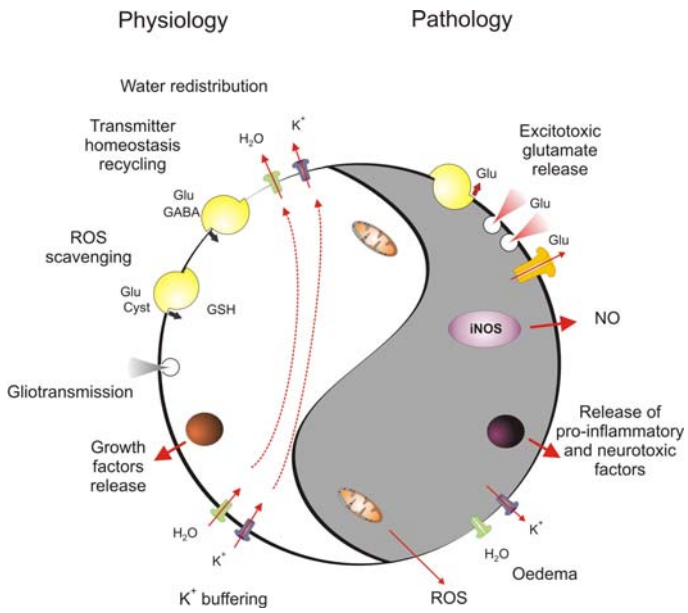
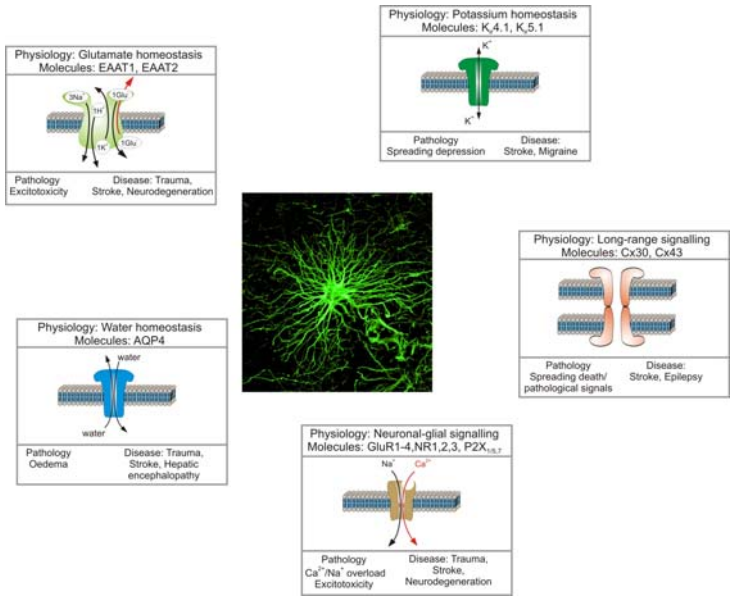
General Pathophysiology of Neuroglia

Neuroprotection and neurotoxicity: astroglial dichotomy

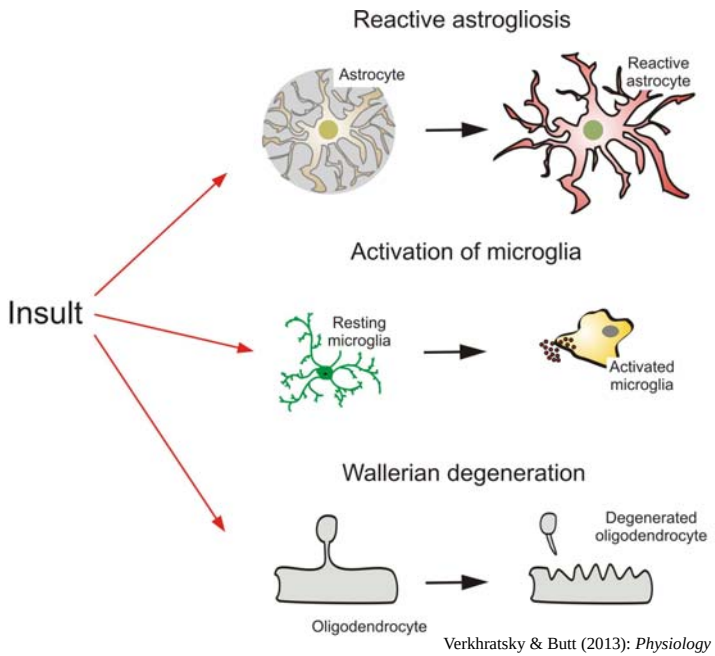


Neuroprotection and neurotoxicity: astroglial dichotomy



Verkhratsky, Sofroniew, Messing, deLanerolle, Rempe, Rodriguez, Nedergaard M (2012) ASN neuro 4, e00082

General pathophysiology of glia



Verkhratsky & Butt (2013): *Physiology and Pathophysiology of Neuroglia*, Wiley, pp/560

Reactive astrogliosis

All types of brain insults, regardless of aetiology, trigger a complex astroglial response, which is manifested by astrocyte hypertrophy and proliferation. This glial response is defined as *reactive astrogliosis*.

Reactive astrogliosis is a defensive brain reaction which is aimed at

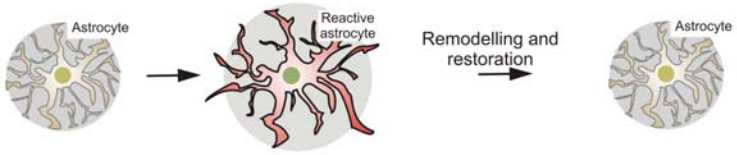
(i) isolation of the damaged area from the rest of the CNS tissue;
(ii) participation in the neuroinflammatory response;
(iii) reconstruction of the blood–brain barrier; and
(iv) facilitation of the remodelling of brain circuits in areas surrounding
(v) the lesioned region.

Isomorphic and anisomorphic astrogliosis

Isomorphic (i.e. preserving morphology) astrogliosis

Astroglial domain structure is preserved

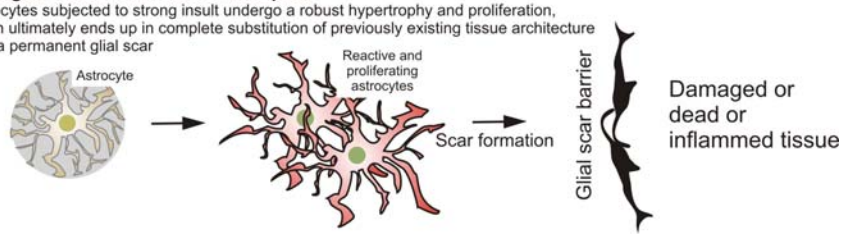
In astrocytes experiencing lesser insult or distal to the lesion site, the reactive changes are much milder and, although astroglial cells modify their appearance and undergo multiple biochemical and immunological changes, they do not distort the normal architecture of CNS tissue, but rather permit growth of neurites and synaptogenesis, thus facilitating the remodelling of neuronal networks.



Anisomorphic (i.e. changing the morphology) astrogliosis

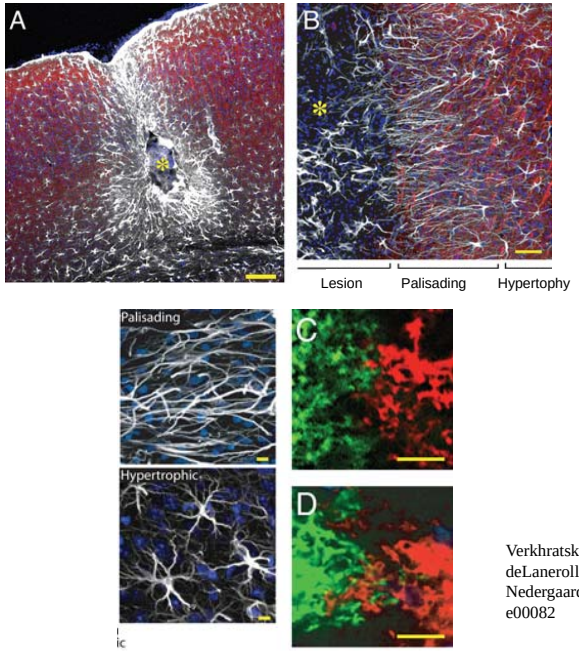
Astroglial domain structure is disrupted

Astrocytes subjected to strong insult undergo a robust hypertrophy and proliferation, which ultimately ends up in complete substitution of previously existing tissue architecture with a permanent glial scar



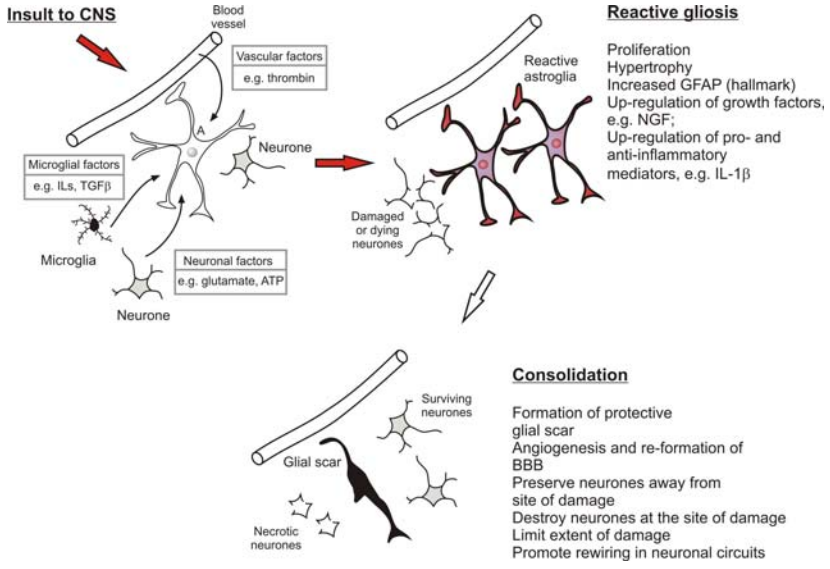
Verkhratsky & Butt (2013): *Physiology and Pathophysiology of Neuroglia*, Wiley, pp/560

Reactive astrocytes in a model of post-traumatic epilepsy induced by cortical injection of a ferrous chloride solution

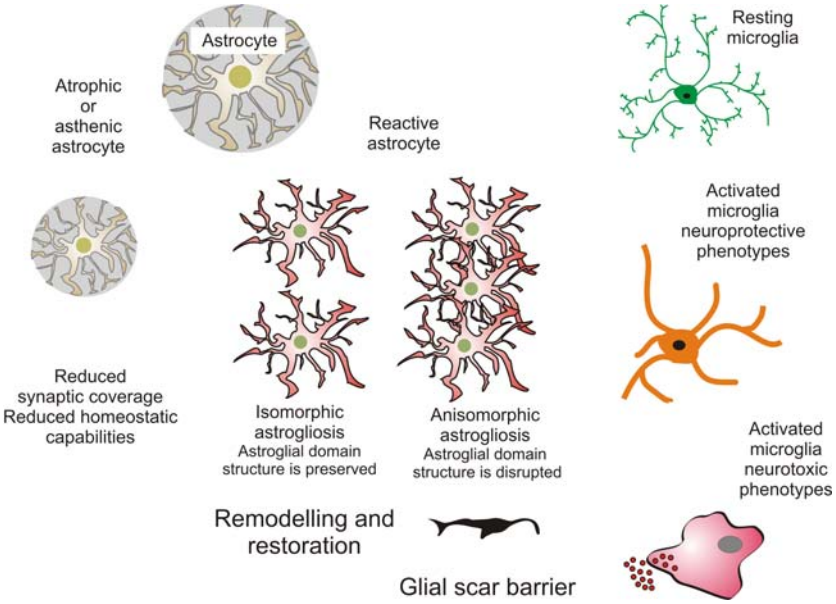


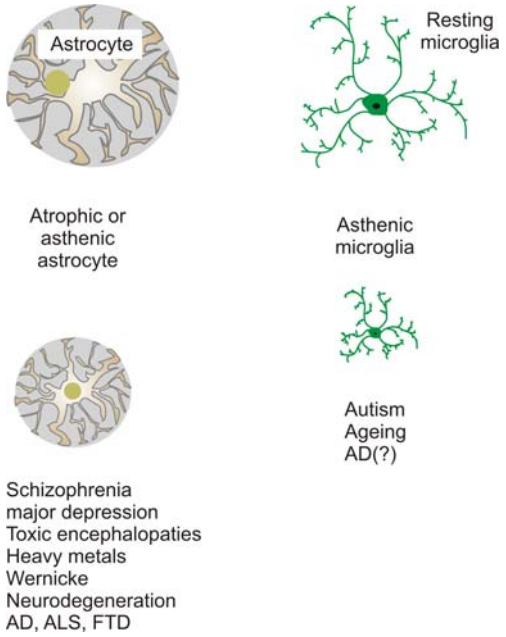
Verkhratsky, Sofroniew, Messing, deLanerolle, Rempe, Rodriguez, Nedergaard M (2012) *ASN Neuro* 4, e00082

Initiation and regulation of reactive astrogliosis



Verkhratsky & Butt (2007): *Glial Neurobiology, A Textbook* Wiley & Sons, pp. 220



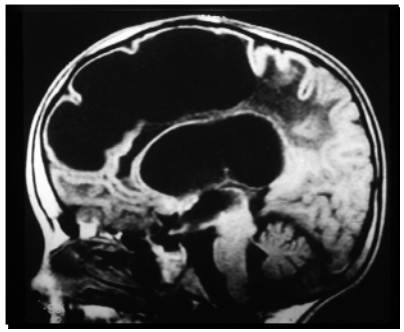


Gliopathololgy in major neurological conditions and diseases

Alexander's disease – primary genetic astrogliopathology

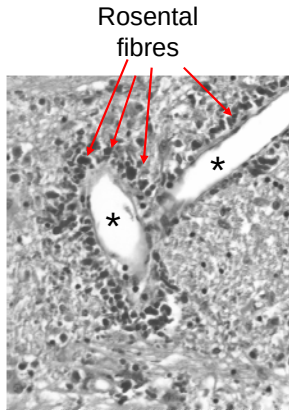
The disease is caused by mis-sense mutations of the GFAP gene; these aberrant genes are absent in parents, and therefore represent de-novo dominant GFAP gene mutations.

Histological hallmarks:
(i) Accumulation of *Rosenthal fibres* in astrocytes
(ii) Enlarged astrocytes.



MRI of the patient at 7 years showing cystic degeneration in the frontal lobes, enlarged ventricles and some atrophy of the vermis

Johnson AB (1996) In: *Handbook of clinical neurology* , pp 701 – 710. Amsterdam : Elsevier Science B.V .



Rosenthal fibers appear as dark nuggets in astrocytic endfeet surrounding blood vessels (asterisks).

Messing A. & Brenner M (2003) *Lancet Neurol* **2,** 75

Alexander's disease – primary genetic astrogliopathology

Normal GFAP-containing cytoskeleton

Abnormal cytoskeleton formed by Pathologically relevant GFAP mutants

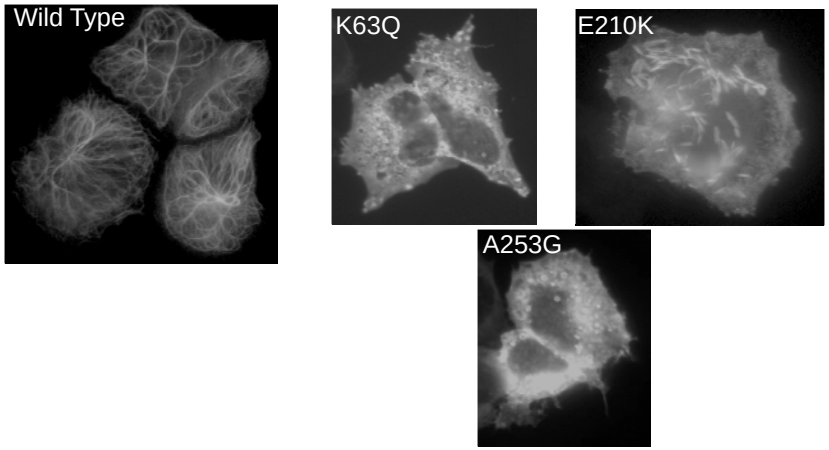
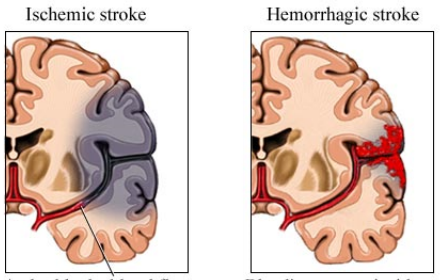


Figure 7. Assembly patterns of wild type and mutant GFAP in transfected cells. SWvim- cells were transfected with the indicated GFAP expression vectors and immunostained for GFAP 2 days later. Wild type and V115I GFAP form normal appearing filament networks, whereas K63Q and A253G form ring-like aggregates and E210K forms needle-like aggregates. Images for wild type, K63Q and E210Q are reprinted with permission from Li et al., 2005; copyright by Wiley-Liss, Inc. Li et al. (2005), *Ann Neurol*, **57,** 310–326,

Ischaemia and stroke

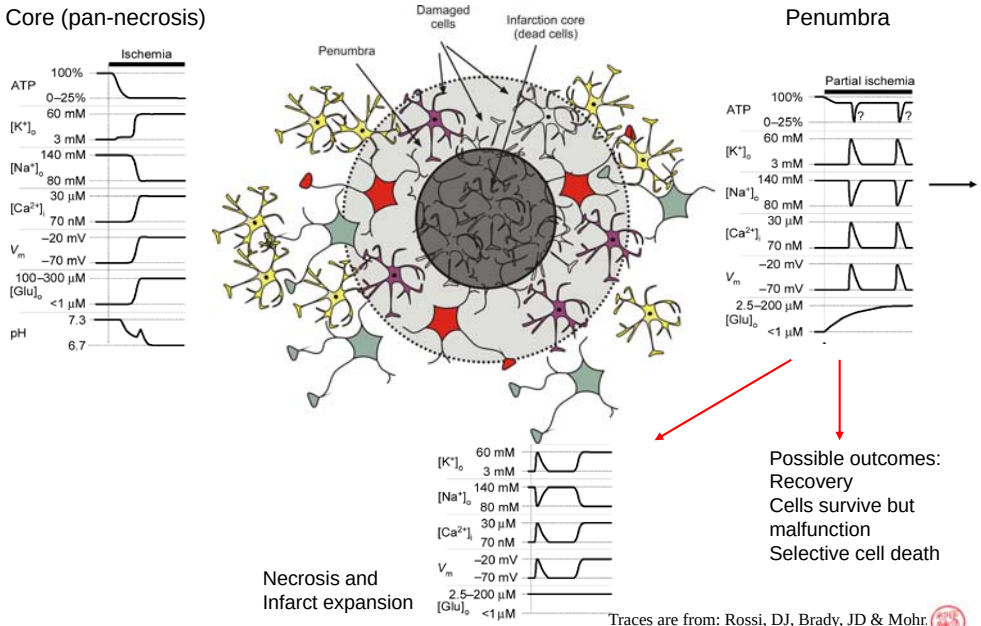
The disruption of blood flow in the brain can be caused either by blood vessel rupture, which results in *haemorrhage*, or by a restriction of blood supply to the brain or parts of the brain, commonly referred to as *brain ischaemia*, due to vascular occlusion (because of thrombosis or embolism), or to a systemic decrease in blood supply (for example, associated with heart failure). As a consequence, brain ischaemia can be either global, or focal, the latter corresponding to a *stroke*.



http://home.smh.com/sections/services-procedures/Stroke/whatis_stroke.html

Spatial and temporal progression of stroke

Core (pan-necrosis)



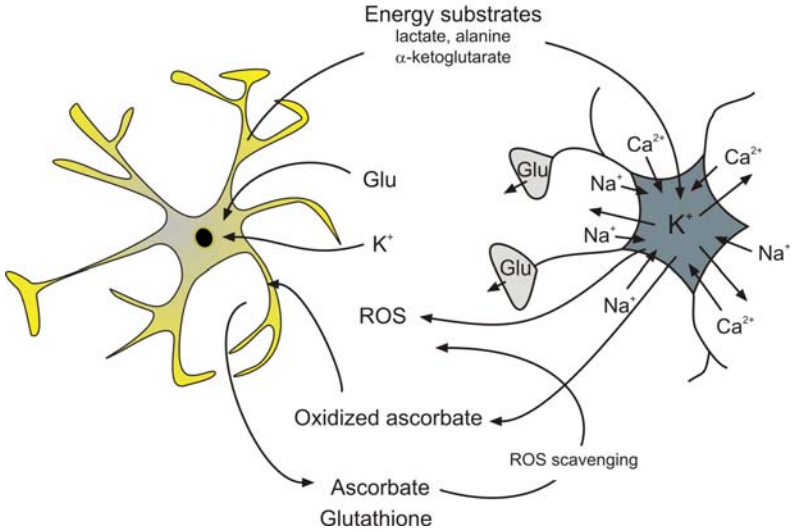
Penumbra

Possible outcomes:
Recovery
Cells survive but malfunction
Selective cell death

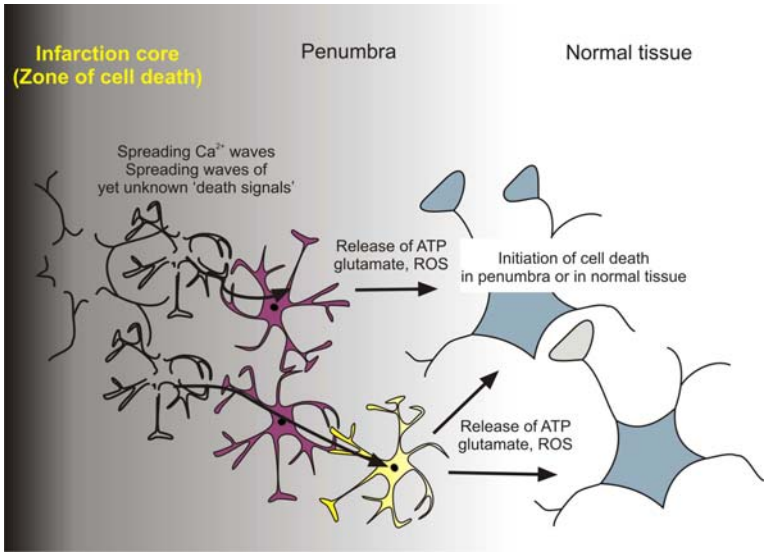
Necrosis and Infarct expansion

Traces are from: Rossi, DJ, Brady, JD & Mohr, (2007) *Nat Neurosci* **10,** 1377-1386.

Astroglia protect the brain against ischaemia



Astrocytes may exacerbate brain damage upon ischaemia and contribute to infarct expansion

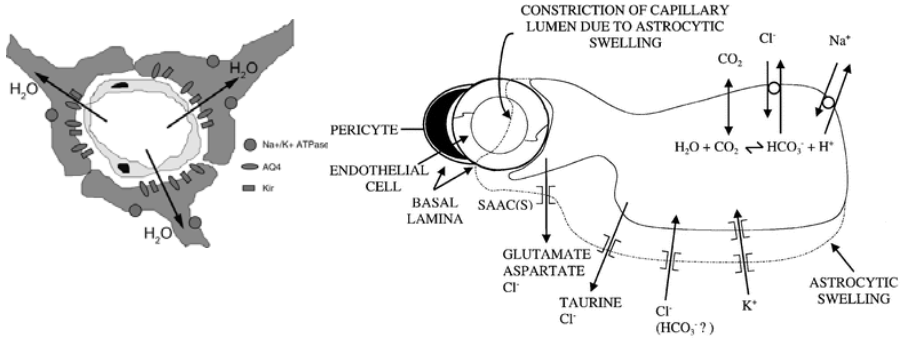


Brain oedema

Cytotoxic oedema

Excitotoxic/ischaemic oedema

Excess of extracellular K+/glutamate

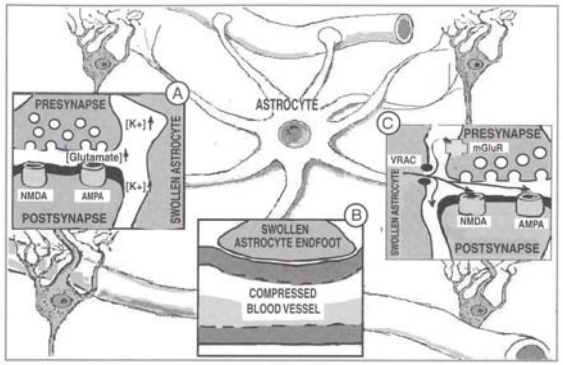


Collapse of extracellular space

Brain oedema: consequences

Collapse of extracellular space
Reduced volume of the synaptic cleft
Compromised uptake of K^+ and glutamate

All promote depolarisation and excitotoxicity



Glutamate release through volume sensitive channels
Further exacerbation of excitotoxicity

Compression of vessels
Further reduction in blood flow

Mongin & Kimelberg (2005): In Neuroglia, OUP

Hepatic Encephalopathy: A Primary Astrogliopathy

Hepatic encephalopathy results from liver failure and subsequent increase in the concentration of ammonia in the blood and in the cerebrospinal fluid.

Exposure of cortical astrocytes to ammonia results in a wide range of molecular and functional changes including cell swelling, decreased glutamate uptake, increased glutamate release, altered glycine transport, altered expression of the glucose transporter GLUT-1, reduced expression of the structural protein GFAP as well as oxidative and nitrosative stress.

This leads to a rapidly progressing failure of astroglial function, brain oedema, failure of brain ion, neurotransmitter and metabolic homeostasis, excitotoxicity and death.

Butterworth (2009): In: Astrocytes in (Patho)Physiology of the Nervous System. Springer, p. 673-692

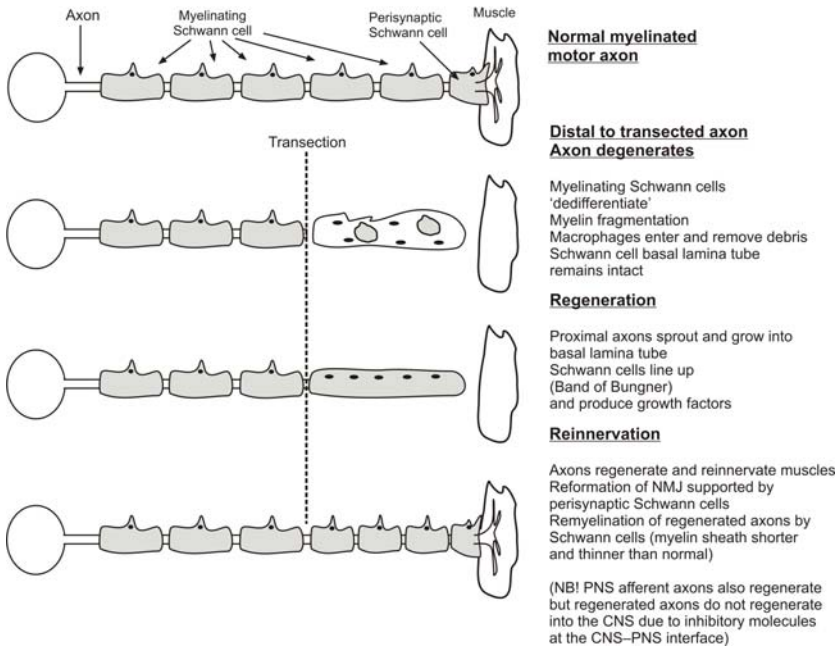
Astroglia in neuropsychiatric disorders

Nosology	Astroglial reaction	Astroglial contribution
Toxic encephalopathies		
Poisoning with metals (Manganese, Aluminium, Lead)	Functional asthenia	Astrocytes are primary target; they preferentially accumulate metals via specific transporters, which down-regulates expression of glutamate transporters, glutamine synthetase and possibly GABA transporter. Failure in glutamate homeostasis underlie excitotoxic neuronal death.
Poisoning with metylmercury, or Minamota disease	Functional asthenia	Astrocytes are primary target; accumulation of methylmercury decreases glutamate transport with ensuing neuronal excitotoxicity
Wernicke encephalopathy	Functional asthenia	Astrocytes are primary target and key component of pathology; the disease is caused by severe (up to 70%) down-regulation of astroglial expression of glutamate transporters, which causes massive neuronal excitotoxicity and death in thalamo-cortical regions.
Hepatic encephalopathy	Functional asthenia	Astrocytes are primary target, being the main system for ammonia removal and utilisation though glutamine synthetase. Increased accumulation of ammonia in astroglial cells triggers cellular oedema and disrupts glutamate homeostasis thus severe disturbing neurotransmission homeostasis.
Neuropsychiatric disorders		
Schizophrenia	Functional asthenia, morphological atrophy and pathological remodelling	Decrease in number of astrocytes and GFAP-positive profiles associated with impaired glutamate uptake and glutamine synthesis. Abnormal glutamate homeostasis together with an increased astroglial production and release of kynurenic acid (exogenous inhibitor of NMDA and ACh receptors) and altered synthesis of D-serine (positive modulator of NMDA receptors) contributes to pathological glutamatergic transmission implicated in pathogenesis of the disease
Major depressive disorder	Functional asthenia and morphological atrophy	Decrease in number of astrocytes and GFAP expression, associated with decreased glutamate uptake and secretion of growth factors and cytokines as well as impaired glutamine synthesis, altered gap junctional connectivity in glial syncytia which all may contribute to abnormal connectivity in neural networks and neurotransmission disbalance.
Dementia and neurodegenerative disorders		
Alzheimer's disease	Atrophic/asthenic changes at the early stages with secondary astrogliosis at late stages	Decrease in GFAP profiles in a region specific manner at the early stages of AD progression; mild astrogliosis of astrocytes associated with plaques. Absence of astrogliotic response (e.g. in entorhinal cortex) may account for higher vulnerability of certain regions to the pathology.
Fronto-temporal dementia, Pick's disease, fronto-temporal lobar degeneration, thalamic dementia	Atrophic changes and astrogliosis	Combination of astrogliodegeneration and astrocytic death with astrogliosis. relevant cellular mechanisms remain as yet unknown.
Addictive disorders		
Alcohol and drug abuse	Atrophic changes and astrogliosis	Decrease in astroglial density and astroglial asthenia at the early stages of the addictive disorders is complemented by secondary astrogliosis associated with progression of pathology.

Verkhratsky, Rodriguez & Steardo (2013) *Neuroscientist*, in revision

Pathological potential of oligodendroglia

Wallerian degeneration in PNS



Normal myelinated motor axon

Distal to transected axon
Axon degenerates

Myelinating Schwann cells 'dedifferentiate'
Myelin fragmentation
Macrophages enter and remove debris
Schwann cell basal lamina tube remains intact

Regeneration

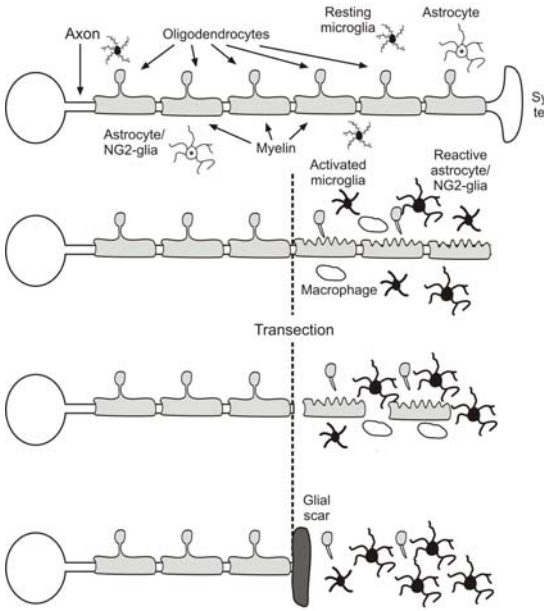
Proximal axons sprout and grow into basal lamina tube
Schwann cells line up (Band of Bungner)
and produce growth factors

Reinnervation

Axons regenerate and reinnervate muscles
Reformation of NMJ supported by perisynaptic Schwann cells
Remyelination of regenerated axons by Schwann cells (myelin sheath shorter and thinner than normal)

(NB! PNS afferent axons also regenerate but regenerated axons do not regenerate into the CNS due to inhibitory molecules at the CNS–PNS interface)

Wallerian degeneration in CNS



Normal myelinated axon

Distal to transected axon
Axon degenerates

Myelin disintegrates
Myelin fragmentation
Microglia activated
Macrophages enter and remove debris
Astrocytes and NG2-glia are activated

Abortive regrowth

Growth of the distal stumps of the transected axons is inhibited
Myelin debris is not removed
Oligodendrocytes survive
Astrocytes and NG2-glia form a glial scar

Regeneration fails

A consolidated glial scar forms and blocks regeneration

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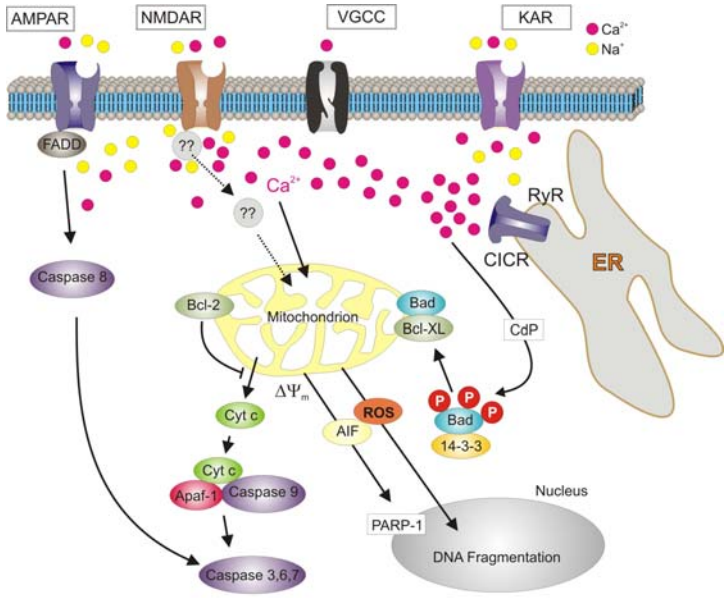
Olgidendrocytes and oligodenroglial precursors are highly vulnerable to excitotoxicity and ischaemic insults



Giaume C, Kirchhoff F, Matute C, Reichenbach A, Verkhratsky A. (2007): *Cell Death Differ*; **14**, 1324-1335.

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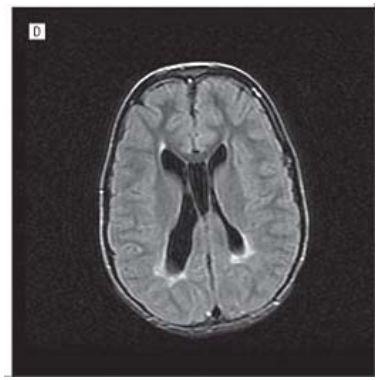
Periventricular leukomalacia

Periventricular leukomalacia (PVL) is the predominant form of brain injury and the leading known cause of cerebral palsy and cognitive deficits in premature infants.

Periventricular leukomalacia results from hypoxic damage to the white matter; the primary target is represented by oligodendroglial precursors and oligodendrocytes. Massive death of oligodendroglial cells initiates activation of microglia and secondary neuroinflammation.



Deng, W. et al. (2008): *Arch Neurol* **65**, 1291-1295.

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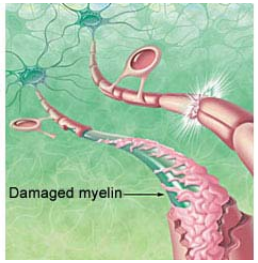
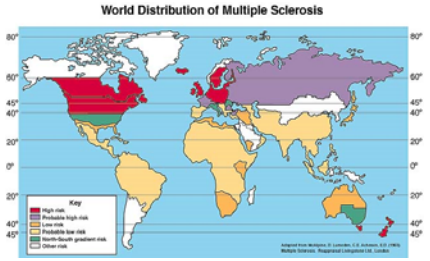
Multiple sclerosis: Oligodendrodegeneration and demyelination

Multiple sclerosis (MS) was recognized by the mid 19th century, and already in 1871 Hammond referred to it as a cerebrospinal sclerosis; it was Charcot who, in 1877, realized the role of disrupted myelin sheath in the pathogenesis of this disease. MS is an inflammatory demyelinating disease of the CNS, which culminates in progressive neurological deterioration. The ethiology of MS remains elusive, as both genetic predisposition and environmental factors are indicated. The importance of genetic predisposition is evident from very high concordance of the disease occurrence between monozygotic twins, whereas the environmental factors are implicated by the existence of geographical areas with remarkable differences in MS prevalence (generally, MS is significantly more frequent in northern than in southern parts of the world).





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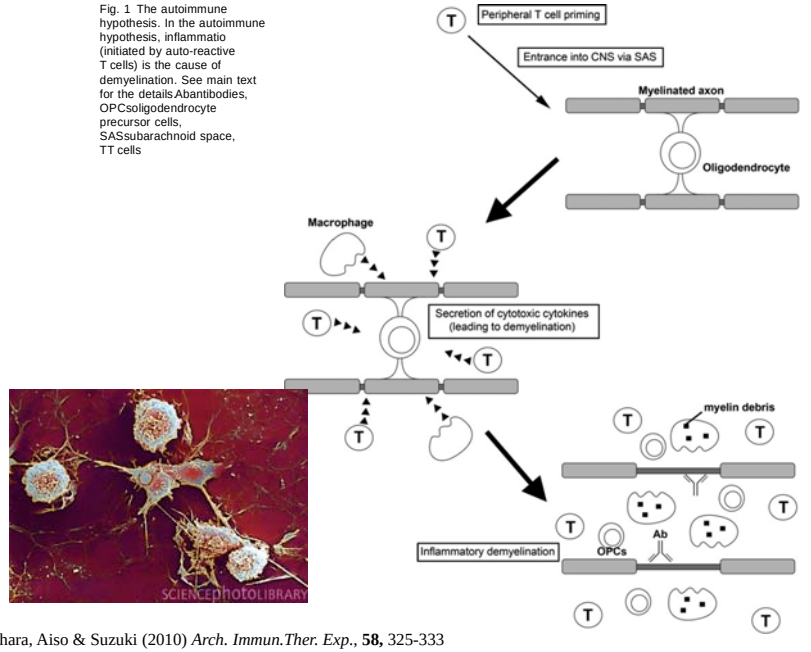
Multiple sclerosis: Autoimmune hypothesis

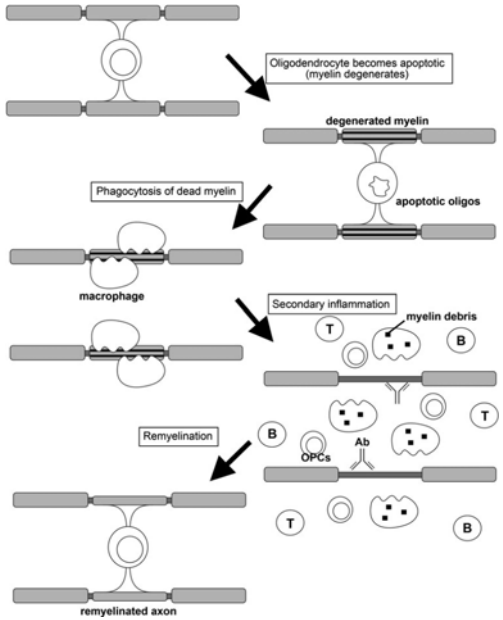
Fig. 1 The autoimmune hypothesis. In the autoimmune hypothesis, inflammatio (initiated by auto-reactive T cells) is the cause of demyelination. See main text for the details.Abantibodies, OPCsoligodendrocyte precursor cells, SASsubarachnoid space, TT cells



Nakahara, Aiso & Suzuki (2010) *Arch. Immun.Ther. Exp.*, **58,** 325-333

Multiple sclerosis: Oligodendrogliopathy hypothesis

Fig. 2 The oligodendrogliopathy hypothesis. In the oligodendrogliopathy hypothesis, oligodendroglial apoptosis (by some undetermined causes) is the cause of demyelination and inflammatio is a mere secondary event to clear up the degenerated myelin. See main text for the details. Abantibodies,BB cells, OPCsoligodendrocyte precursor cellsŦT cells



Nakahara, Aiso & Suzuki (2010) *Arch. Immun.Ther. Exp.*, **58,** 325-333

Conclusion

1. The brain pathology, is, to a very great extent, a pathology of glia, which, when falling to function properly, determines the degree of neuronal death, the outcome and the scale of neurological deficit.
2. Glia acts as a brain warden, and as such it is intrinsically endowed with two opposite features: it protects the nervous tissue as long as it can, but it also can rapidly assume the guise of a natural killer, trying to eliminate and seal the damaged area, to save the whole at the expense of the part.