Cell biology and physiology of astroglia

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The University of Manchester, UK

Astrocytes (literally “star-like cells”): the homeostatic cells of the brain

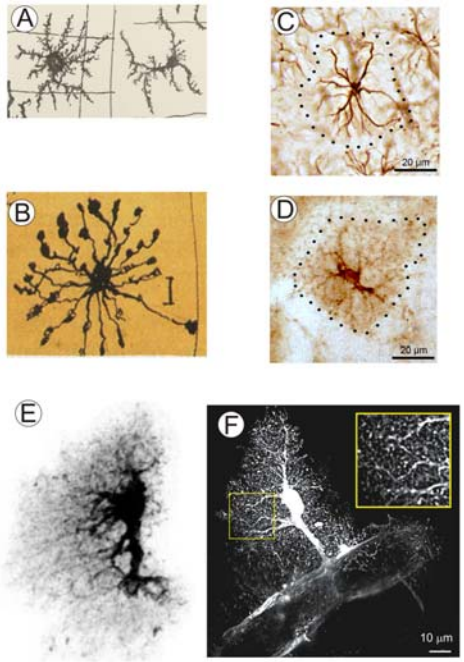
Michael von Lenhossek
(1863 – 1937)

Von Lenhossek M. (1893) Zur Kenntnis der Neuroglia des menschlichen Ruckenmarkes. *Verh Anat Ges* **5,** 193-221, 1891.

Protoplasmic astrocytes
Andriezen WL. The neuroglia elements of the brain. *Br Med J* **2,** 227-230, 1893.

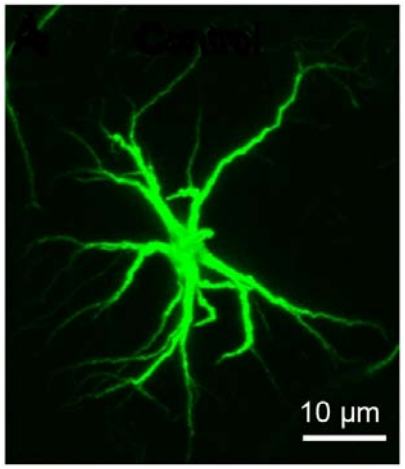
Fibrous astrocytes
Kölliker A. Handbuch der Gewebelchre des menschen. Leipzig: Wilhelm

How to visualise astrocytes



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

A subpopulation of astrocytes can be specifically labelled by GFAP antibodies

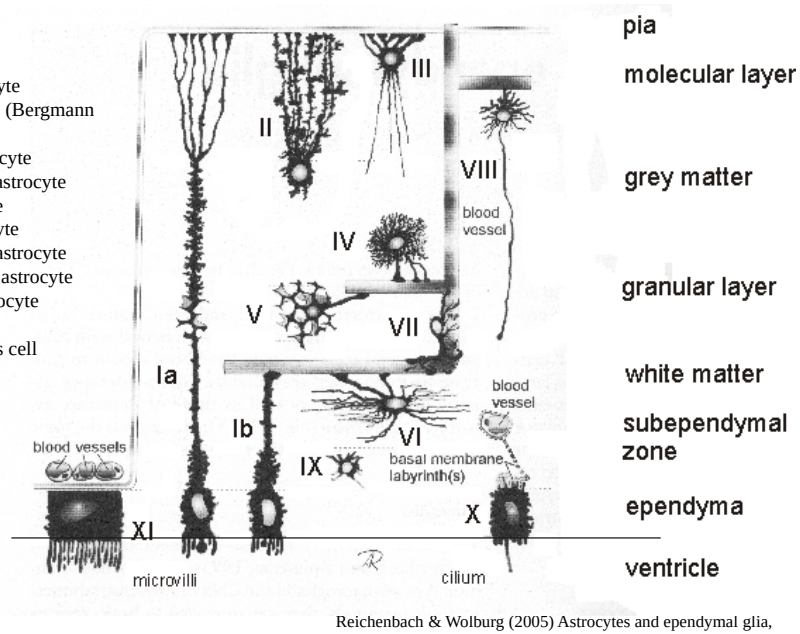


Astrocytes express intermediate filaments, which form the cytoskeleton. The main types of intermediate filament proteins are Glial Fibrillary Acidic Protein (GFAP) and vimentin; expression of GFAP is commonly used as a specific marker for identification of astrocytes.

GFAP is expressed in
100% of cerebellar Bergmann glia
80% of hippocampal astrocytes
20% of cortical astrocytes

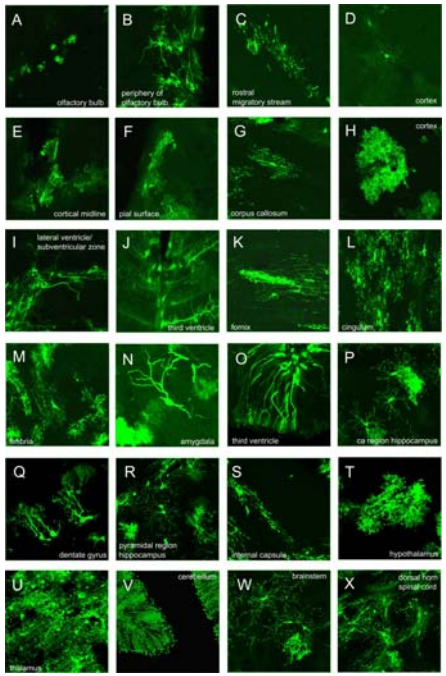
Heterogeneity of astrocytes (morphological)

Ia – pial tanycyte
Ib – vascular tanycyte
II – radial astrocyte (Bergmann glial cell)
III – marginal astrocyte
IV – protoplasmic astrocyte
V – velate astrocyte
VI – fibrous astrocyte
VII – perivascular astrocyte
VIII – interlaminar astrocyte
IX – immature astrocyte
X – ependymocyte
XI – choroid plexus cell



Reichenbach & Wolburg (2005) Astrocytes and ependymal glia, In: *Neuroglia*, Kettenmann & Ransom, Eds, OUP, p. 20

Heterogeneity of astrocytes (morphological)



Emsley JG, Macklis JD. 2006. Neuron Glia Biol 2(3):175-186.

Heterogeneity of astrocytes (functional)

	AMPARs	NMDARs	P2XRs	Dopamine receptors	GABARs	Glycine receptors	MGluRs	P2YRs
Cortex	+	+	+	-	-	-	+	+
Hippocampus								
GluR cells	+	-	-	-	+	-	?	+
GluT cells	-	-	-	-	?	-	+	+
Cerebellum	+	-	-	-	+	-	+	+
Basal ganglia	?	-	-	+	-	-	?	?
Spinal cord	+	+	-	-	-	+	+	+

Functions of astroglia

1. Developmental
- Regulation of neuro and gliogenesis – astroglia are stem elements of the CNS.
- Neuronal path finding.
- Regulation of synaptogenesis.

2. Structural
- Astroglia form the scaffold of the nervous system, thus defining the functional architecture of the brain and spinal cord.
- Astrocytes form a continuous syncytium and integrate other neural cells into this syncytium.

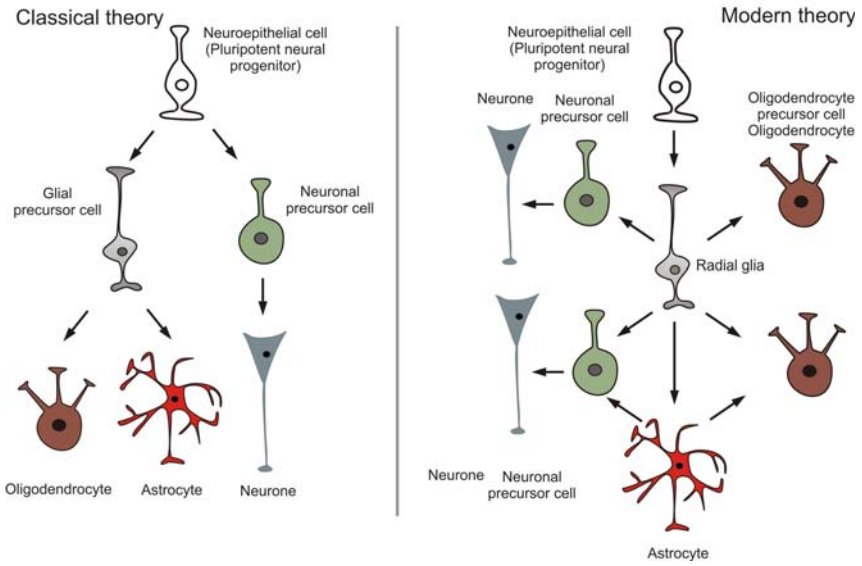
3. Formation and regulation of the blood–brain barrier
- Formation of the glial–vascular interface.
- Regulation of cerebral microcirculation.

4. Metabolic
- Providing energy substrates for neurones.
- Collecting neuronal waste.

5. Homeostatic: Control of the CNS microenvironment
- Regulation of extracellular ion concentrations; in particular sequestration and redistribution of K^+ following fluctuations associated with neuronal activity.
- Regulation of extracellular pH.
- Removal of neurotransmitters from the extracellular space.
- Brain water homeostasis.

6. Signalling
- Modulation of synaptic transmission.
- Metabolism and synthesis of neurotransmitters
- Release of neurotransmitters.
- Long-range signalling within the glial syncytium.
- Integration of neuronal–glial networks.

Embryonic neuro- and gliogenesis



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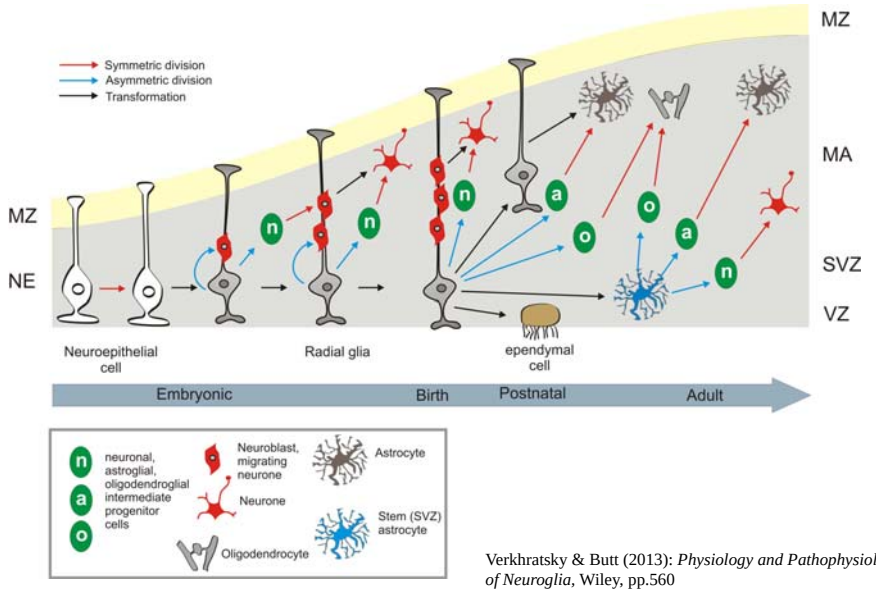
Embryonic neuro- and gliogenesis



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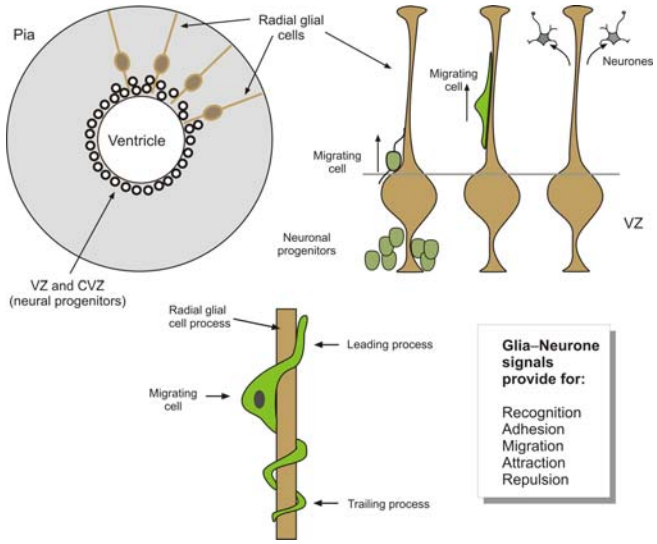
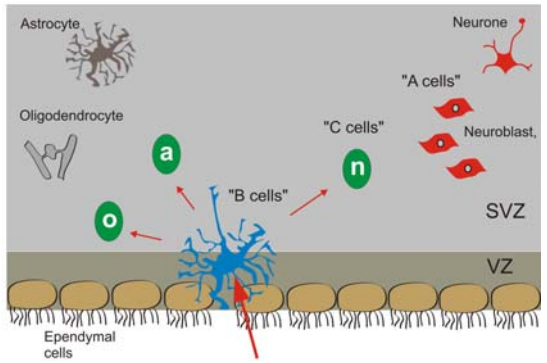
Radial glial forms the scaffold of the developing CNS and act as pathfinders for migrating neuroblasts



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

Adult neurogenesis

Factors favouring gliogenesis	*Factors favouring neurogenesis*
Fibroblast growth factor 2	Epidermal growth factor 2
Bone morphogenetic protein	Transforming growth factor α
Notch	Vascular endothelial growth factor
Platelet-derived growth factor	Insulin-like growth factor 1
Neuregulins	Platelet-derived growth factor
Unmyelinated axons	Activated astrocytes



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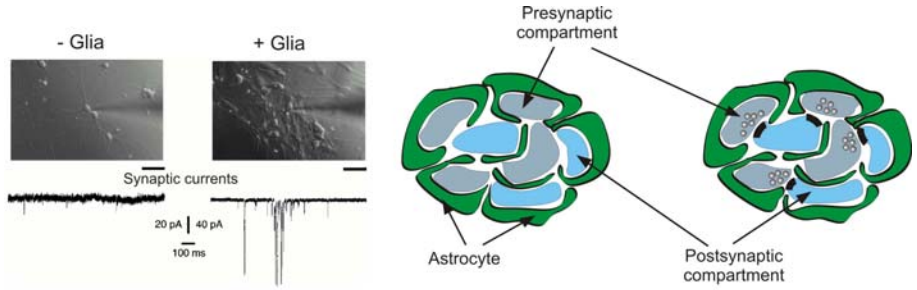
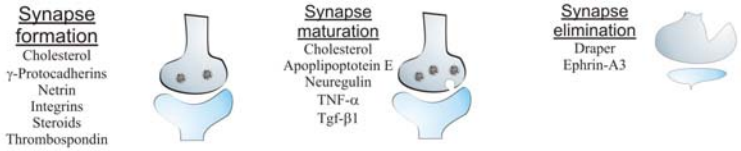
Astrocytes promote and regulate synaptogenesis

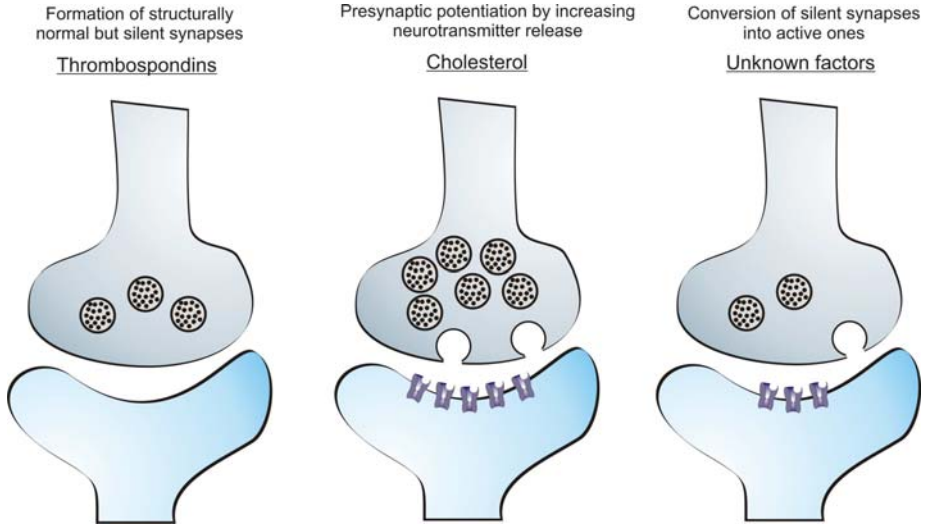


Pfrieger & Barres (1997): *Science* **v. 277,** p.1684-1687

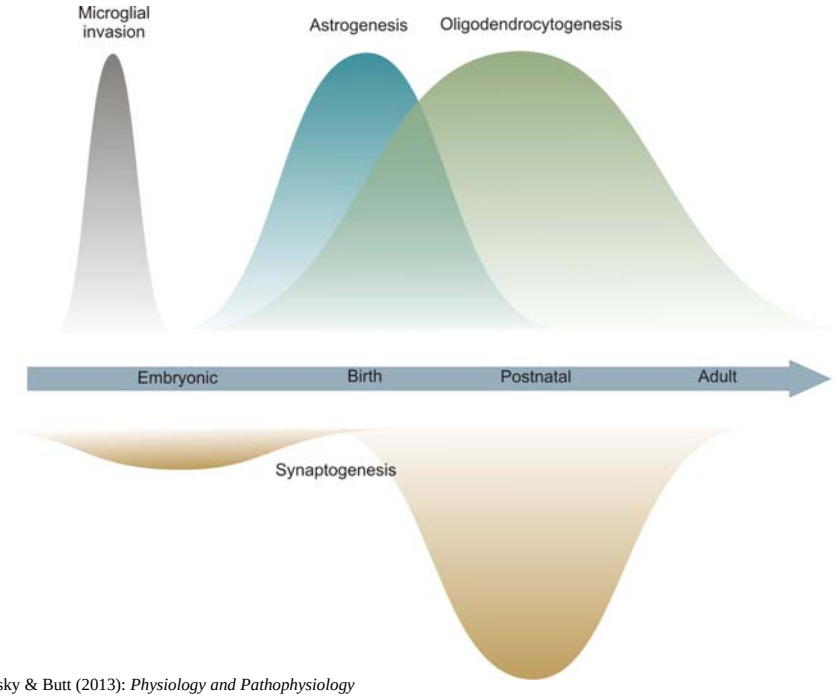


Modified and redrawn from
Pfrieger (2011): *Brain Res Rev* **v.63**, p. 39-46

Astroglia-derived factors regulate functional status of synapses



Redrawn from Eroglu & Barres (2010): *Nature* **v. 468** p. 223-231



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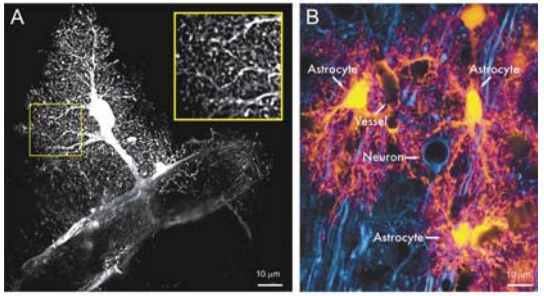
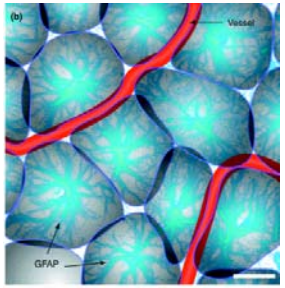
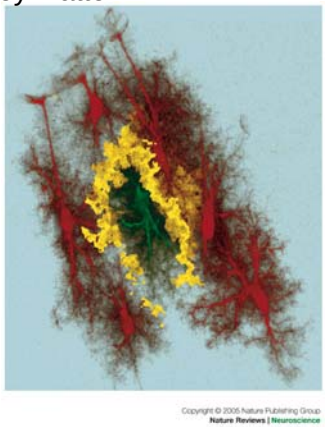
Defining the functional architecture of grey matter

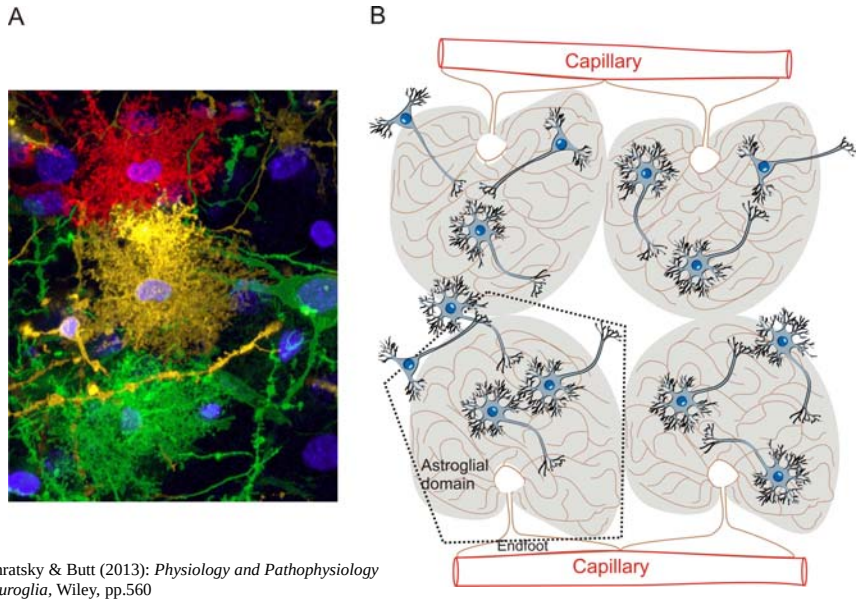






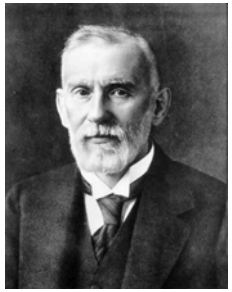
Nedergaard et al., 2004, 2006, 2008
Volterra & Meldolesi, 2005
Nedergaard, Rodriguez & Verkhratsky, 2010

Glial cells define micro-architecture of the brain, integrate neurones and capillaries into glial-neuronal vascular units and regulate microcirculation



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

The blood-brain barrier (BBB) is a system that separates the circulating blood from cerebrospinal fluid and allows selective transport of various molecules through this interface. This is a dynamic and highly regulated system involved in active transport of nutrients and redistribution of ions, while preventing potentially harmful molecules from entering the CNS.

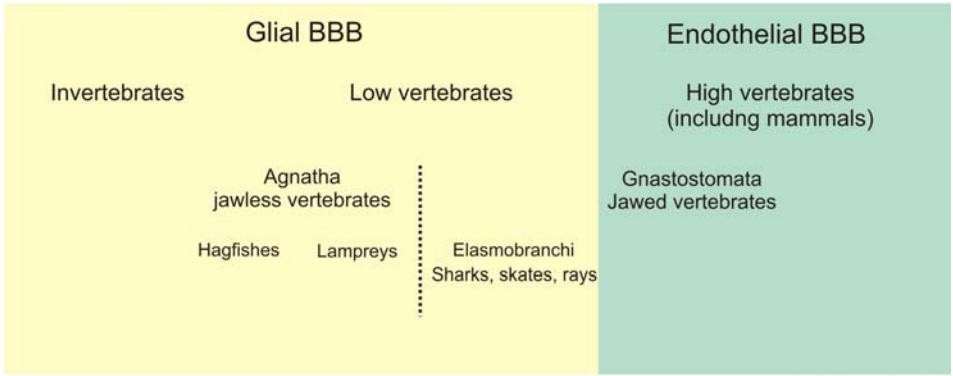


Paul Ehrlich
(1854 –1915)

The BBB was discovered by Paul Erlish in 1885, when he found that pharmacological agents and dyes injected into the bloodstream do not appear in the brain, in the spinal cord and in the retina.

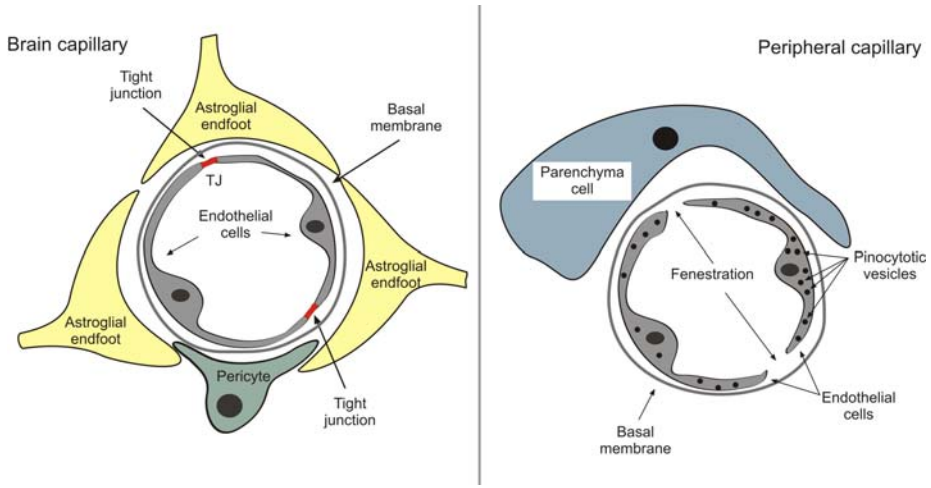
Ehrlich (1885): Das sauerstuffbedürfnis des organismus. In: *Eine Farbenanalytische Studie*, Berlin, Hirschwald

Evolution of blood-brain barrier



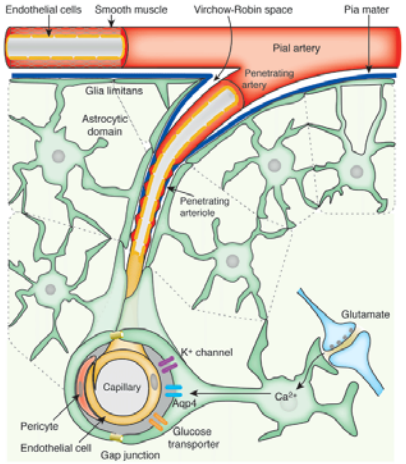
In the insects the barrier is made by perineural glia, sheath glia and fenestrated glia.
In cephalopodes the barrier is made at the level of pericytes and smooth muscle cells.
In the Elasmobranch fish the barrier is formed by perivascular glial endfeet or else vesicles are completely surrounded by astroglia (endocellular capillaries).

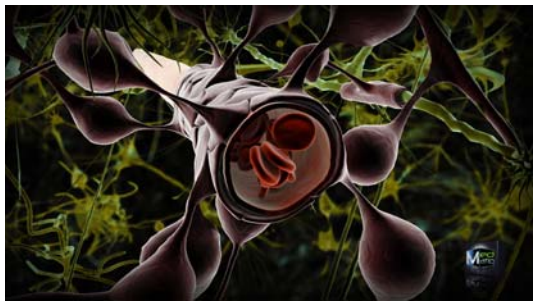
Blood-Brain barrier – glial-vascular interface



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

Astroglial perivascular processes completely cover brain vessels and capillaries

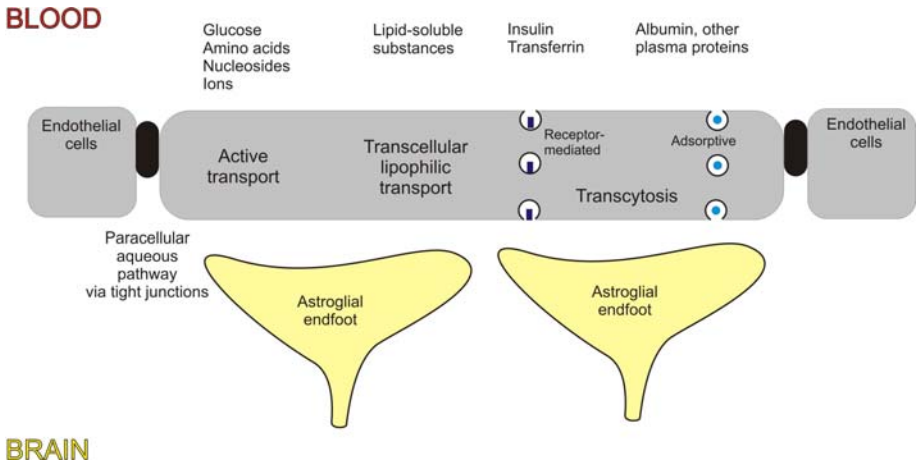




Ben Brahim Mohammed; http://en.wikipedia.org/wiki/File:Blood_Brain_Barriere.jpg

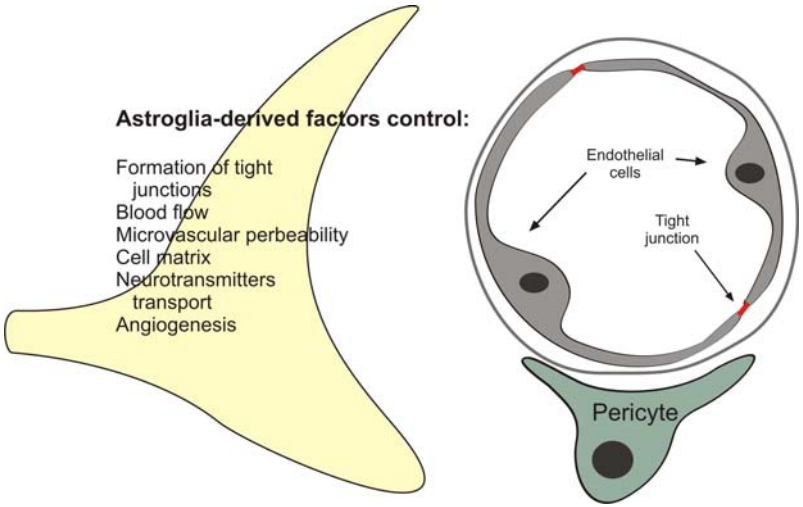
Iadecola, C & Nedergaard, M, (2007): *Nat Neurosci*, **10**, 1369-1376.

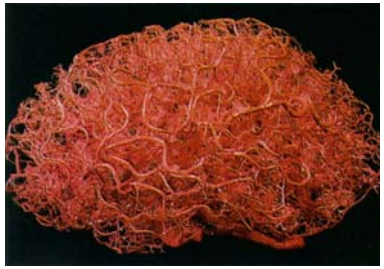
Mechanisms of molecular traffic through the blood-brain barrier



Redrawn from
Abbott, Ronnback & Hansson (2006): *Nat Rev Neurosci* **v. 7**, p. 41-53.

Astrocytes regulate development and function of blood-brain barrier



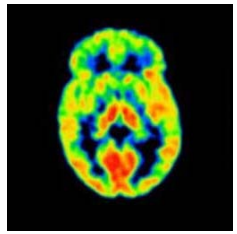


The brain is one of the most vascularised organ in the human body.

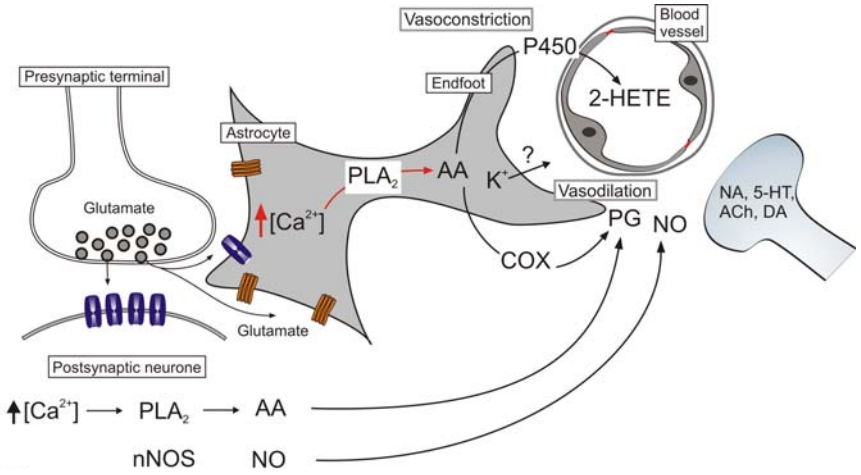
Zlokovic & Apuzzo, 1998 taken from
http://www.scholarpedia.org/article/Neurovascular_coupling

Increase in neuronal activity triggers a local increase in cerebral blood flow, a response known as functional hyperaemia. The concept of functional hyperaemia postulating that "…the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity" was introduced (independently) by Angelo Mosso in 1880 and by Charles Roy and Charles Sherrington in 1890.

The local fluctuations of blood flow can be visualised *in vivo* by different brain imaging techniques



Astrocytes create neurovascular units and link synaptic activity to the tonus of brain capillaries thus regulating microcirculation

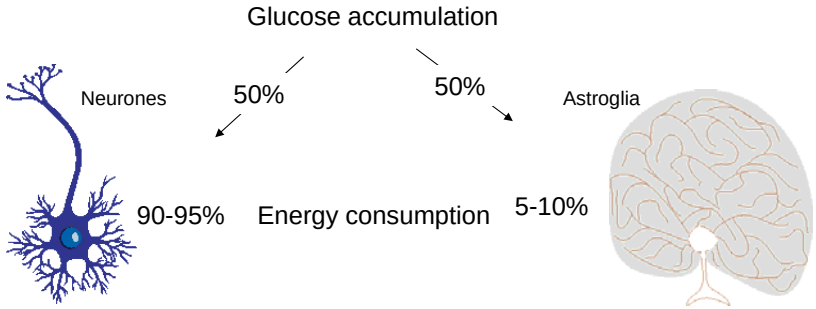


Verkhratsky & Butt (2013): *Physiology and Pathophysiology of Neuroglia*, Wiley, pp.560

Brain energetics

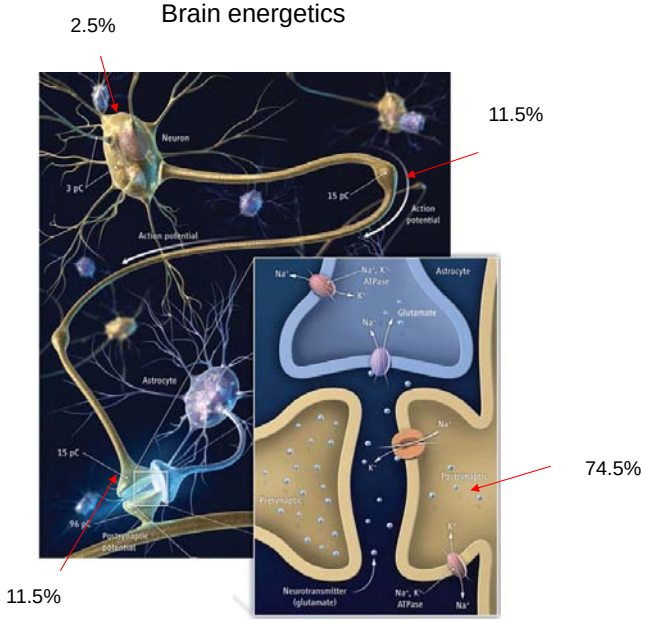
The brain, which represents ~ 2% of the total mass of the human body consumes ~ 20% of the total energy produced by the organism (as judged by glucose and oxygen utilization) whereas the brain blood flow approaches ~10% of total cardiac output.

The energy consumption is directly linked to the brain activity. During sleep the brain energy uptake decreases by ~ 40%, while under cognitive stress increases by ~ 12%.



Brain energetics

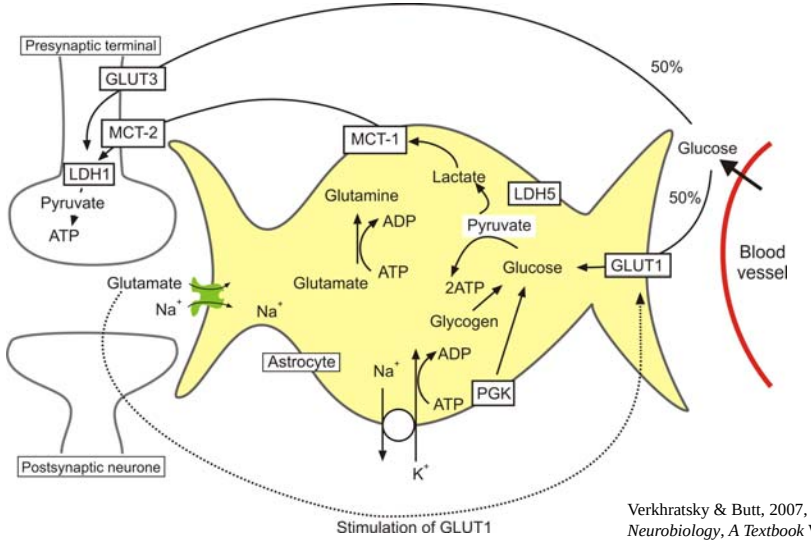
Most of energy is consumed at the synaptic level



Magistretti (2009): *Science*, **v. 325**, p.1349-1351

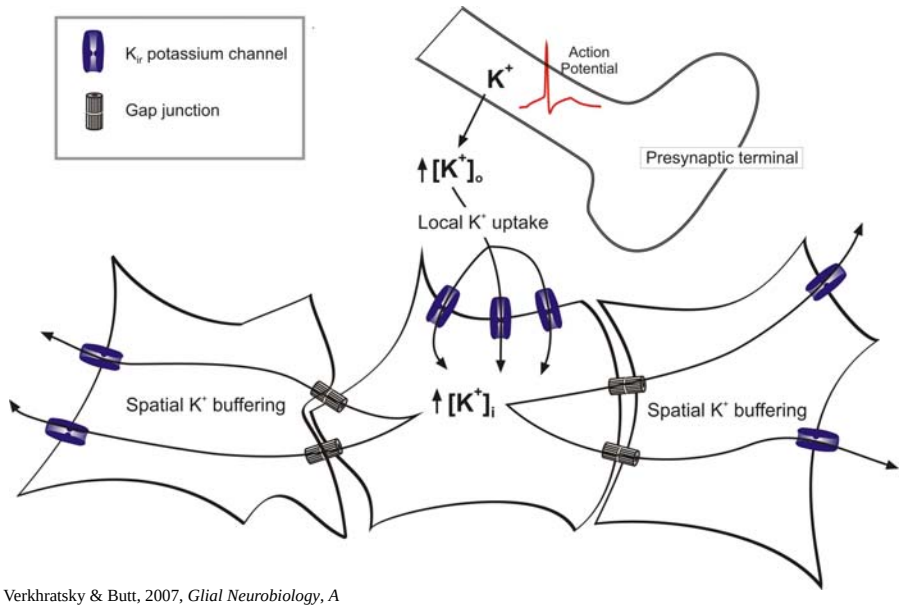
Published by AAAS

Lactate produced in astrocytes and transported to neurones provides additional metabolic substrate to functionally active synapses (Lactate shuttle)



Verkhratsky & Butt, 2007, *Glial Neurobiology, A Textbook* Wiley & Sons

Potassium buffering



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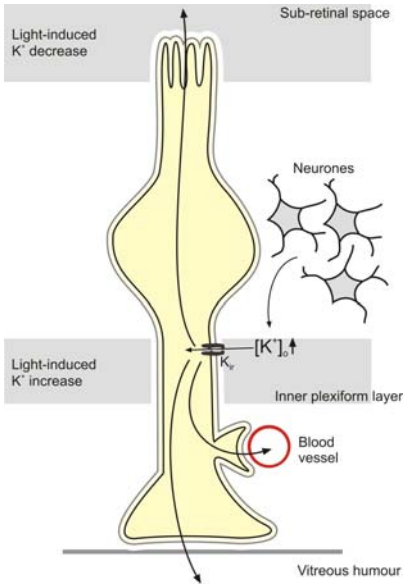
Potassium siphoning in the single Muller glial cell



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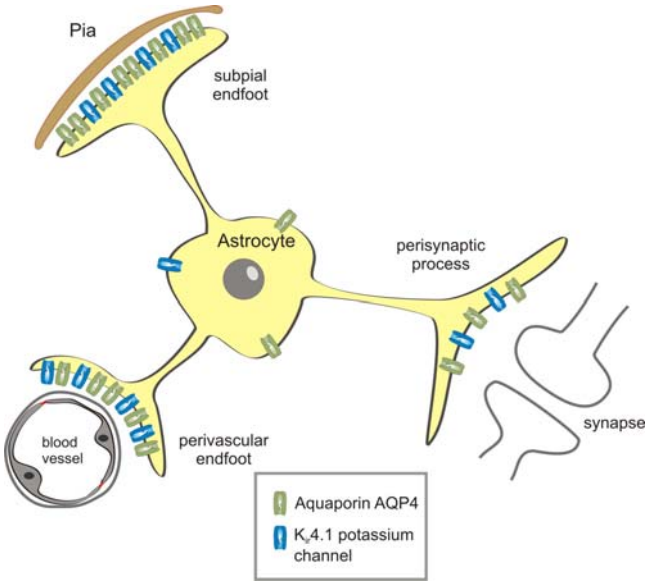
Astrocytes express water channels (aquaporins)



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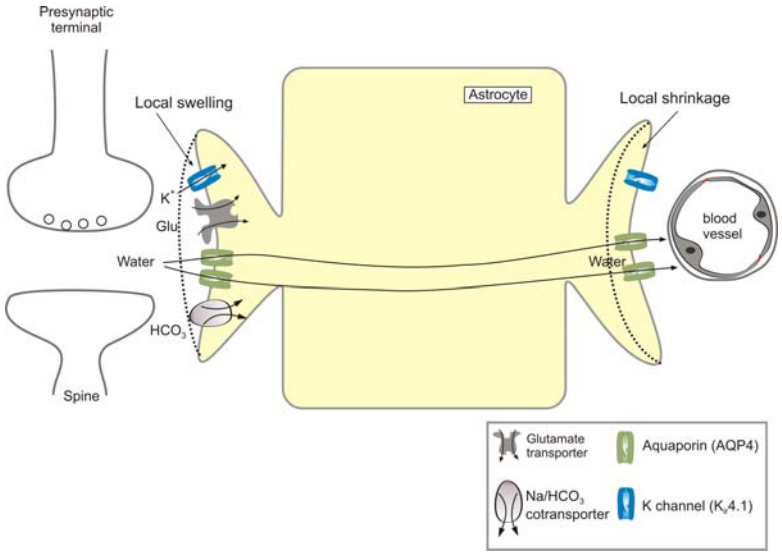
Control over water movements/redistribution



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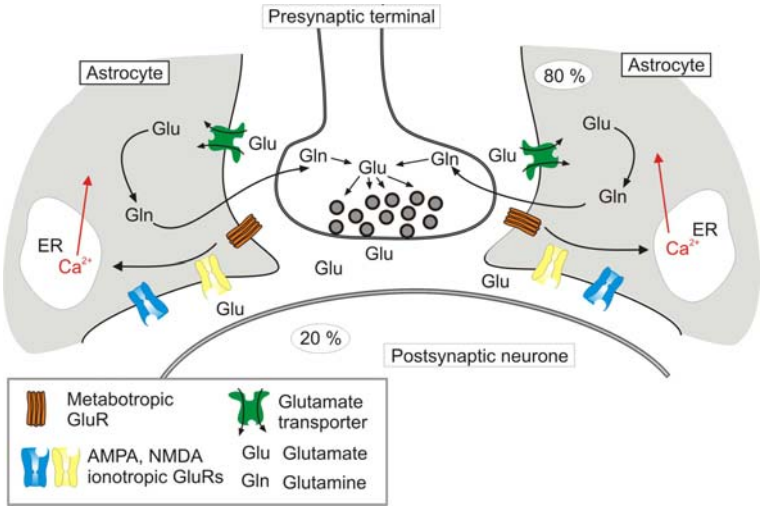
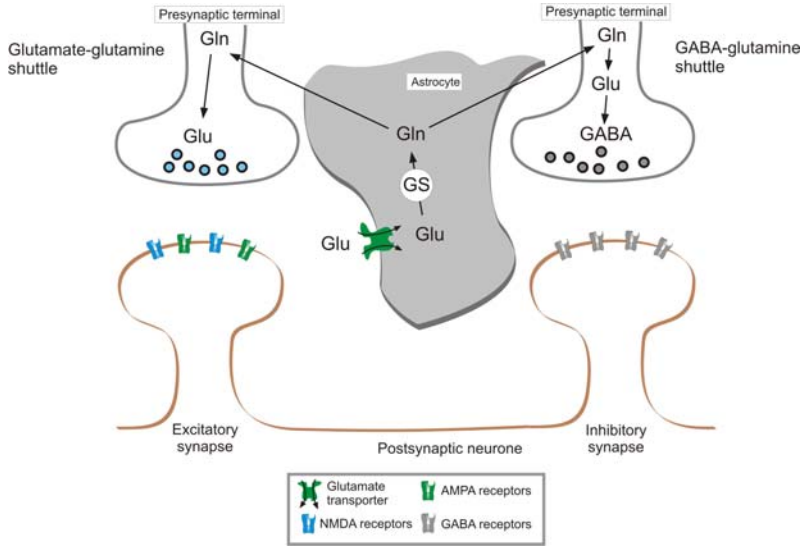
Astrocytes control brain glutamate homeostasis through glutamate-uptake and glutamate-glutamine shuttle



Verkhratsky & Butt, 2007, *Glial Neurobiology, A Textbook* Wiley & Sons

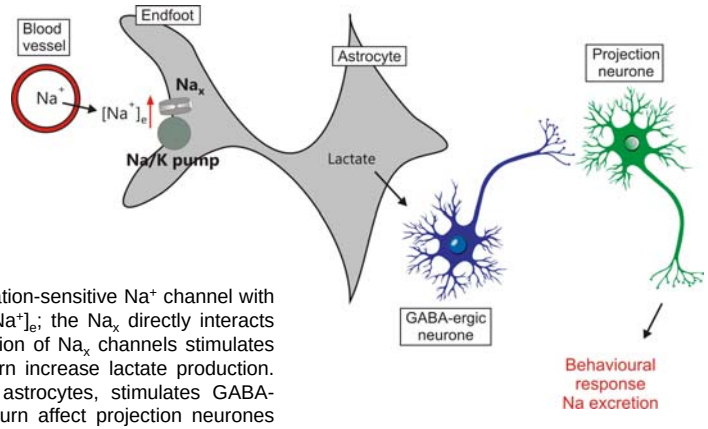
Astrocytes control neurotransmission by supplying neurones with glutamine, precursor of glutamate and GABA



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

Astrocytes are essential for Na^+ homeostasis being "Salt sensors" of the CNS

Astrocytes from subfornical organ (which is one of the circumventricular organs involved in regulation of Na^+ homeostasis) express a specific "salt sensing" machinery build around atypical sodium channel, Na_x.

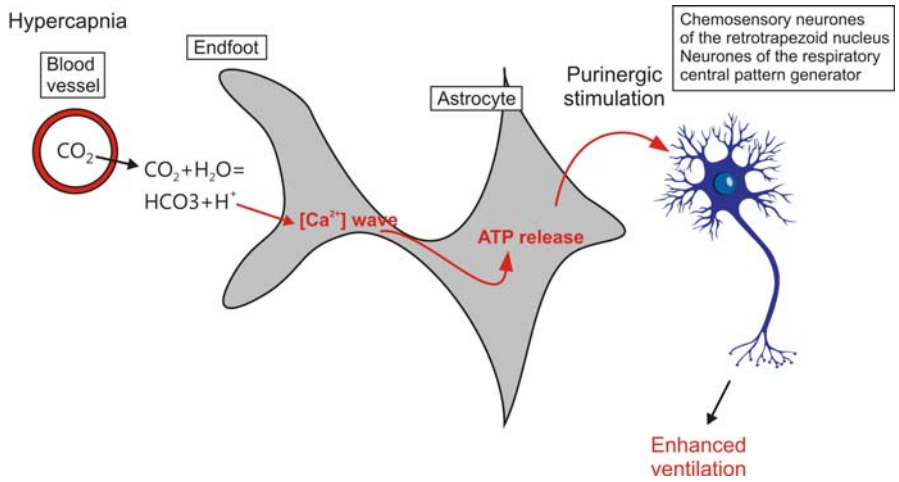


The Na_x is a a concentration-sensitive Na^+ channel with a threshold ~150 mM $[Na^+]_e$; the Na_x directly interacts with Na/K pump. Activation of Na_x channels stimulates Na/K pump, which in turn increase lactate production. Lactate, released from astrocytes, stimulates GABA-ergic neurones that in turn affect projection neurones involved in salt aversive behaviour and regulation of Na^+ excretion.

Shimizu, H, Watanabe, E, Hiyama, TY, Nagakura, A, Fujikawa, A, Okado, H, Yanagawa, Y, Obata, K & Noda, M, (2007): *Neuron*, **v. 56**, p. 59-72.

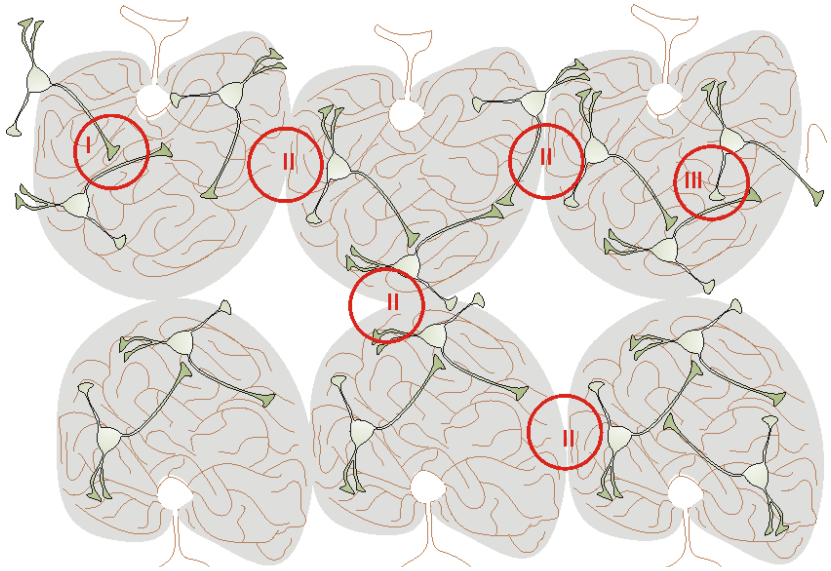
Modified and redrawn from:
Iadecola, C, (2007): *Neuron*, **v. 54**, p. 3-5.

Astrocytes provide for CO_2/H^+ chemosensitivity of the CNS And are instrumental for regulation of ventilation



Drawn based on concepts described in:
Gourine & Kasparov (2011): *Exp Physiol*.

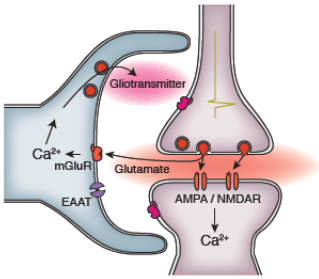
Signalling in neuronal-glial networks



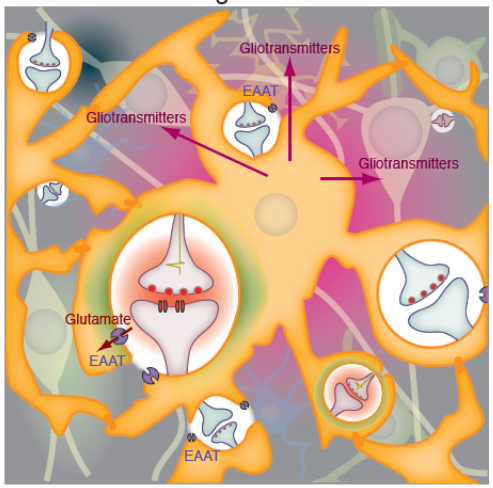
I - Local signalling in tripartite synapse
II - Propagating signalling in glial syncytium
III - Distal signaling through the release of gliotransmitters

Astroglia in synaptic transmission: Tripartite synapse versus astroglial cradle?

Tripartite synapse

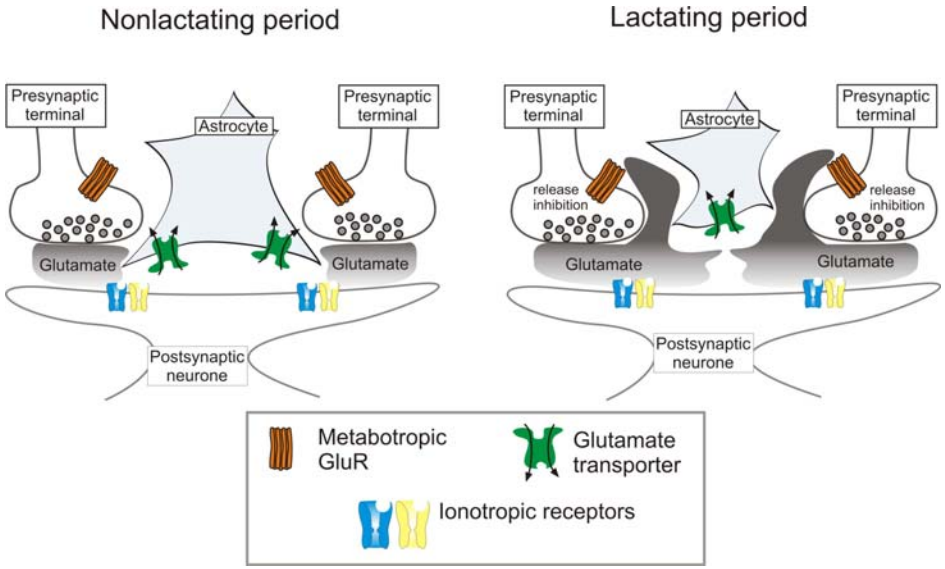


Astroglial cradle



Nedergaard & Verkhratsky, submitted

Astroglia regulate synaptic plasticity though remodelling perisynaptic coverage



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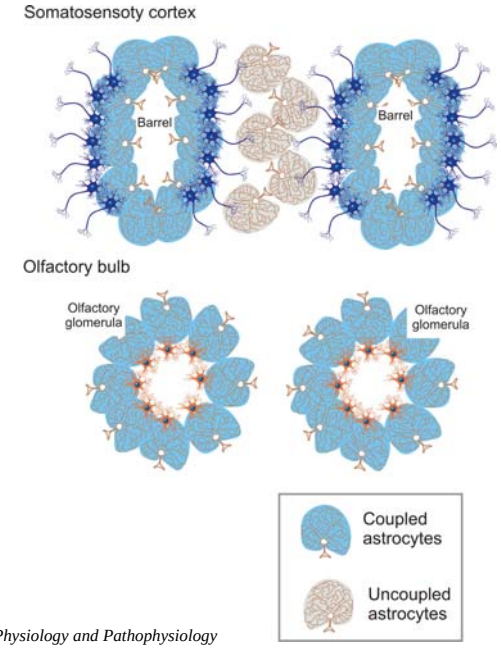
Astroglial syncytia



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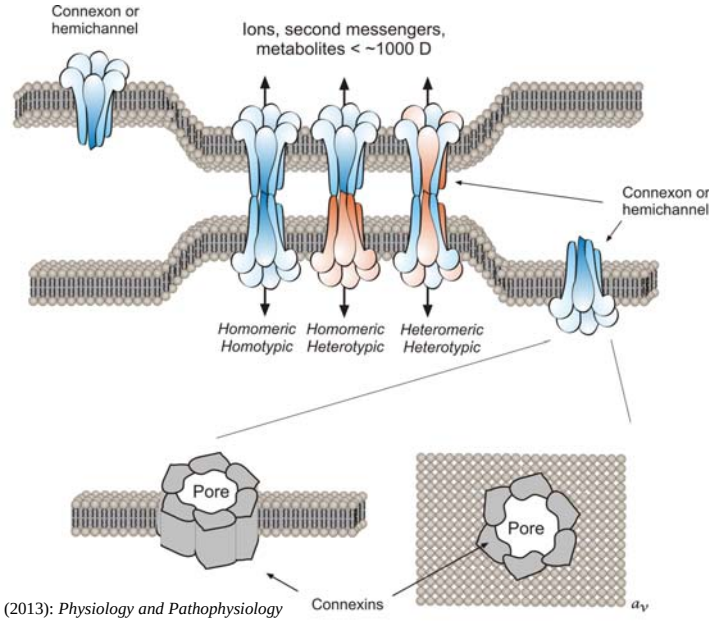
Propagating molecular signalling through gap junctions



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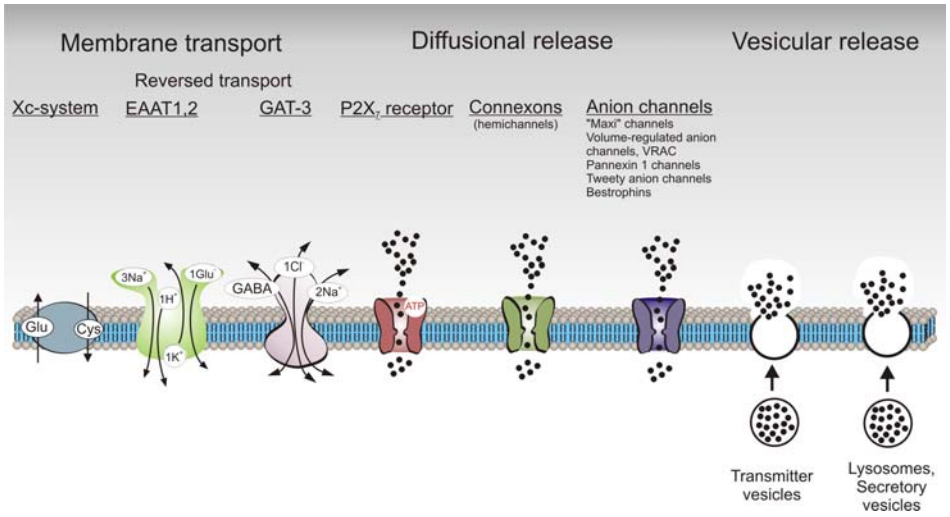
Neurotransmitter release from astroglia: multiple pathways



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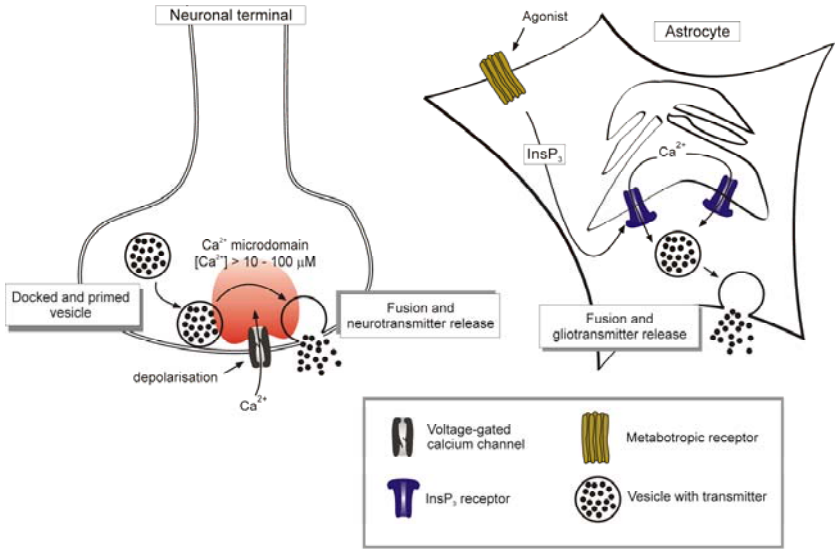
Neurotransmitter release from neuronal terminals and astrocytes are fundamentally different



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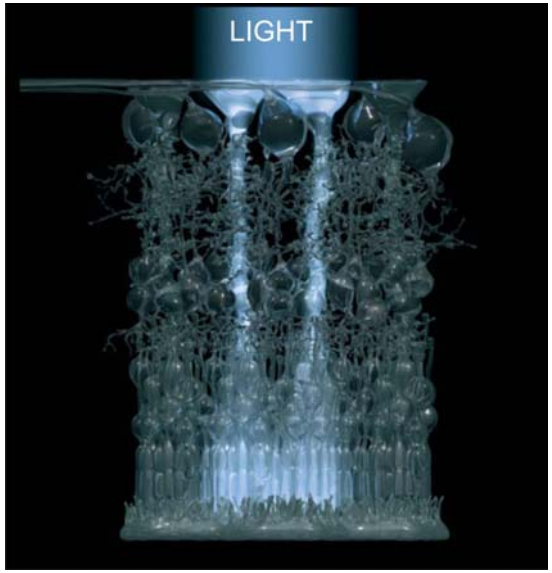
Müller glial cells act as light guides in the retina



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Conclusions

Astrocytes provide a scaffold and canvass of the grey matter. They parcellate the CNS parenchyma creating relatively independent neurovascular units. Astrocytes control all aspects of the CNS homeostasis, regulating microcirculation, energy supply, water and ion movements and turnover of many neurotransmitters. Astrocytes also act as a CNS chemosensors being instrumental in monitoring changes in pCO_2 and concentration of protons and sodium. Astrocytes are integrated into internally connected and anatomically segregated syncytia and are in a possession of complex mechanisms for intercellular signalling.