มหาวิทยาลัยมหิดล
คณะแพทยศาสตร์
ศิริราชพยาบาล

Role of glia cells in pathogenesis of epilepsy

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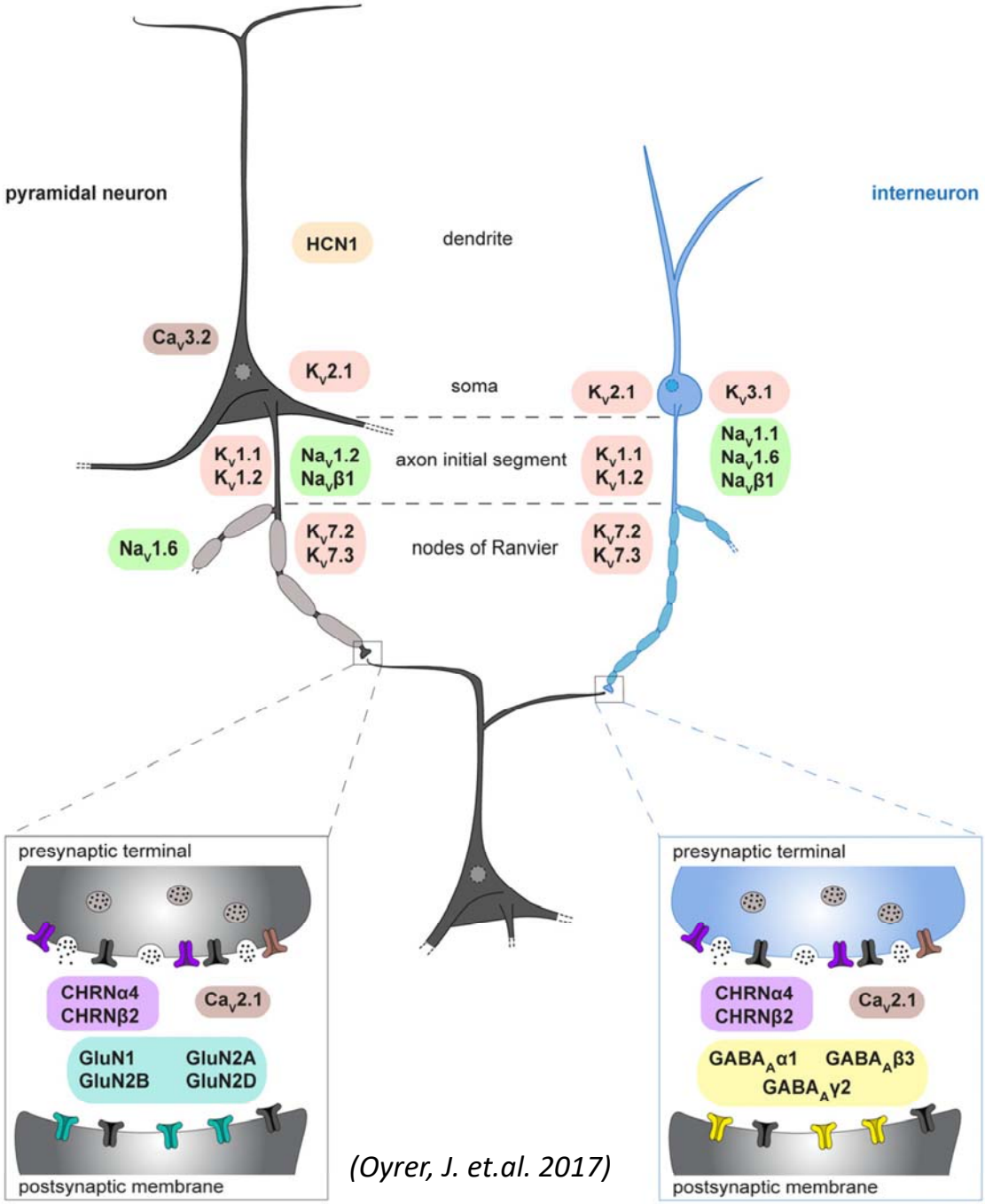
Epilepsy

- An alteration of neurologic function caused by the hyperexcitability, excessive, hypersynchronous discharge of neurons in the brain.
- Mechanism: distortion of the normal balance between excitation and inhibition in the brain
  - Alteration of ion channels
    - voltage gated ion channels
  - Alteration of synaptic transmission
    - Excitatory post synaptic potentials (EPSPs)
    - inhibitory post synaptic potentials (IPSPs)

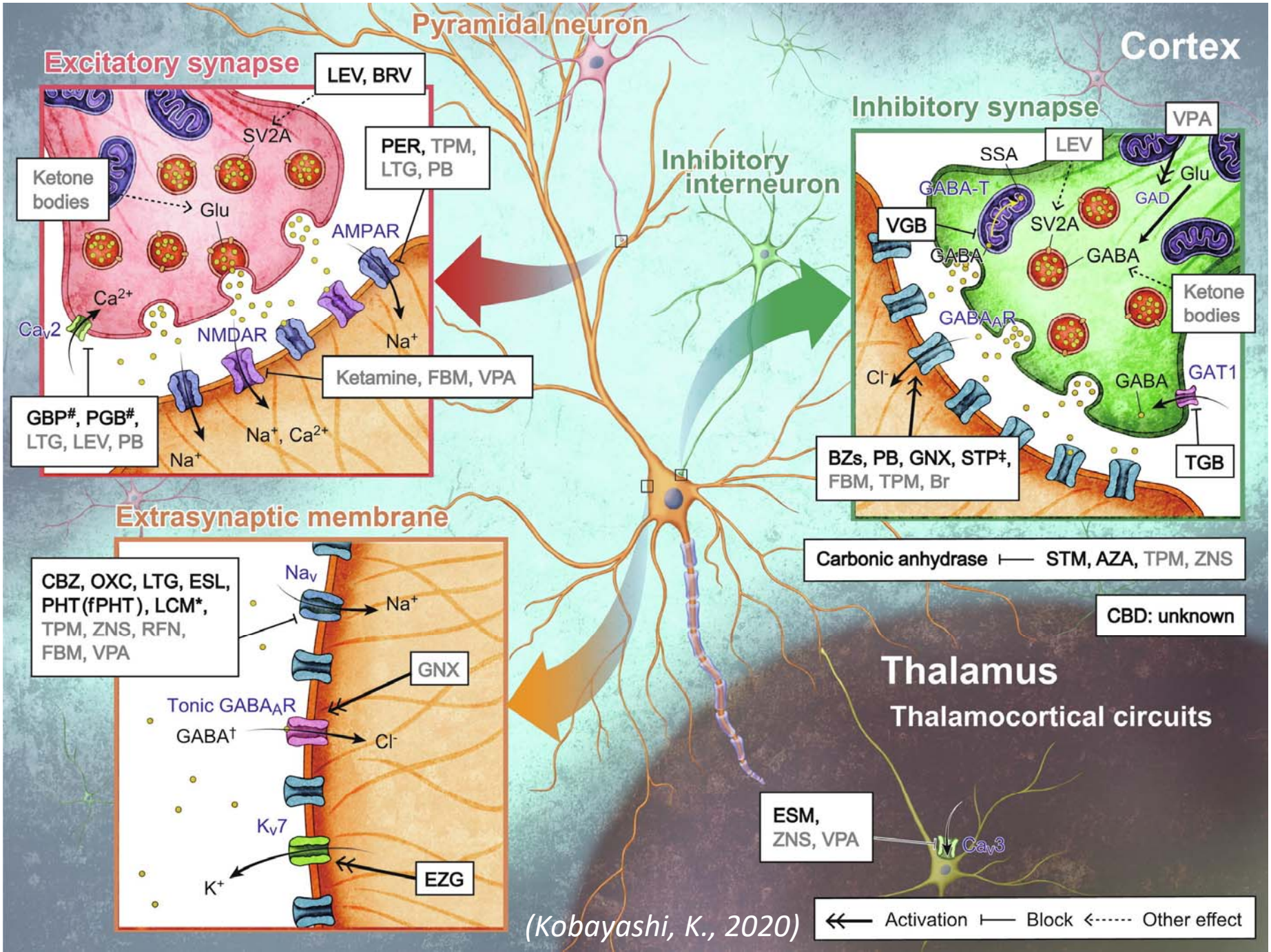
- *Consideration*
  - *Ictogenesis vs Epileptogenesis*

Pathophysiology: Neuronal basis



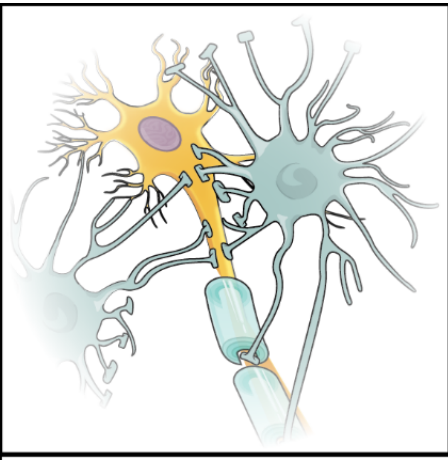
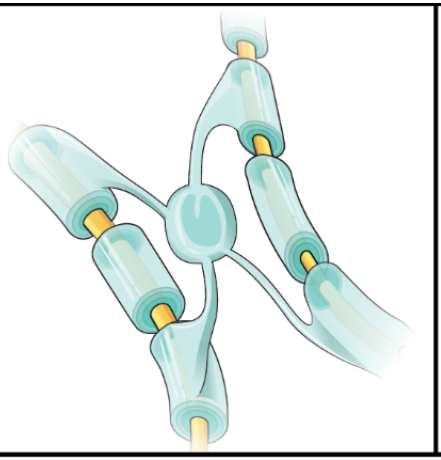
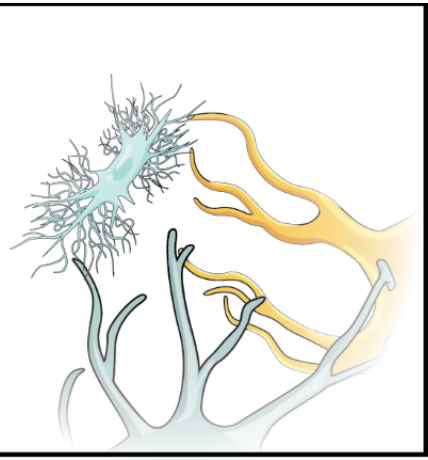
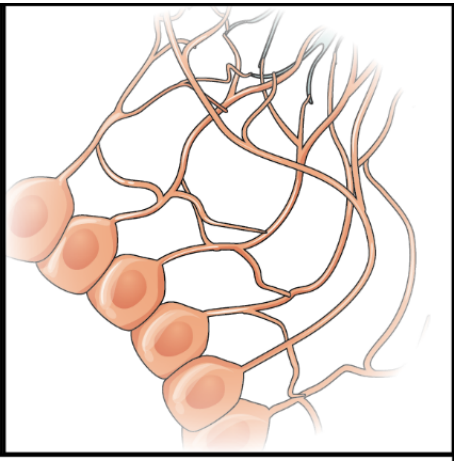
(Oyrer, J. et.al. 2017)

Antiepileptic drugs



(Kobayashi, K., 2020)

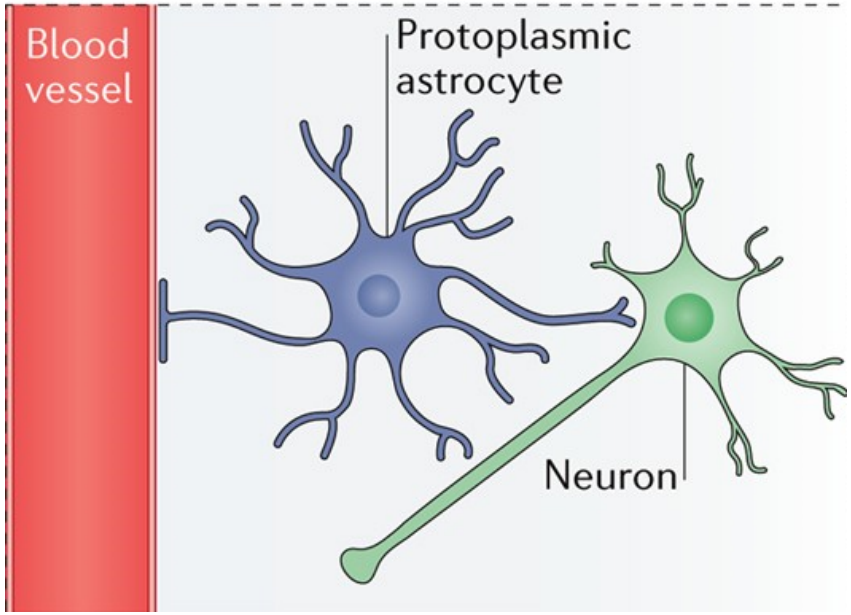
Neuroglia

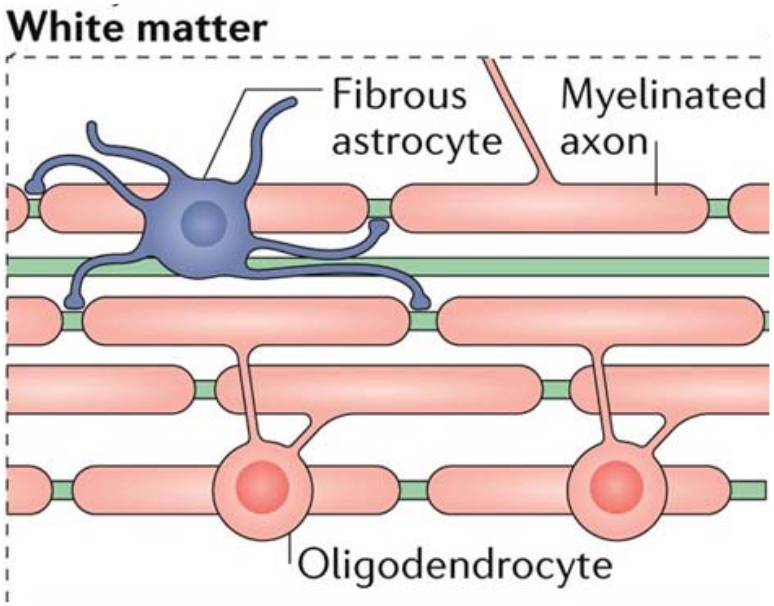
CNS glia				
	Astrocyte	Oligodendrocyte	Microglia	Ependymal cell
PNS glia	Satellite cell	Schwann Cell	--	--
Functions	Maintain extracellular environment, remove excess neurotransmitter, direct neural growth, induce blood-brain barrier in CNS (astrocyte only)	Create myelin	Immune surveillance and phagocytosis	Create and circulate Cerebrospinal fluid (CSF)

- The unifying fundamental function of these cells is homeostasis of the nervous system.

Astrocyte

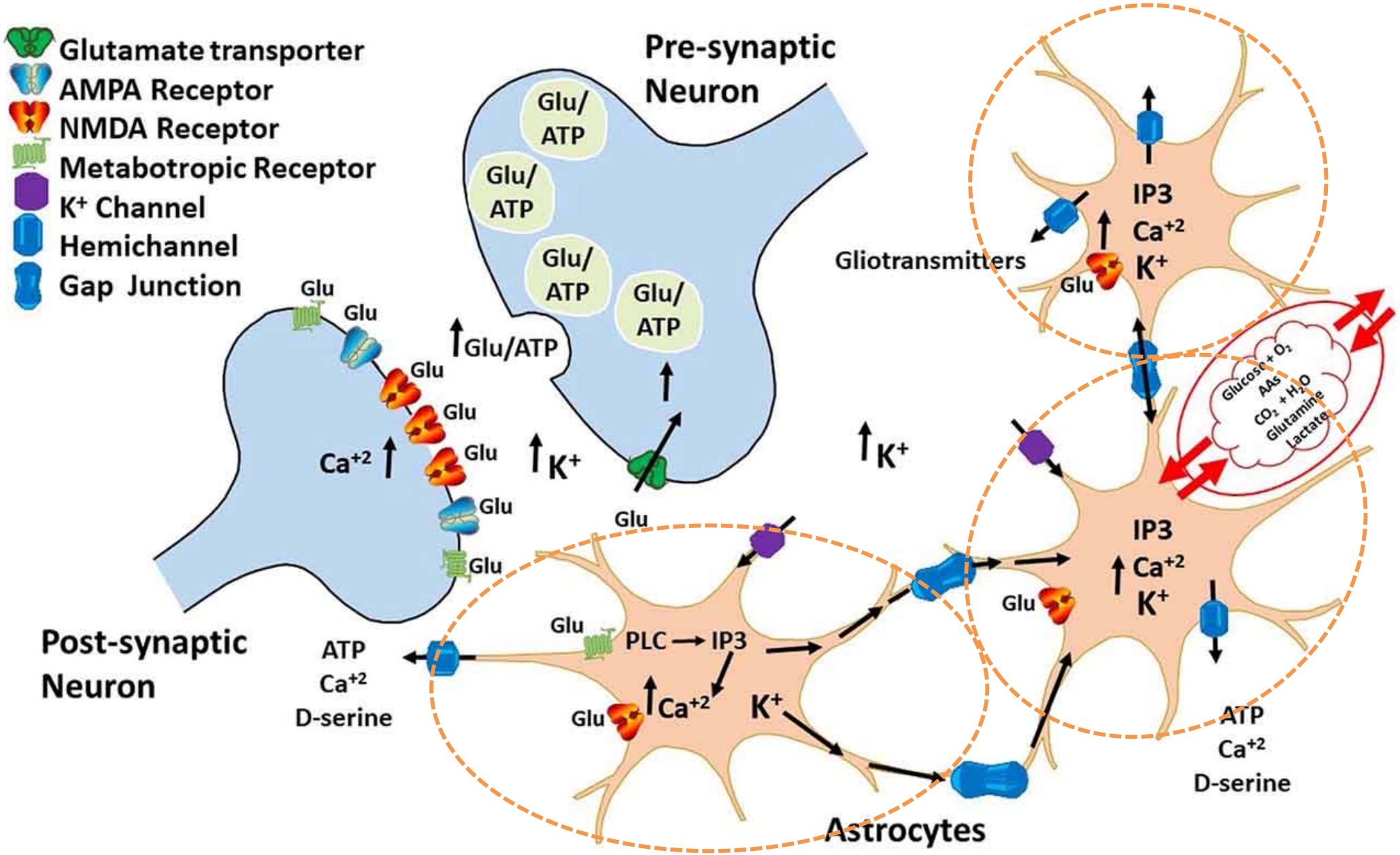
- Develops from neuroectoderm
- Electrically non-excitable and more negative resting membrane potential (RMP about−80 mV) compared to neurons
- High resting membrane permeability for K^+
- Heterogeneous morphology across different brain structures





(Haim, LB. et.al. 2017)

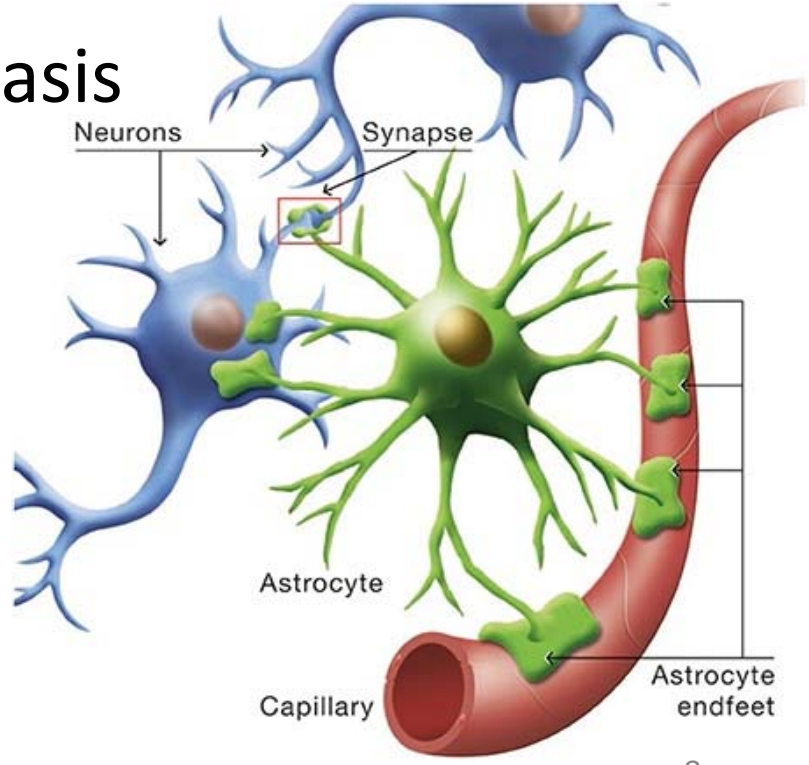
Astrocyte domain and Gap junctions



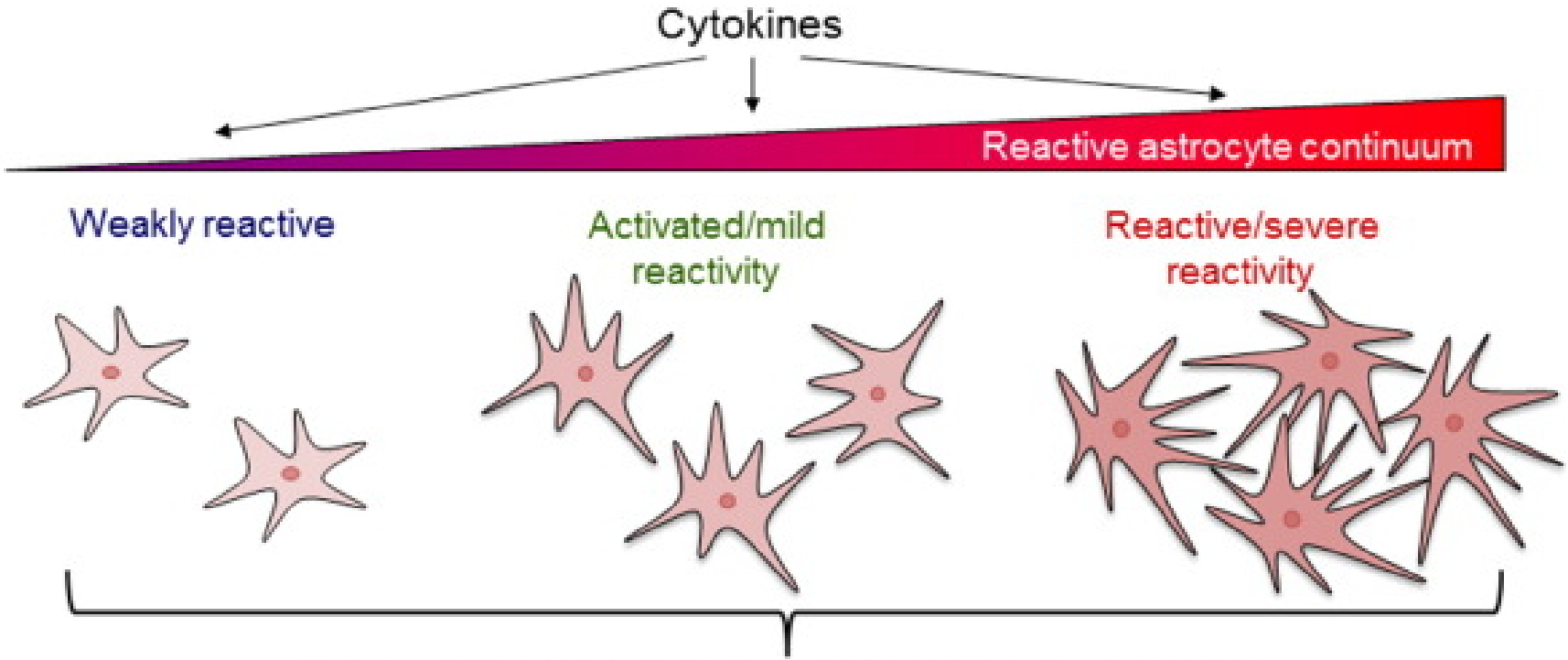
(Mayorquin, LC. et.al. 2018)

Astrocyte functions

- Maintenance of extracellular ionic concentration
  - K^+ and Water homeostasis
- Regulation of neurotransmission
  - Glutamate and GABA homeostasis
- Gliotransmission
- Blood brain barrier functions
- Brain energy metabolism



Reactive astrogliosis

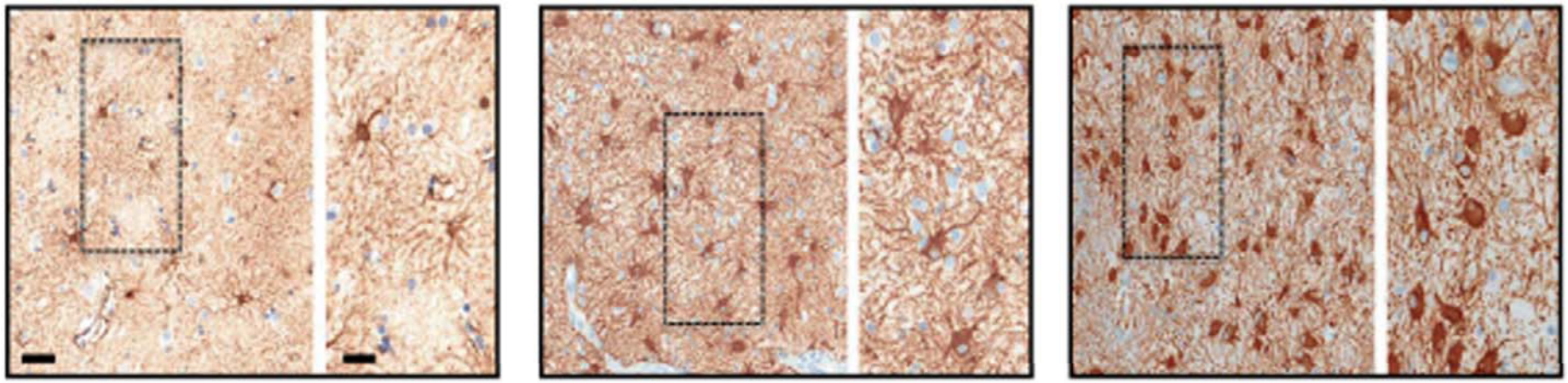


Cytokines/chemokines and growth factors produced by astrocytes directly or via their indirect effects on other cells

(e.g., ADNF, BDNF, CNTF, LIF, HGF, FGF-2, NGF)	(e.g.,FGF-2)	(e.g., CNTF, LIF, FGF-2, IL-6)	(e.g., TNF-α)	(e.g., IFN-γ)	(e.g., CXCL10)
Promote: • Neuronal survival • Neurite outgrowth	Promote neurogenesis via NSCs	Role in remyelination of demyelinated CNS lesions by promoting: • OPC survival • OPC proliferation • OPC maturation • EAE amelioration • Formation of glial scar	• Expression correlates with extent of demyelination in MS. • Myelin and oligodendrocyte damage *in vitro*. • May increase PDGF expression in demyelinated lesions.	• Suppresses remyelination. • Delays disease recovery in EAE. • Leads to regional hypomyelination.	• Expression is correlated with MS disease severity. • Suppresses myelination in myelinating cultures.

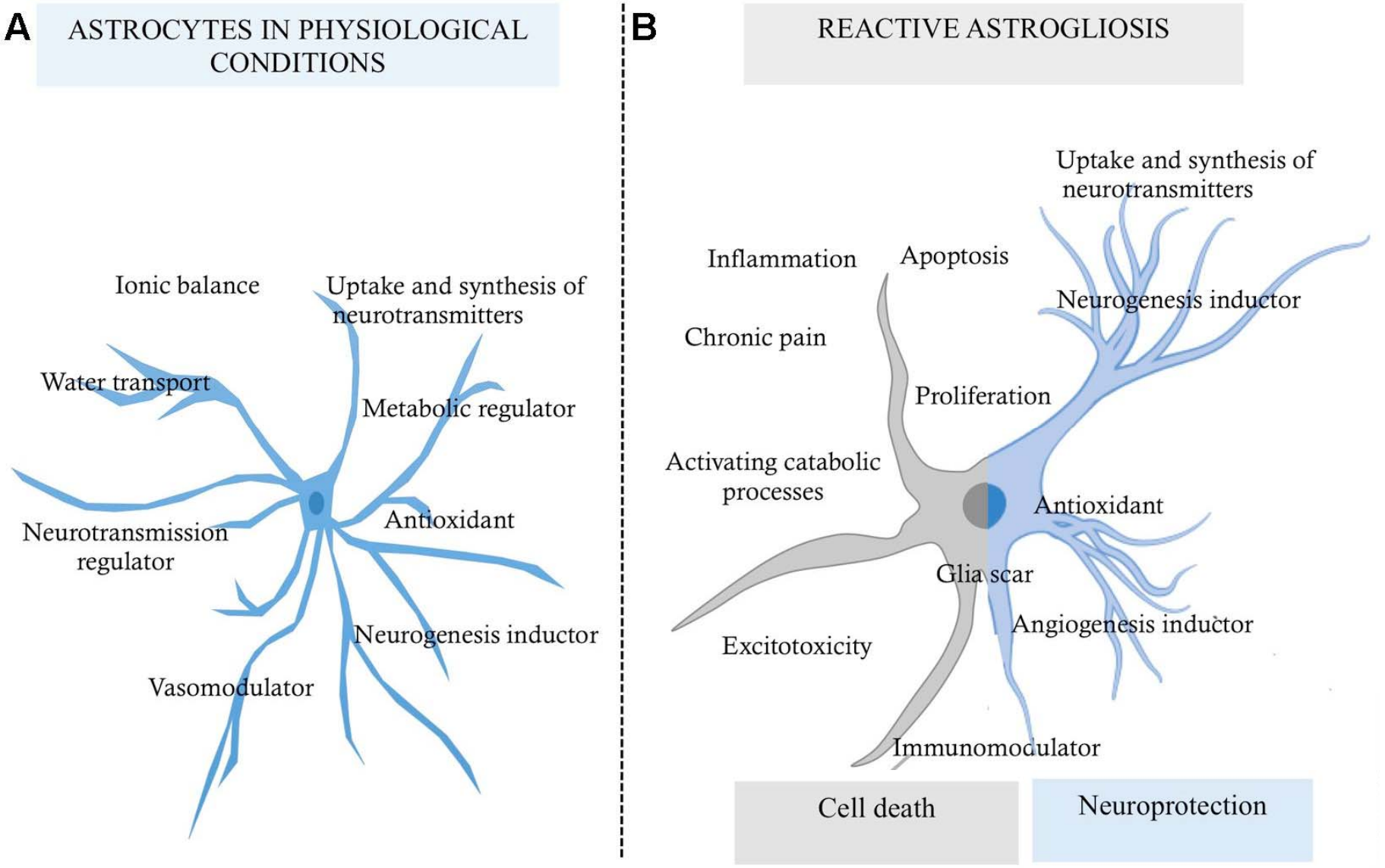
Reactive astrogliosis

healthy	mild to moderate insult	severe insult
moderate GFAP expression/ non-overlapping domains	hypertrophy/molecular and functional changes	persisting mature glial scar



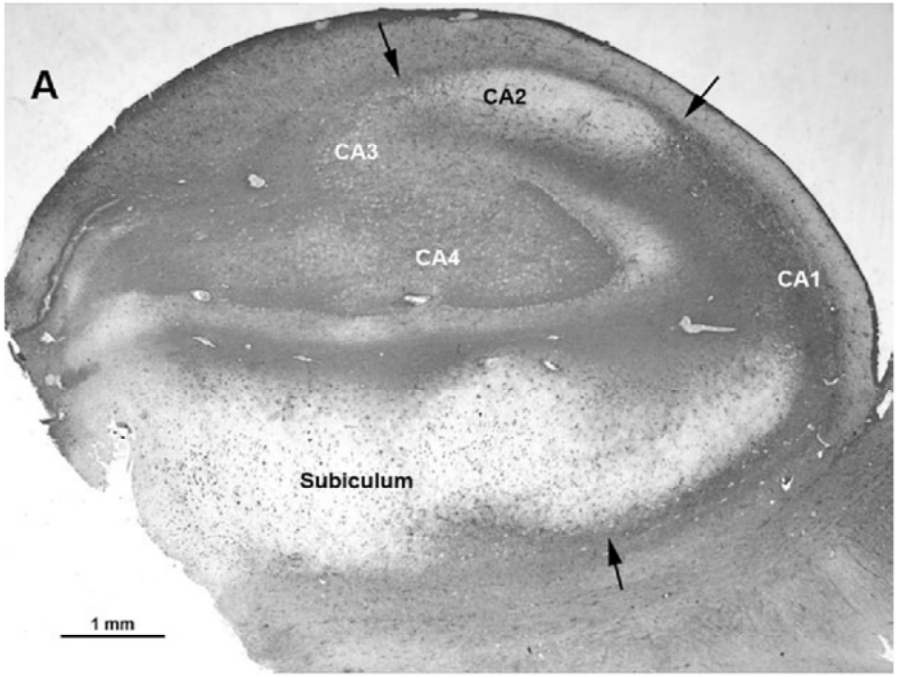
(Dossi, E. et.al. 2018)

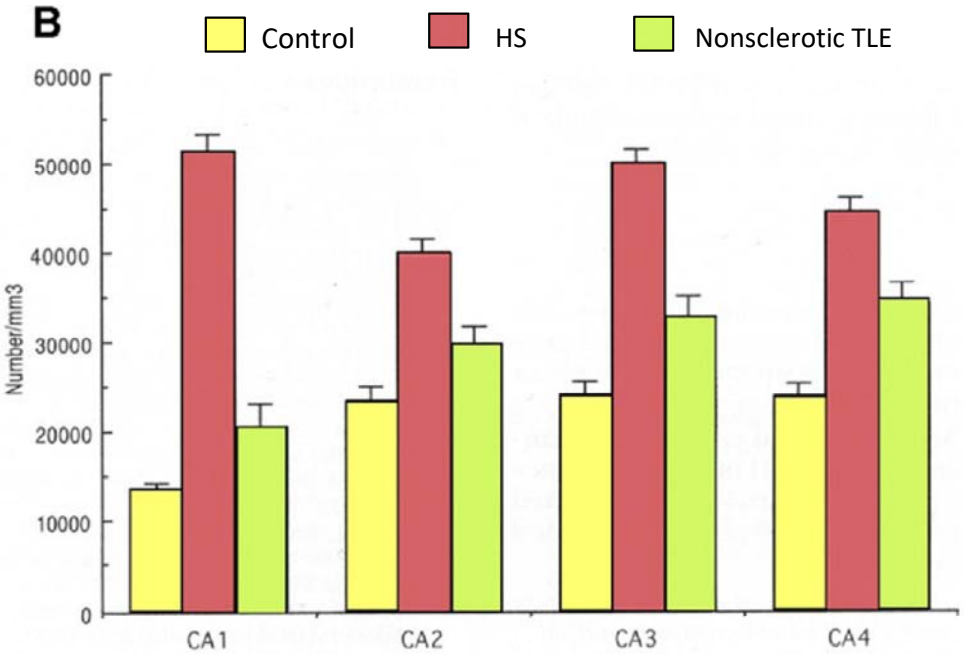
Reactive astrocyte



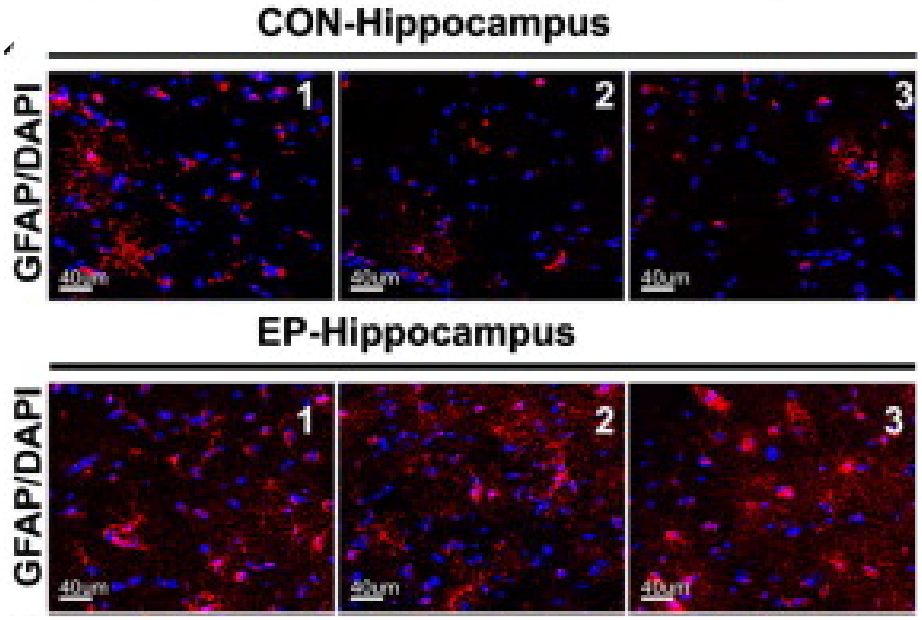
(Becerra-Calixto, A. and Cardona-Gomez, GP. 2017)

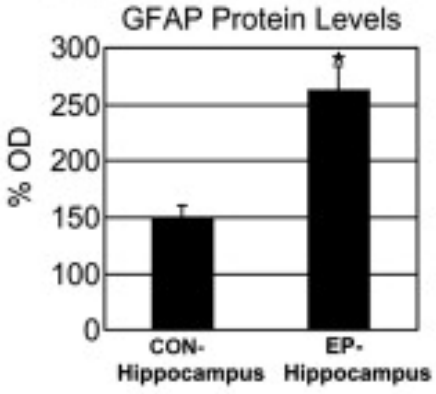
Reactive astrogliosis in Epilepsy

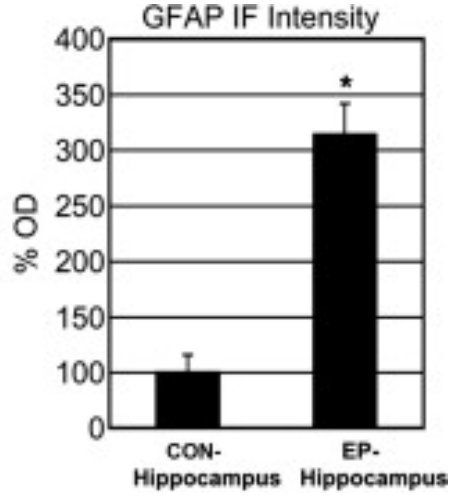




(de Lanerolle, NC. 2010)

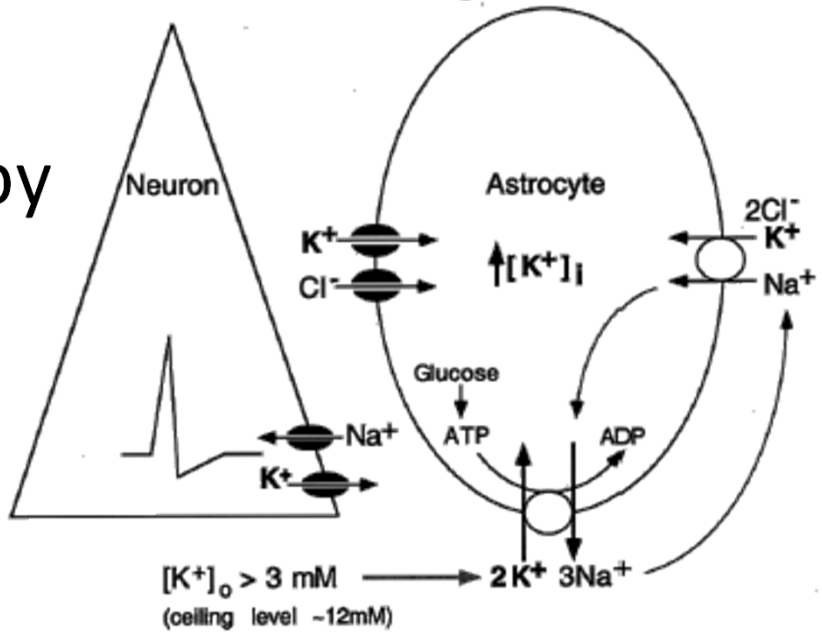






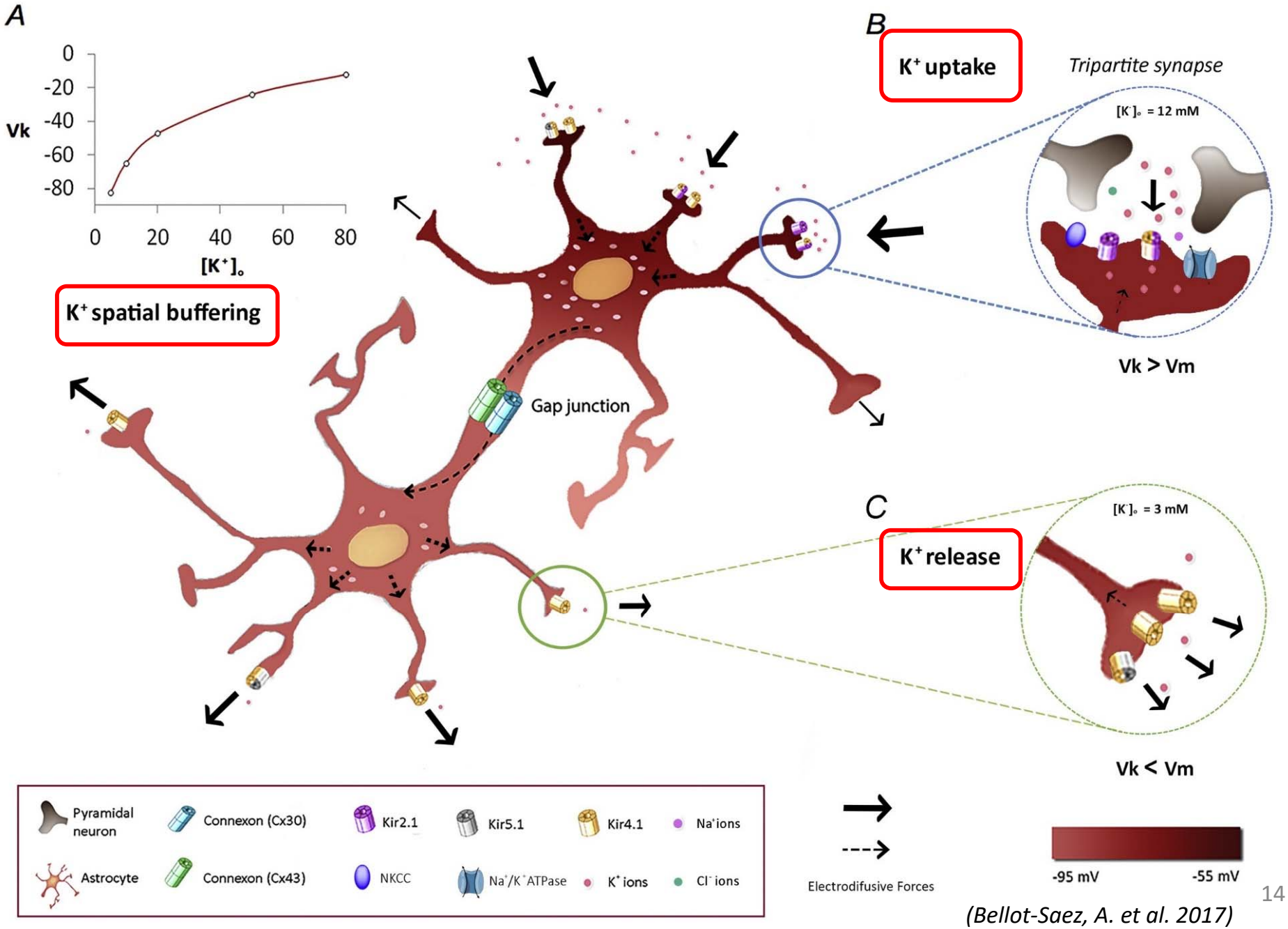
Maintenance of extracellular ionic concentration

- Basal extracellular K^+ ($[K^+]_o$) is 3 mM
- The $[K^+]_o$ increases during neuronal activity
- Astrocyte membrane is very sensitive to change in $[K^+]_o$
- The increased $[K^+]_o$ is removed by
  - Na^+-K^+ pump
  - Anion transporter (NKCC)
  - Inward rectifier K^+ channels (Kir)



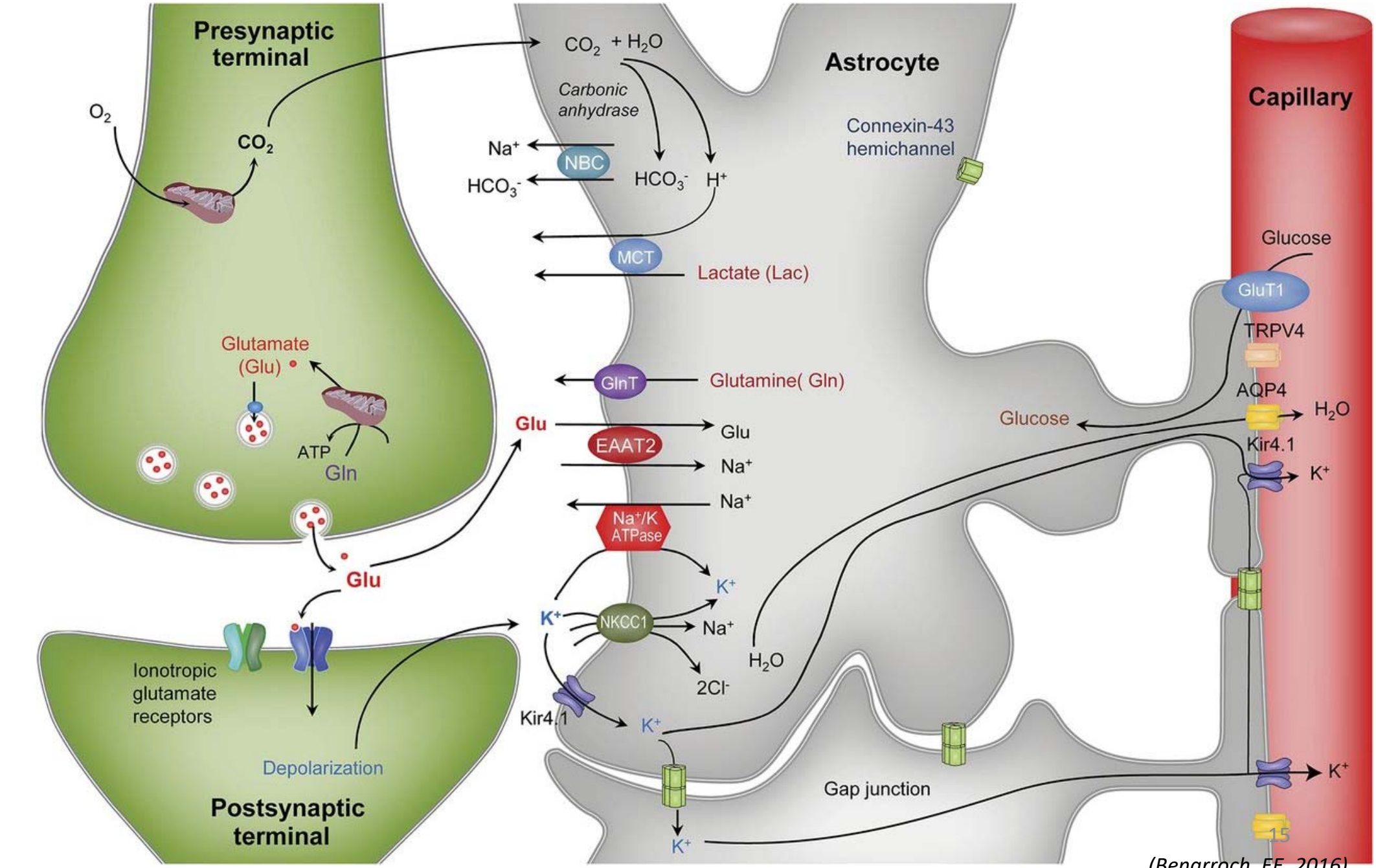
- Water is transported through aquaporin 4 channel accompanying K^+ transport
  - Osmotically neutral spatial buffering

K^+ Homeostasis



(Bellot-Saez, A. et al. 2017)

K^+ and Water Homeostasis

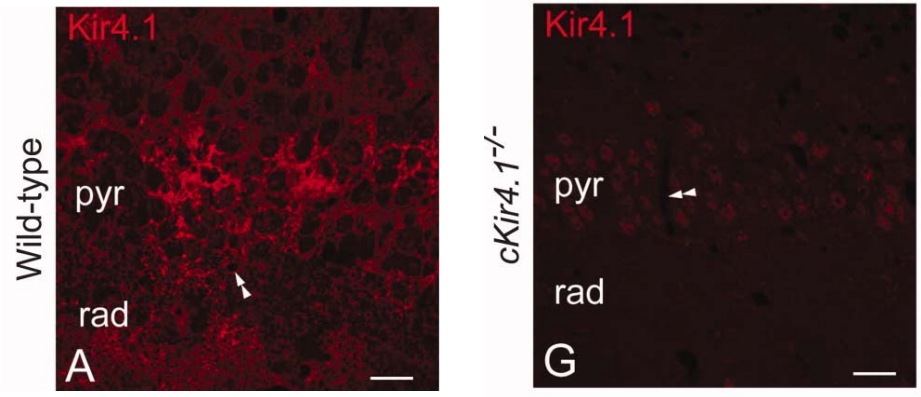


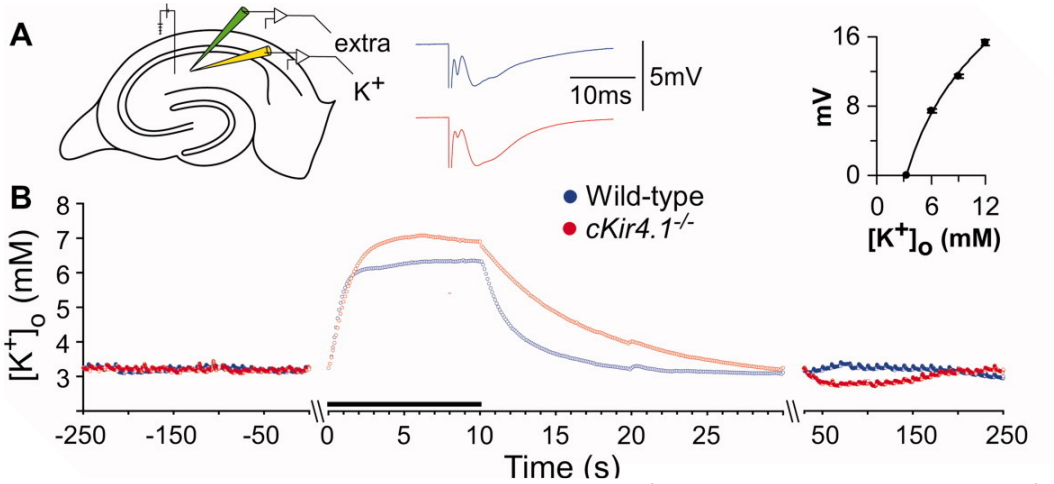
(Benarroch, EE. 2016)

Epilepsy and Kir channels

- Decreased Kir4.1 protein levels in HS tissues compared to non-HS TLE patients (Heuser, K. et al., 2012)

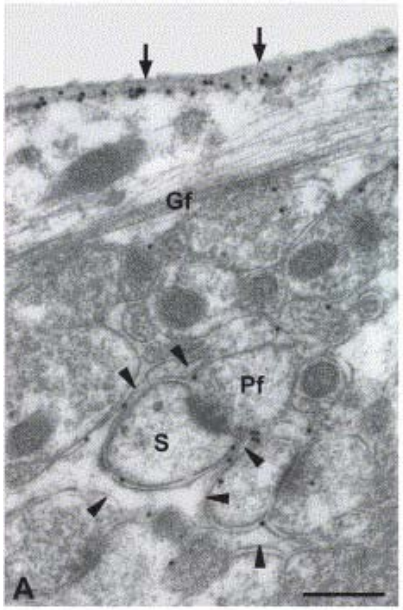
- Mutations of *KCNJ10*, which encodes the astroglial Kir4.1 are associated with epilepsy

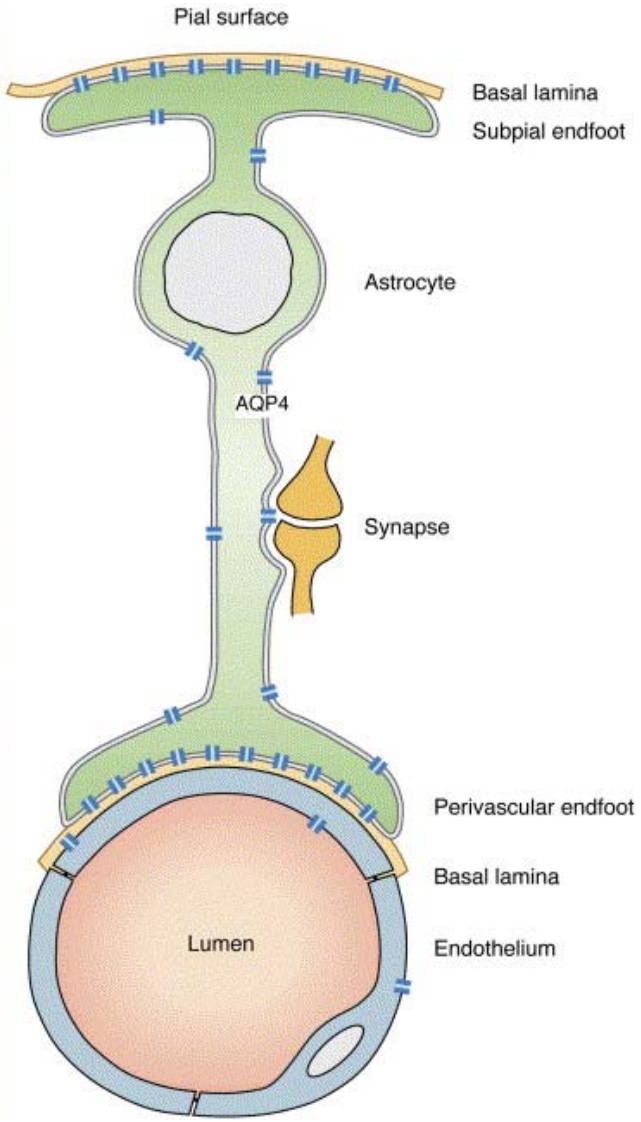




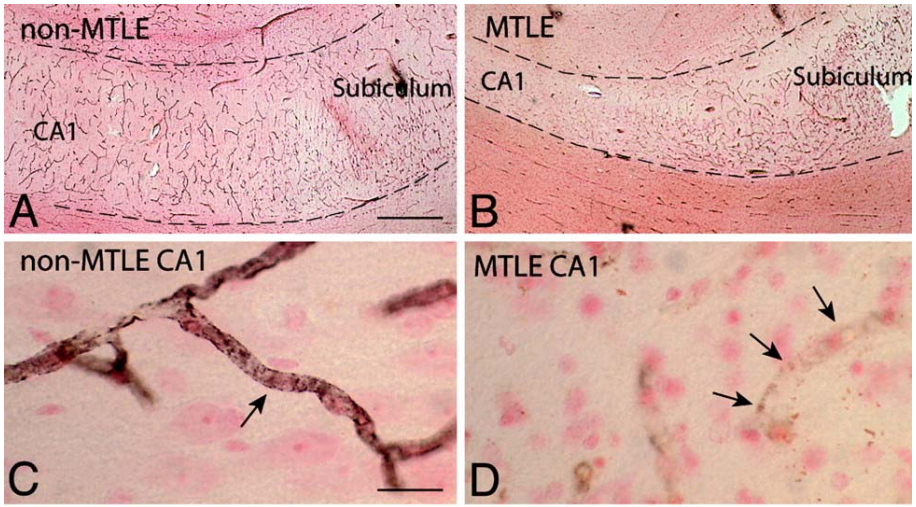
(Haj-Yasein, NN. et al. 2011)

Epilepsy and AQP4

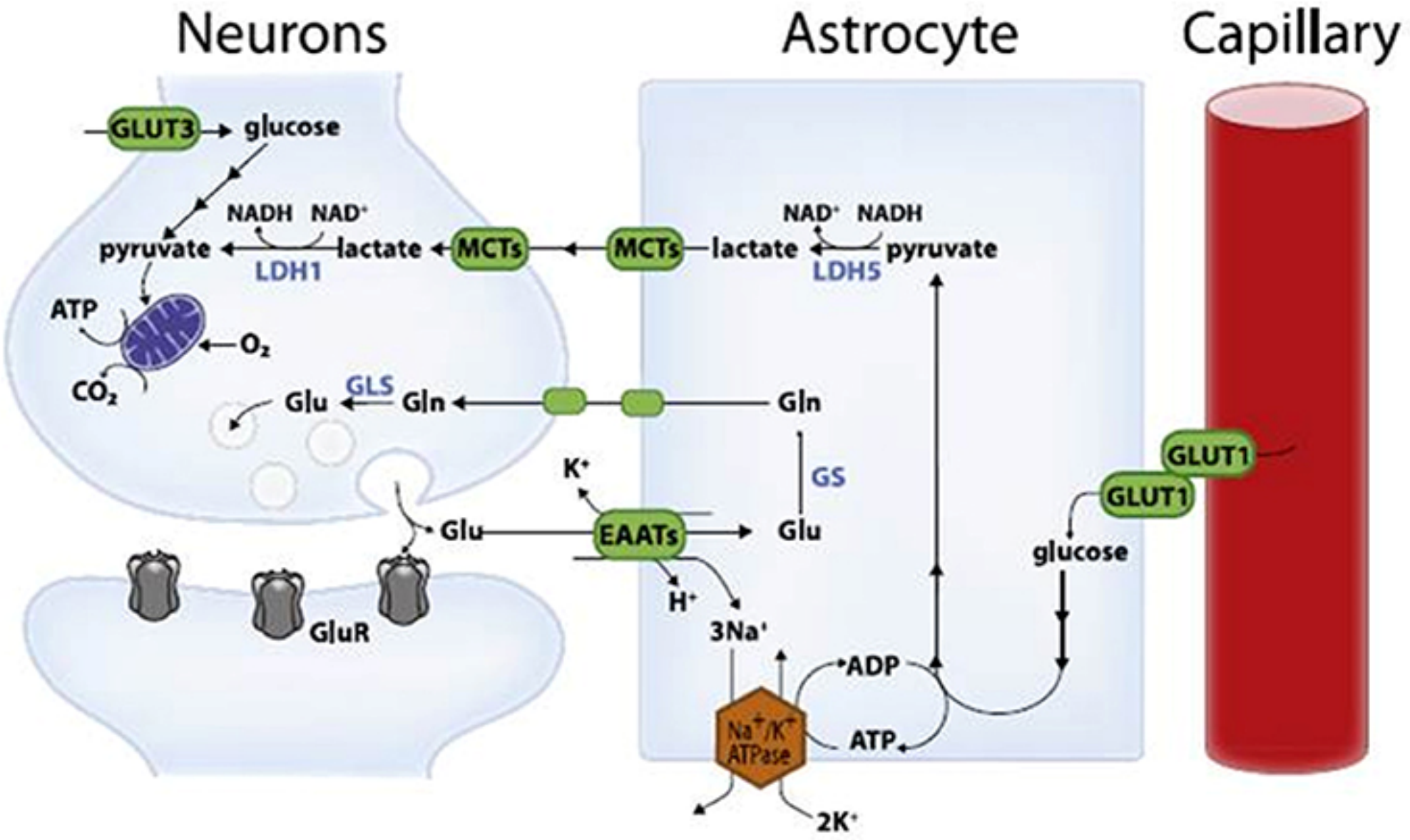




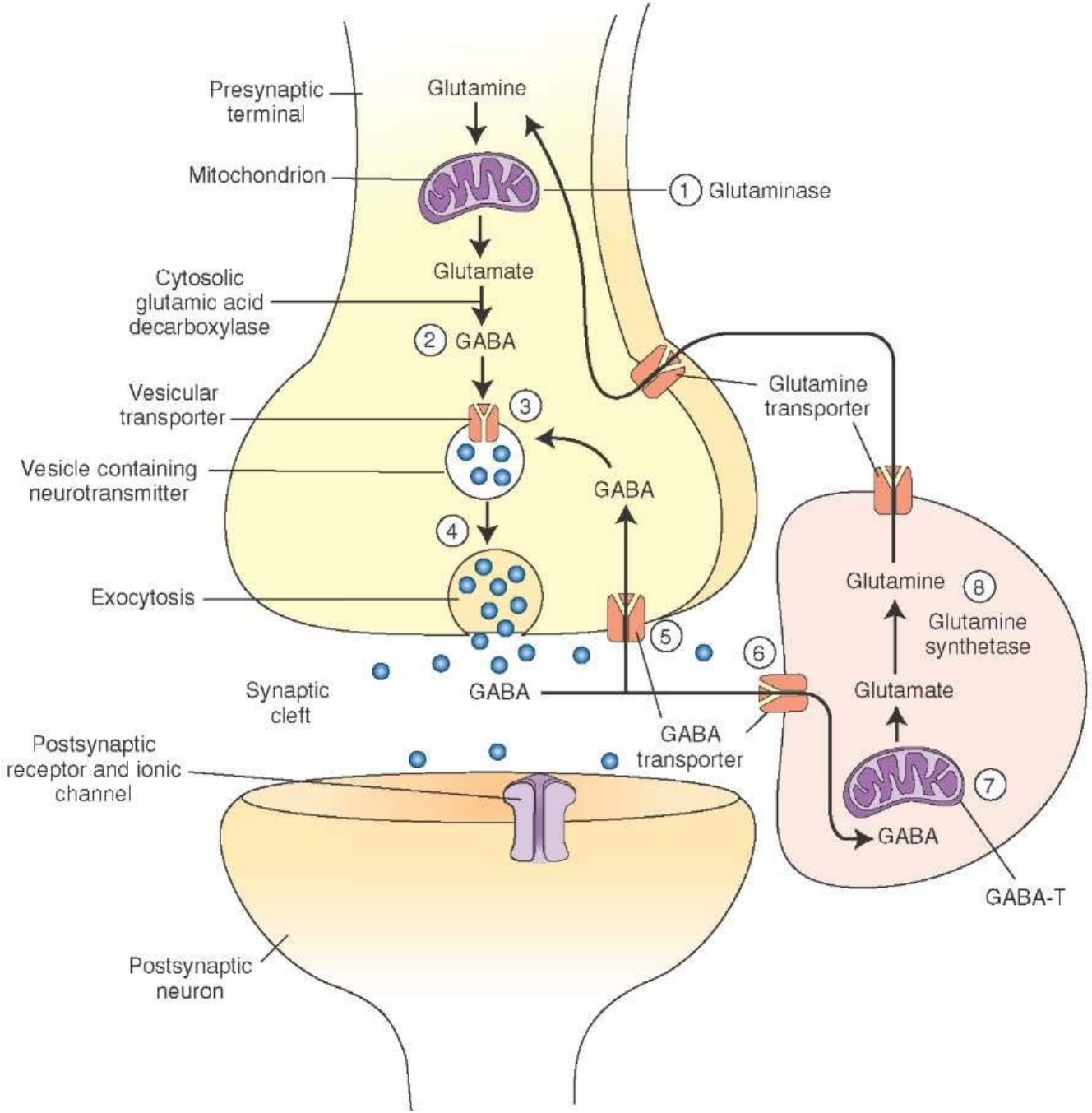
- AQP4 localized in astrocytic perivascular endfeet and perisynaptic processes. (Nagelhus, EA. et al., 2004).
- Reduced AQP4 density along the perivascular membrane domain of astrocytes in MTLE CA1 region (Eid, T. et al.,2005).



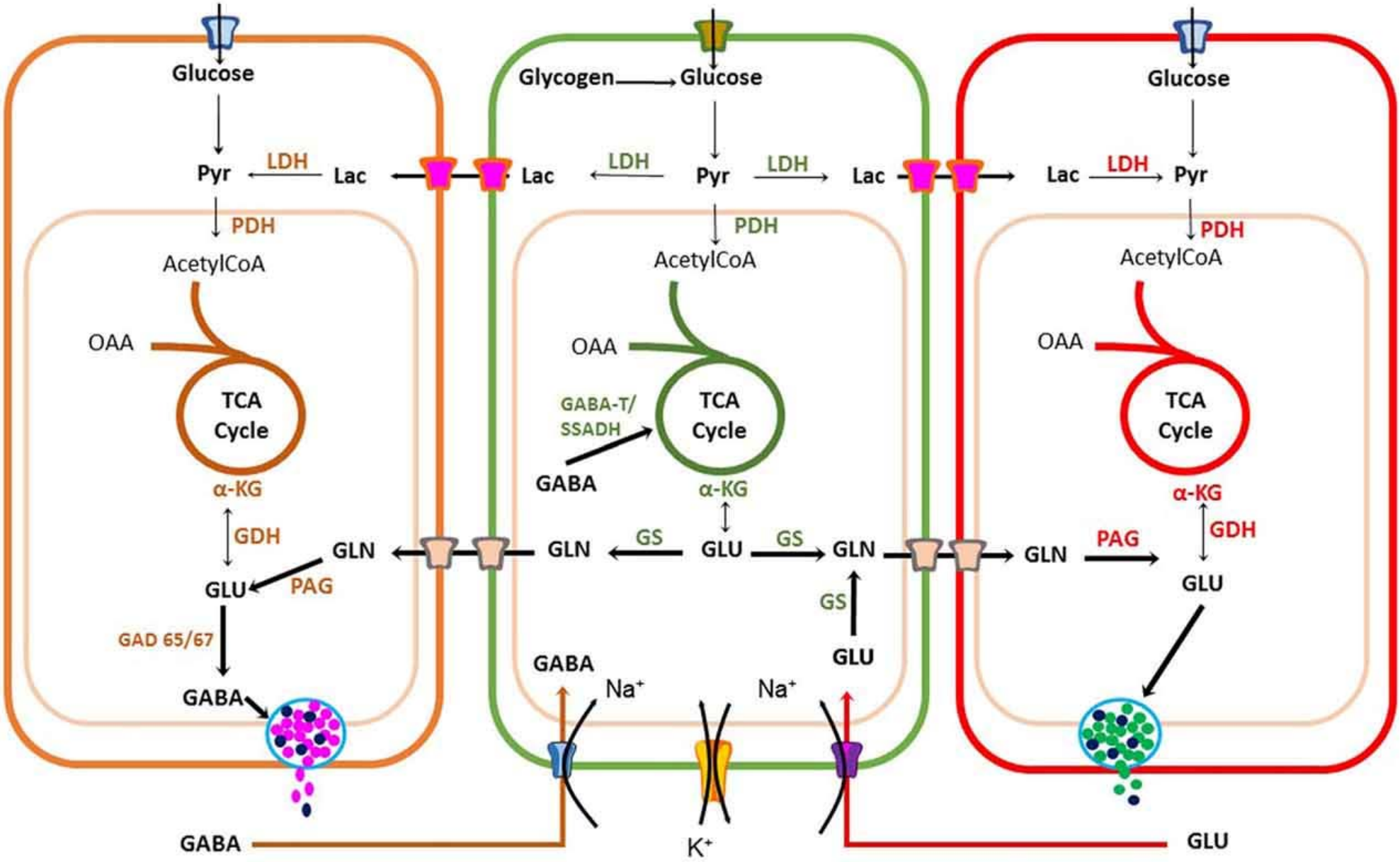
Astrocyte glutamate homeostasis



Astrocyte GABA homeostasis

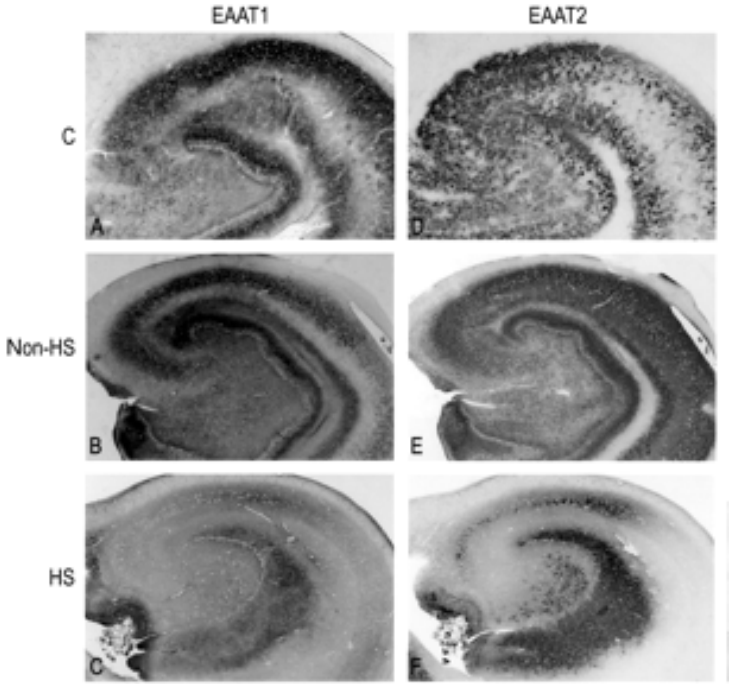


Glutamate and GABA homeostasis



Epilepsy and Glutamate

- Medial temporal lobe epilepsy patients have higher extracellular glutamate levels in the epileptic sclerotic hippocampus compared to non-HS and non-epileptic hippocampus. (Cavus, I. et al., 2005).
- Decreased astroglial GLT-1 and GLAST expression in hippocampal sclerotic temporal lobe epilepsy (Proper, EA. et al., 2002).



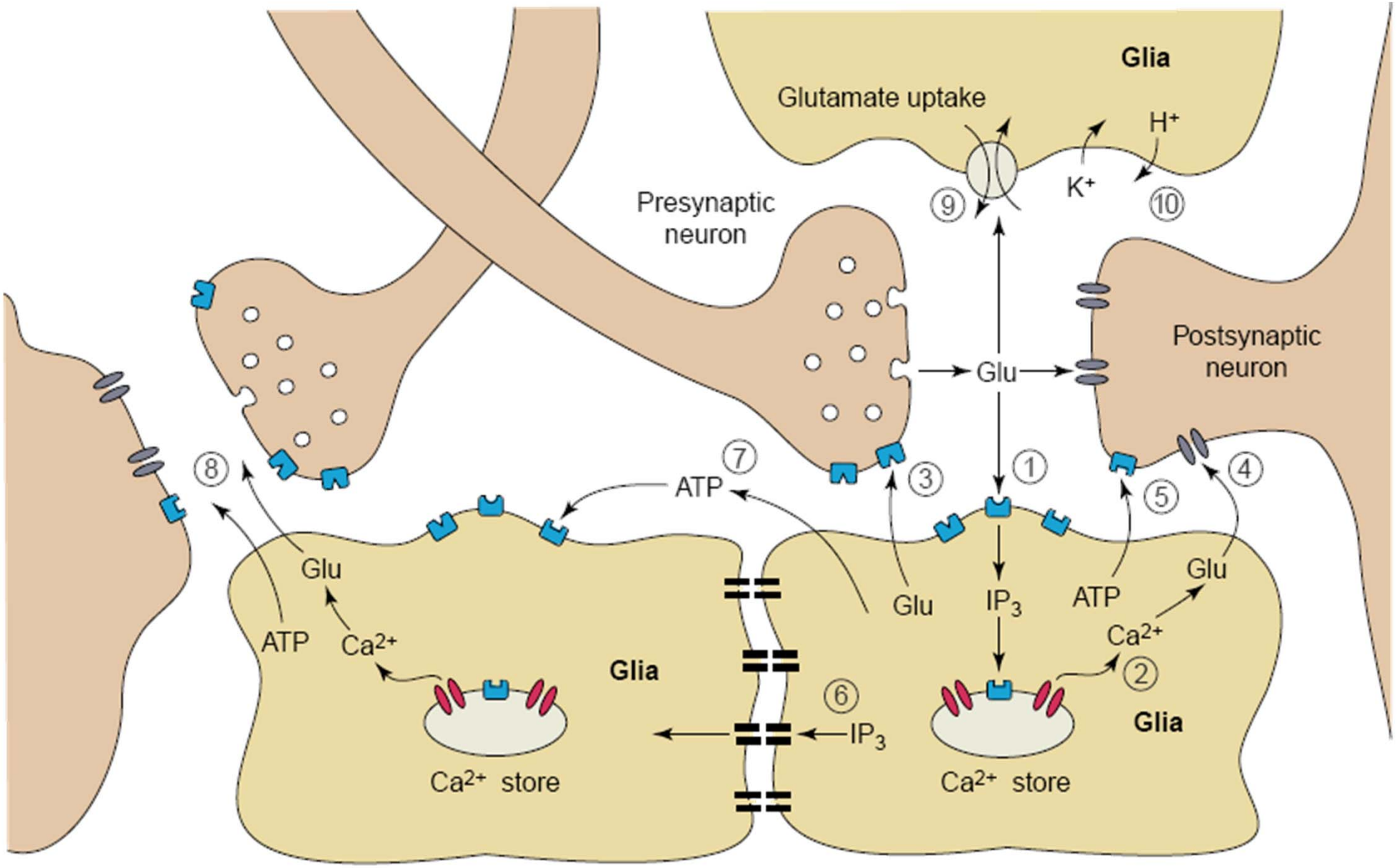
- Reduced Glutamine synthetase (GS) expression and function in astrocytes of human sclerotic hippocampi (Eid, T. et al., 2004)
- Mutations of GS gene have been found in epileptic patients (Häberle, J. et al., 2005).

Epilepsy and GABA

- Lower extracellular GABA levels and higher glutamate concentrations were found in hippocampus of TLE before the onset of seizures (During, MJ. and Spencer, DD., 1993)

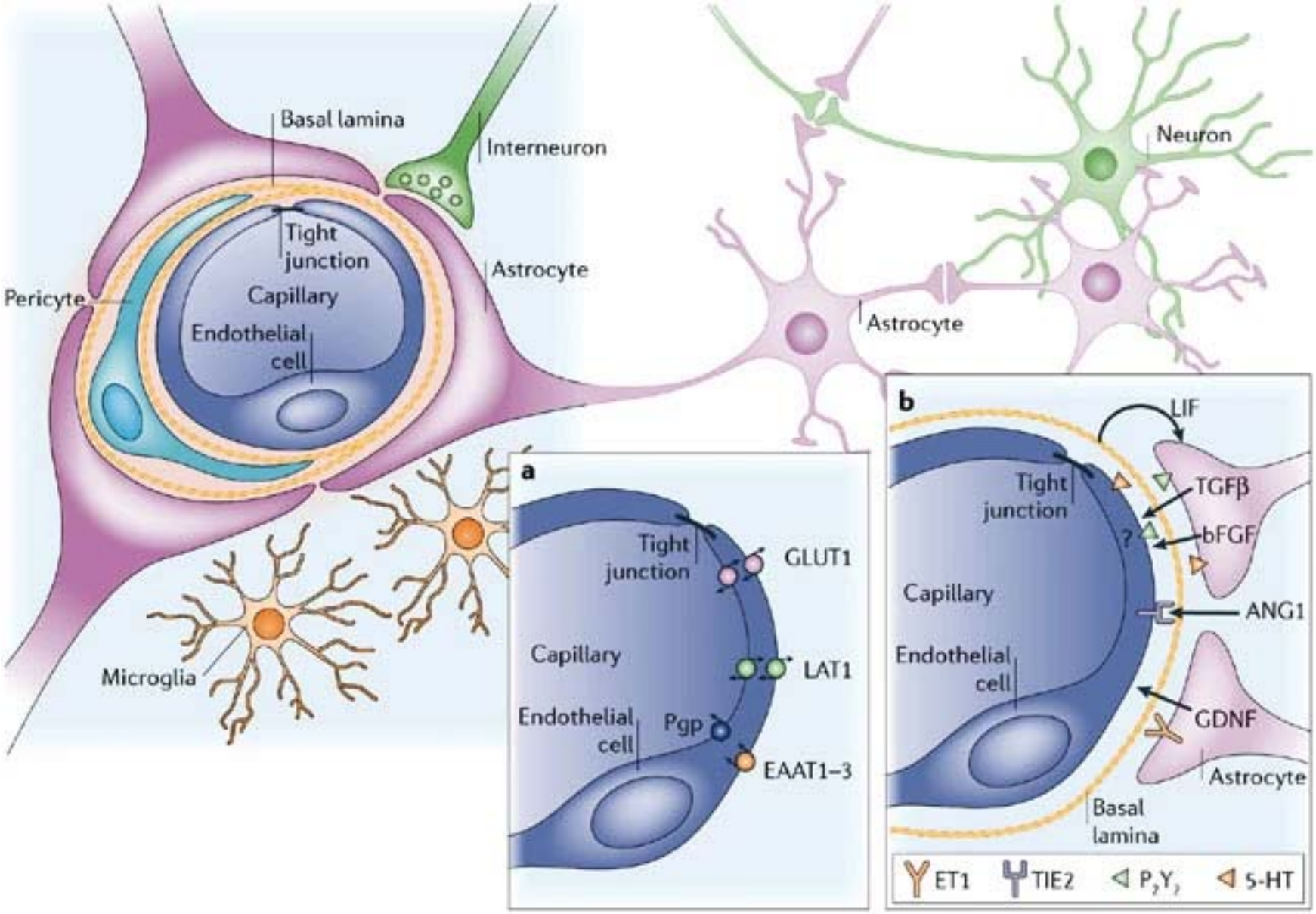
- Increased expression of the astrocytic GABA transporter GAT3 in human hippocampal astrocytes (Lee, TS. et al., 2006)

Astrocyte gliotransmission



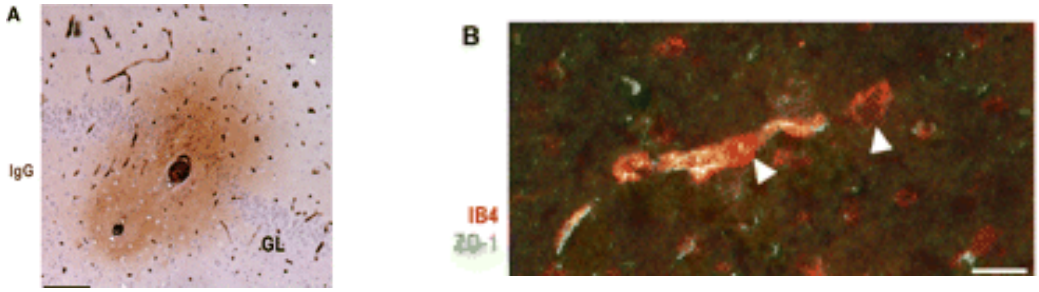
- Bidirectional interaction between neurons and astrocyte

Astrocyte BBB

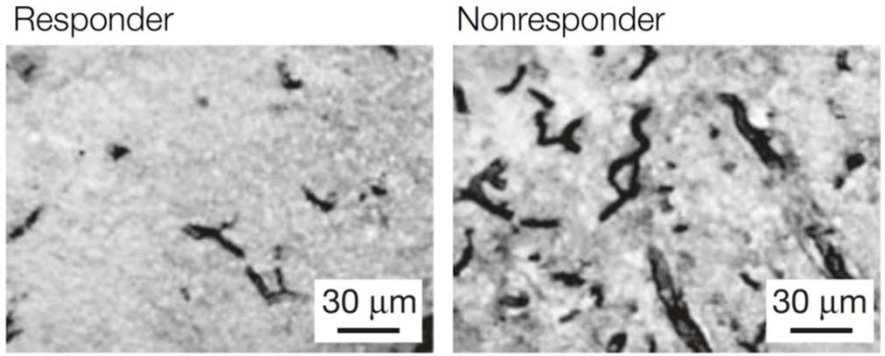


Disruption of BBB in epilepsy

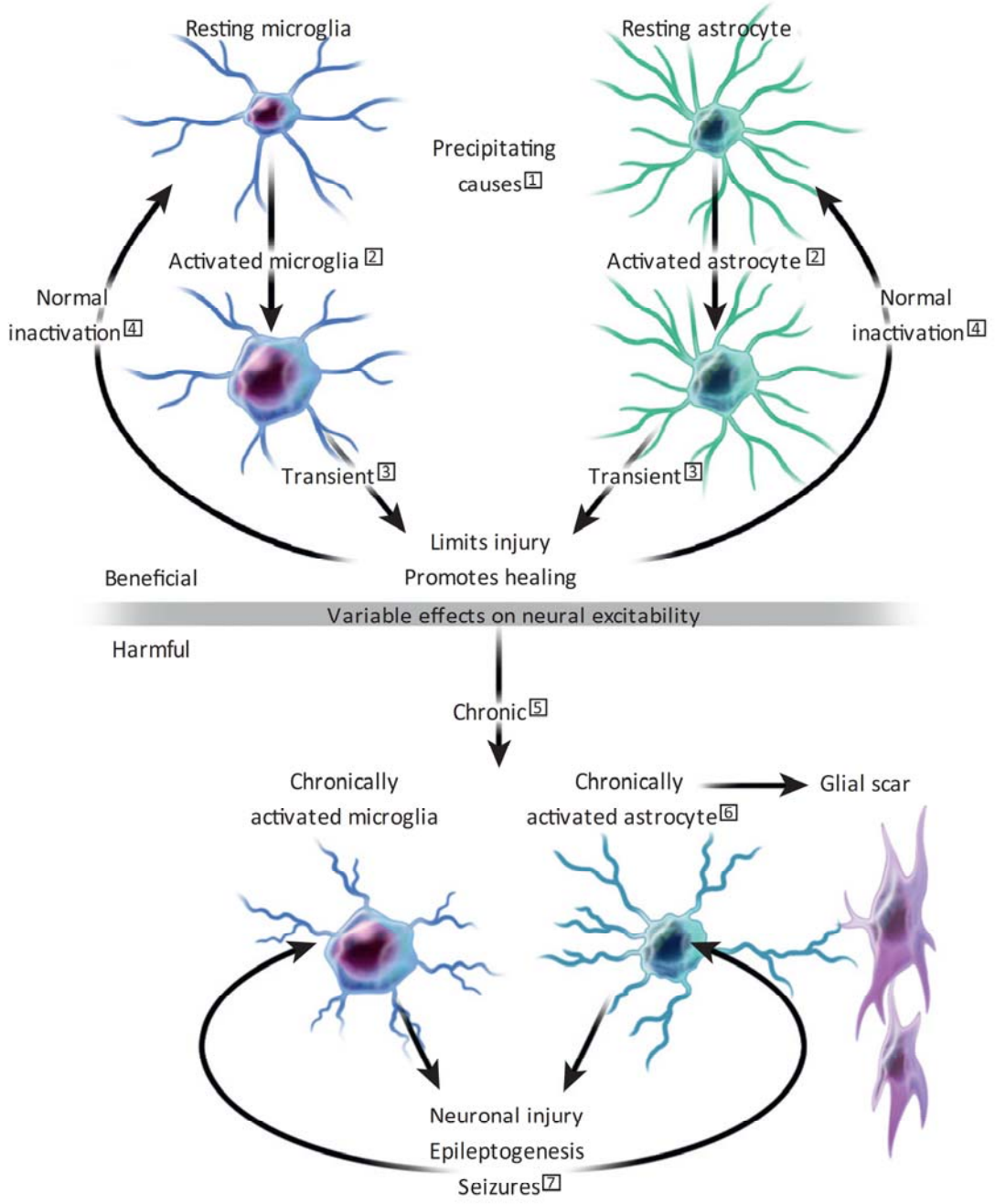
- An impairment of the BBB was demonstrated by Immunoglobuline G (IgG) leakage and accumulation in neurons. Also reduction of tight junction protein zonula-occludens-1 (ZO-1). (Rigau, V. et al., 2007)



- Increased expression of P-glycoprotein in endothelial cells of drug-resistant epileptic rats. (Loscher, W. and Potschka, H. 2005)

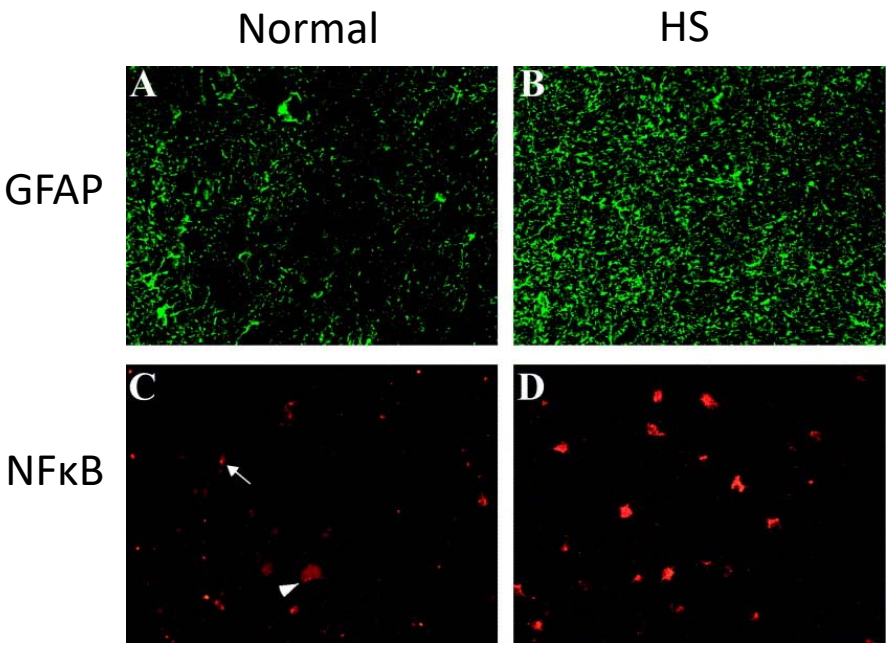


Glial-mediated inflammation

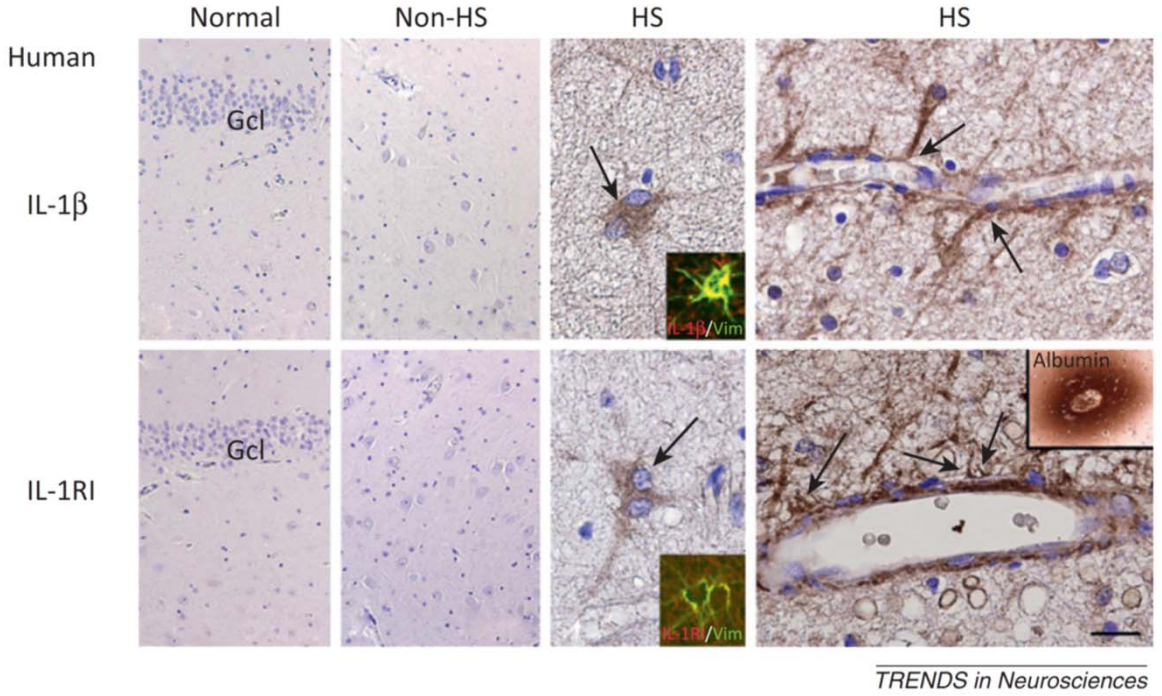


Epilepsy and Inflammation

- Hippocampi from patients with MTLE and HS displayed severe neuronal loss surrounded by gliosis and overexpressed NFκB indicated inflammatory process.
- Strong IL-1b immunoreactivity inperivascular astrocytic endfeet and IL-1RI immunoreactivity in the sclerotic hippocampus.



(Crespel, A. et al. 2002)



Summary

- Neuronal basis of epileptogenesis has limitations.
- AEDs has limited efficacy and mostly prevent seizures but did not modify the underlying causes.
- Glial cells are promising
  - They are important for homeostatic regulation both in physiological and pathological conditions.
  - They participate in signaling.
  - They are involved with inflammation.