ASTROCYTE FUNCTION CHANGES IN EPILEPSY: NOVEL THERAPEUTIC TARGETS?

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What is epilepsy?

Epilepsy, one of the most prevalent diseases, is a neurological disorder characterized by the occurrence of recurring and spontaneous seizures, behavioral abnormalities and disturbances of consciousness. It can develop as a result of brain damage from other disorders (e. g. brain tumors or infections), and also by genetic alterations. Epileptic seizures are due to an abnormal electrical activity of certain neuronal brain networks, which suffer a hyperexcitation and a hypersynchronization. Inflammation and neuronal cell death, specially of GABAergic neurons, contribute to the hyperexcitation.

Involvement of astrocytes

Not only neurons are involved in epilepsy. Abnormal astrocytes play a significant role in this characteristical neuronal hyperexcitability of epilepsy. As a result of a brain damage, astrocytes become 'reactive' and undergo morphological and molecular changes as down- or up-regulation of many enzymes or alterations of specific astrocyte membrane channels, receptors and transporters. These changes are behind altering astrocyte functions, and this in turn, is related with epileptic seizures development.

This work reviews the functional changes of astrocytes that contribute to hyperexcitability in epilepsy.

Some astrocyte functions	Non-epileptic brain	Epileptic brain
Neuroprotection	✓	✗
Modulating synaptic activity	✓	✗
Water & Potassium balance	✓	✗
Neurotransmitter homeostasis	✓	✗

Functional changes

Glutamine synthetase (GS)

- Normal function: conversion of glutamate to glutamine, the main neuronal precursor of glutamate and GABA
- Change in epilepsy: ↓ expression
- Functional effect: ↓ conversion of glutamate to glutamine
- Mechanism of hyperexcitability: ↑ basal glutamate, ↓ glutamine; ↓ GABA synthesis / ↓ GABAergic inhibition

Adenosine Kinase (ADK)

- Normal function: conversion of adenosine, an inhibitory metabolite of neurons, to 5'AMP
- Change in epilepsy: ↑ expression
- Functional effect: ↑influx of adenosine into astrocytes, ↑ adenosine phosphorylation
- Mechanism of hyperexcitability: ↓ basal adenosine, ↓ neuronal inhibition

Aquaporin 4 (AQP4)

- Normal function: osmolarity regulation
- Change in epilepsy: redistribution of AQP4 from perivascular to perisynaptic space, ↑ overall expression
- Functional effect: ↑ water entry near synapses , ↓ water egress into perivascular space → astrocytic swelling
- Mechanism of hyperexcitability: shrinkage of extracellular space (ECS)

Inwardly Rectifying Potassium channel 4.1 (Kir4.1 channels)

- Normal function: clearance of excessive K+ from ECS
- Change in epilepsy: ↓ expression
- Functional effect: ↓ K+ buffering
- Mechanism of hyperexcitability: ↑ extracellular K+

Excitatory amino acid transporters (EAAT1, EAAT2)

- Normal function: glutamate uptake from the ECS
- Change in epilepsy: ↓ expression
- Functional effect: ↓ glutamate uptake by astrocytes
- Mechanism of hyperexcitability: ↑ extracellular glutamate

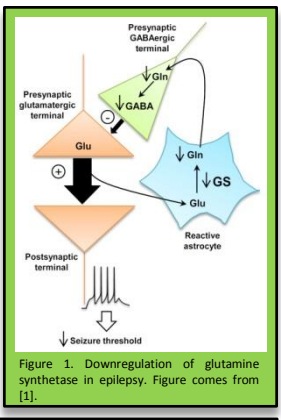

Figure 1. Downregulation of glutamine synthetase in epilepsy. Figure comes from [1].

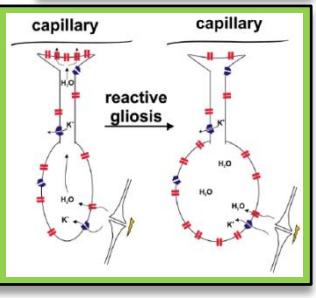

Figure 2. Impaired water and potassium balance in epilepsy. Figure comes from [2].

Gliotransmission in epilepsy

Astrocytes detect some neurotransmitters and respond to them releasing gliotransmitters through a Ca2+ -dependent process called gliotransmission.

In epilepsy, reactive astrocytes release TNFα. TNFα promotes prostaglandin formation and this in turn, through an unknown mechanism, increases intracellular Ca2+. Furthermore, astrocytic metabotropic glutamate receptors mGluR5 are upregulated, further increasing the levels of intracellular Ca2+. The final effect is a significant increase of gliotransmitters release (e. g. glutamate) into the ECS, contributing to the hyperexcitation.

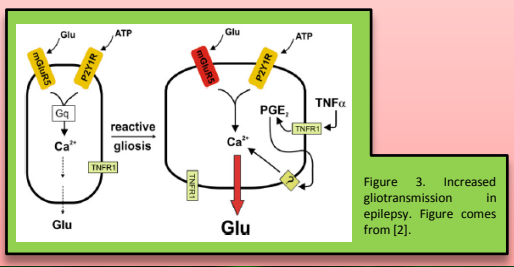

Figure 3. Increased gliotransmission in epilepsy. Figure comes from [2].

Conclusions and future directions

• In epilepsy, astrocytes exhibit functional changes that contribute to the neuropathology and hyperexcitability characteristic of this disease. Some of the most studied changes have been explained in this work, but are not the only.

• The available data about the functional astrocyte changes in epilepsy represent only the "tip of the iceberg".

• A deeper understanding of these astrocyte altered functions will lead to the identification of novel molecular targets that might lead to the development of antiepileptic therapies.

References

[1] Clasadonte, J., Haydon, P. G. Astrocytes and Epilepsy. Jasper's Basic Mechanisms of the Epilepsies, fourth edition. NCBI Bookshelf Online Book Version (2012).

[2] Wetherington, J., Serrano, G., Dingledine, R. Astrocytes in the Epileptic Brain. Neuron 58, 168 (2008).