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How may astrocytes hypersynchronize neuronal networks causing epilepsy?

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Recently, the Nedergaard group (Tian et al, 2005) showed in a series of experiments that astrocytic glutamate release constitutes a mechanism for the generation of hypersynchronous neuronal firing typical of seizure disorders. According to Robertson (2005) epilepsy probably represents a pathological response of astrocytes to their normal control of neuronal synchrony. Let me shortly elaborate on this interpretation of the astrocytic function in the genesis of seizures.

Already in 1996 we published "The neuro-glial synchronization hypothesis" (Mitterauer et al). According to this hypothesis the stimulus-induced synchronization of the activity of neuronal ensembles is affected by glia (particularly astrocytes) in the following way:

1. Astrocytes modulate the efficiency of synaptic transmission and, therefore, the amplitude and phase of the postsynaptic potentials.
2. Astrocytes influence neural signal processing by enacting delays via neuro-glial circuits.
3. Astrocytes provide a global threshold modulation in the region of active ensembles, for phase coupling resp.phase separation of the activity of the individual ensembles.

Together, astrocytes may exert both a local (synaptic) and a global (extrasynaptic) function in the synchronization of neuronal networks.

Meanwhile, this hypothesis has been experimentally verified by the Carmignoto group (Fellin et al, 2004). These researchers found a functional link between astrocytic glutamate and extrasynaptic NMDA receptors responsible for neuronal synchrony. Therefore, we have to focus on the global or extrasynaptic modulatory functions of astrocytes.

What epilepsy concerns, Tian et al (2005) reported that glutamate released by astrocytes and oscillatory increases of astrocytic Ca^{2+} signalling can trigger seizure activity independent of an action potential source. This suggests that pathological activation of astrocytes may play a central role in the genesis of epilepsy. However, what may be the cause of this pathological function of astrocytes?

My hypothesis is as follows: it is experimentally well established that astrocytes show spontaneous Ca^{2+} oscillations that trigger the release of glutamate and activate a neuronal response independent of neuronal activity (Zonta and Carmignoto, 1002). This rhythmic oscillation of astrocytes has a boundary setting function in the sense of synchronization of a specific set of temporally and spatially limited neurons. One could also say that astrocytes normally control the synchronization of neurons in a pulsatile manner. If astrocytes lose this autonomous oscillatory or temporal boundary setting function, then the activation of extrasynaptic NMDA receptors persists. This may lead to a hypersynchronization of neuronal groups. Dependent on the brain regions affected, epilepsy shows various phenomena as Robertson described. In addition to the well established neurogenic mechanism, seizure activity may be based on such a pathological astrocytic function. It may be caused by mutations of genes that are responsible for the spontaneous oscillations of astrocytes.

Finally, let me shortly compare my schizophrenia hypothesis with that of epilepsy. In both disorders there is a loss of glial (especially astrocytic) boundary-setting function. In schizophrenia the synaptic information flux may be unconstrained, in epilepsy the same

mechanism may be at work but in the extrasynaptic domain. According to my "gliocentric" brain theory, a real breakthrough in the research of psychobiological disorders can only be achieved if the different mechanisms responsible for a loss of the glial spatiotemporal boundary setting function are detected.

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