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Astrocyte chloride, excitatory-inhibitory balance and epilepsy

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Excitation and inhibition are at the core of brain function and malfunction. To sustain the activity of neuronal networks over time and space, glutamate-driven excitation is balanced by GABAergic inhibition. The exquisite of excitation and inhibition, known as the excitation/inhibition (E/I) balance, is crucial for proper brain function. Interneuron-mediated E/I balance is highly dynamic and shifts across different brain states: wakefulness primarily augments excitatory activity, while sleep promotes inhibitory activity and an increase in inhibition (Bridi et al., 2020). Neuronal activity during various brain states is primarily regulated by neurotransmitters (Schiemann et al., 2015), although non-synaptic mechanisms also play a significant role; altering extracellular ion concentrations affects sleep, arousal, and electroencephalogram patterns, and behavioral states (Ding et al., 2016).

Chloride ion is the major anion in the body, and it mediates ionotropic inhibition in the central nervous system. The inhibitory neurotransmitter GABA activates ligand-gated anion channels, known as GABA receptors (GABA-R). Neurons in the mature brain have low (~5 mM) intracellular Cl− concentration ([Cl−]i) and hence the opening of GABA-R generates Cl− influx leading to hyperpolarization. Sustained inhibitory activity depletes extracellular Cl−, which is replenished by astrocytes acting as a dynamic Cl− reservoir in the central nervous system (Untiet et al., 2023). Astrocytes, which cover synapses with their terminal leaflets thus forming a synaptoglial synapse, is likely controlled by astrocytic [Cl−]i reservoir dynamically changes (Verkhratsky and Nedergaard, 2014), in contrast to neurons have high [Cl−]i, which may reach the level of 20–50 mM (Engels et al., 2021; Untiet et al., 2023). Astrocytic Cl− reservoir dynamically changes in various brain states: during sleep [Cl−]i is higher and it is stable (Untiet et al., 2017); during wakefulness, it decreases and fluctuates in parallel to sensory stimulation and locomotion (Untiet et al., 2023). Astrocytic leaflets ensheathing inhibitory synapses are rich in GABA-R, which, when opened, generate Cl− flux into the synaptic cleft thus maintaining inhibitory transmission. Sustained inhibition therefore relies on both astrocytic GABA-R and astrocytic Cl−, whereas reduction of either may shift the E/I balance towards excitatory activity and promote seizures. Astrocyte supply of Cl− also depends on gap junctions and astroglial syncytium where Cl− may intracellulary diffuse towards sites of inhibitory activity; pharmacological inhibition of astrocytic gap junctions in brain slices accelerates the decline of inhibitory transmission (Egawa et al., 2023, Figure 1).

In epilepsy, the aberrant E/I balance is likely to be the central biological mechanism. Excitatory responses to GABA were observed in approximately 30% of neurons from brain slices of epilepsy patients (Cohen et al., 2002). This phenomenon has also been replicated in vitro using various convulsive agents and related procedures (Yamada et al., 2004). Increased neuronal [Cl−]i was linked to seizures, spinal cord lesions, and other pathophysiological conditions. Most studies analyzing the excitatory effects of GABA focus on neuronal [Cl−]i and the associated regulatory mechanisms involving Na+–K+–Cl− cotransporter 1 (NKCC1/Slc12A1) and K+–Cl− cotransporter 2 (KCC2/Slc12A5) (KCC2/Slc12A5) (Cohen et al., 2002). However, recent demonstration of astrocytic Cl− directly modulating neuronal activity highlights the role of astroglial Cl− regulation in the pathophysiology of seizures. Dynamic fluctuations of [Cl−]i in the synaptic cleft dictate activity-dependent disinhibition, which can differ between different neuronal compartments or be globally regulated by astrocytes.

Increased anion conductance of astroglia leading to a decrease in [Cl−]i triggers apoptotic loss of these cells (Kovermann et al., 2020). Such astroglial loss is observed in ataxia and epileptic disorder manifested by ataxia and epileptic seizures, suggesting that depletion of astroglial Cl− reservoir is a significant pathological factor. When astrocytes are unable to provide sufficient Cl−, GABAergic inhibition can mutate into excitatory thus instigating seizures and epileptiform pathology.

Seizures are closely influenced by sleep patterns. Sleep deprivation upregulates excitatory activity in the cortex during sleep compared to wakefulness. This reduced demand for astroglial Cl− depletion during sleep would potentially contribute to an increase in astroglial Cl−, soluble Glutamate Cl− uptake promoting depolarizing GABA actions in immature rat neocortical neurones is mediated by NKCC1. J Physiol 557:829–844. Hence astrocytic Cl− reserve builds up during sleep thus promoting a slower timescale. The non-synaptic mechanisms and the ionic composition of the extracellular space playing a significant role; altering extracellular ion concentrations affects sleep, arousal, and electroencephalogram patterns, and behavioral states (Ding et al., 2016).

References


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