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Untiet, Verena; Nedergaard, Maiken; Verkhratsky, Alexei

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Astrocyte chloride, excitatory-inhibitory balance and epilepsy

Verena Untiet1, Maiken Nedergaard, Alexei Verkhratsky

Excitation and inhibition are at the core of brain function and malfunction. To sustain the activity of neuronal networks over time and space, glutamatergic 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. The E/I balance is highly dynamic and shifts across different brain states: wakefulness primarily augments excitatory activity, while sleep progressively switches inhibition on 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 neuronal and glial cells are also involved in a slower timescale. The non-synaptic mechanisms are many, with the ionic composition of the extracellular space playing a significant role; altering extracellular ion concentrations affects sleep, arousal, 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 chloride channels (GABAAR), and this effect is further enhanced by astrocytes (Verkhratsky and Nedergaard, 2014), in contrast to neurons having high [Cl−]i and hence the opening of GABAAR 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 foot processes, glial maturing astroglial synapses (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 foot processes enmeshing inhibitory synapses are rich in GABAAR, which, when opened, generate Cl− efflux into the synaptic cleft thus maintaining inhibitory transmission. Sustained inhibition therefore relies on both astrocytic GABAAR and astrocytic Cl−, whereas reduction of either may shift the E/I balance toward excitation thus potentially leading to pathological seizures. Astrocyte supply of Cl− also depends on gap junctions and astroglial syncytium so that Cl− may intracellularly diffuse towards sites of inhibitory activity; pharmacological inhibition of astrocytic gap junctions in brain slices accelerates the decline of inhibitory transmission (Egawa et al., 2013, 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 pathological 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/Slc12A2) and K+–Cl− cotransporter 2 (KCC2/Slc12A5) (KCC2/Slc12A5) (Ben-Ari et al., 2012). 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 dictating activity-dependent inhibition, 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 physiologic 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 exacerbates epileptic seizures and interictal epileptiform discharges. Conversely, astrocytic [Cl−]i displays a brain state-dependent pattern. Earlier studies have described lower neuronal activity in the cortex during sleep compared to wakefulness. This reduced demand for astrocytic Cl− release during sleep potentially contributes to an increase in astrocytic [Cl−]i. High demand for Cl− during wakefulness could be a limiting factor facilitating epileptic seizures, especially in the background of sleep deprivation.

Equilibrium potential for Cl− (which is the function of Cl− gradient, consisting of [Cl−]i and [Cl−]o) (Alfonsa et al., 2022) that defines the direction of GABAergic currents (ECl,astro) in pyramidal neurons depends on the ionic composition of the synaptic cleft. In the synaptic cleft, which is likely controlled by astrocytic [Cl−]i, elevated astrocytic [Cl−]i levels during sleep supply Cl− to maintain a hyperpolarizing ECl,astro. Conversely, lower levels of Cl− during wakefulness limit Cl− availability, making GABAAR depolarizing and excitatory. Consequently, astrocytic [Cl−]i modulates neuronal GABAergic inhibition in a brain state-dependent manner. Aberrant astrocytic Cl− supply can therefore be considered as a relevant mechanism explaining the generation of seizures, and hence astrocytic Cl− homeostasis can represent a valid target for anti-epileptic therapies.

Figure 1: Astrocyte Cl− modulates E/I balance thus potentially contributing to pathogenesis of seizures and epilepsy.

Intracellular chloride concentration is regulated by symporter (EgG): electroencephalogram; E/I: balance: excitation/inhibition balance; IPSP: inhibitory postsynaptic potential.

References


