Effects of a reduced efficacy of the KCC2 co-transporter and its relevance for epilepsy

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Abstract

Epilepsy is one of the most common neurological disorders. Despite much research seizures in about 40% of patients are pharmaco-resistant [1]. Surgical removed focal tissue from these patients may be used for studies on the pathological mechanisms underlying seizures. Thus in the human epileptogenic subiculum the KCC2 cotransporter is absent or non-functional in about 20 % of pyramidal cells[2] . This molecule normally assures the homeostatic maintenance of intra-neuronal chloride levels[3]. Chloride concentration changes in pyramidal neurons caused by intensive GABAergic input during seizures could reverse the effects of GABA currents from inhibitory to excitatory[4 5]. Such changes may shift a pyramidal cell into the continuous spiking regime associated with the tonic phase of seizures. Using a biophysical model of a single cell and a neural population model representing a simple network we show that that decreasing the activity of KCC2 pump leads to repetitive seizure-like firing in response to the extracellular stimulation near the epileptogenic focus[6 7]. This model provides the insights into how the functional pathology of pyramidal cells associated with the absence of the KCC2 cotransporter leads to seizures in the epileptogenic human subiculum.

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