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Effects of a reduced efficacy of the KCC2 co-transporter in temporal lobe epilepsy: single neuron and network study

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Epilepsy is one of the most common neurological disorders. Seizures in about 40% of patients with temporal lobe epilepsies are pharmaco-resistant [1]. In surgically removed hippocampal tissue from these patients, the KCC2 cotransporter is absent or non-functional in about 20 % of subicular pyramidal cells [2]. KCC2 normally assures the maintenance of low intra-neuronal chloride levels [3] and also regulates potassium levels [4]. Chloride concentration changes in the remaining pyramidal cells due to intensive GABAergic input during seizures could reverse the effects of GABA currents from inhibitory to excitatory [5,6]. Such changes may shift a pyramidal cell into a periodic bursting regime associated with ictal discharges. Using a detailed biophysical model of a single cell incorporating these mechanisms of ionic homeostasis and a neural network model, we show that decreasing the activity of KCC2 pump leads to repetitive seizure-like firing in the pathologic network due to increased extracellular potassium and intracellular chloride (Fig. 1). This model provides insights into how a dysregulation of pyramidal cell chloride homeostasis due to reduced levels of the KCC2 cotransporter may lead to seizures in the epileptic human subiculum.

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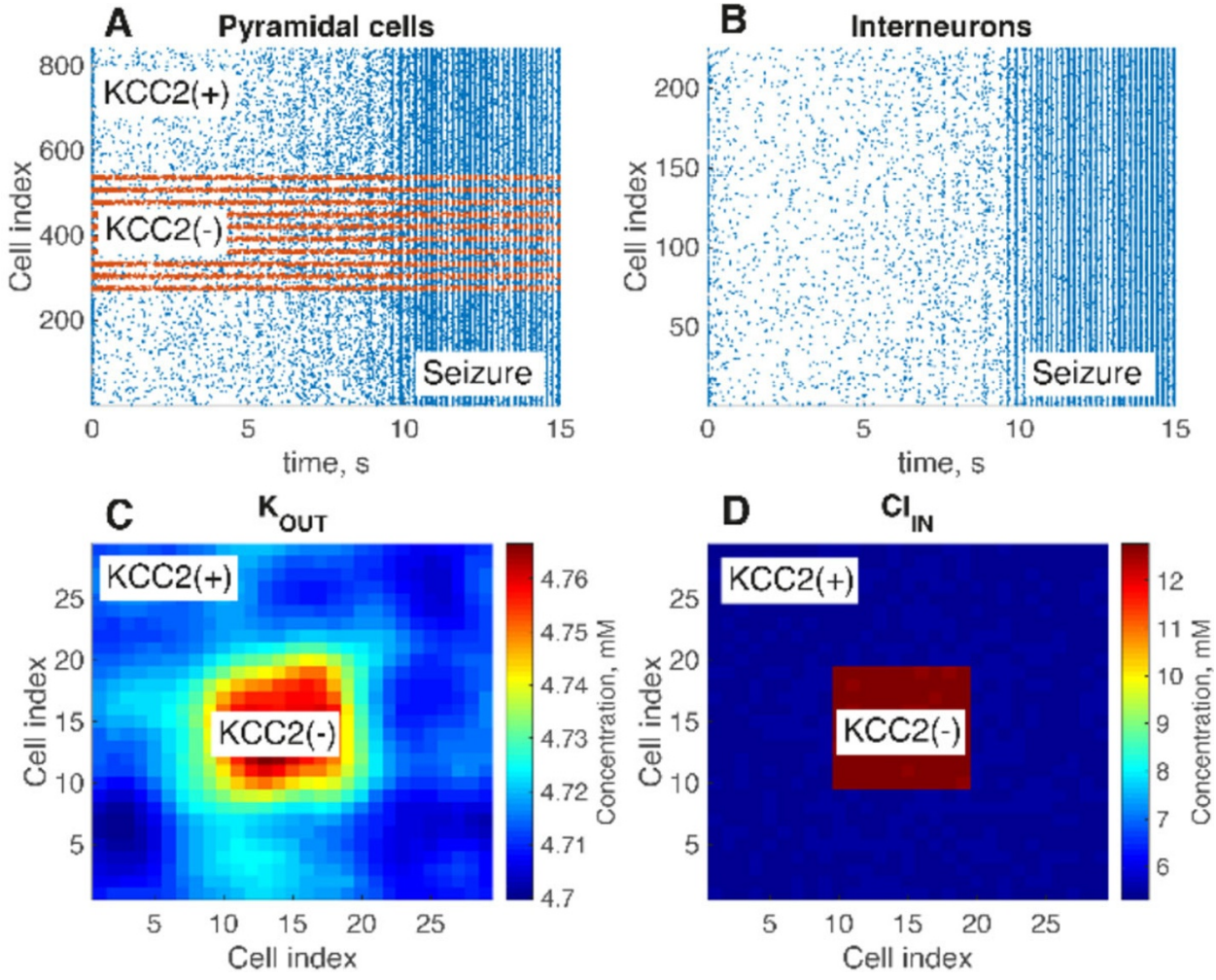

Figure 1 A raster plot of pyramidal cell population firing; B raster plot of interneuron firing; C spatial distribution of extracellular potassium; D intracellular chloride distribution.