Computational Model for the Effects of Phenobarbital and the NKCC1 Inhibitor Bumetanide in the Pilocarpine Model of Temporal Lobe Epilepsy

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Abstract

In this research, we have computationally investigated a mechanism for antiepileptic drugs (AED) and proposed bumetanide as a possible temporal lobe epilepsy (TLE) treatment. Experimentally it is difficult and devastating to determine the ionic mechanisms of depolarizing currents. It is obvious that chlorine and potassium transients are challenging to isolate pharmacologically and much γ-aminobutyric acid (GABA) signaling occurs in small, difficult to measure, dendritic compartments. So many computational studies have been done to confirm the mechanisms of TLE. Despite widespread acceptance of GABA as the transmitter of inhibition in the central nervous system, in one of the most frequent reported TLE data, GABA plays role of excitatory neurotransmitter. In this computational study we have modeled three hippocampal neurons. We have modeled healthy, patient and bumetanide treated neuron and the compared the firing rate of these three neurons. The computationally based model neuron was morphologically reconstructed from hippocampal pyramidal neuron n123 taken from the published Duke Southhampton neuronal morphology: http://www.compneuro.org/CDROM/nmorph/index/n123_t.html. The model was modified to include an axon, as described in Poirazi and et al. The neuron contains 183 compartments. Voltage gated ionic currents were modeled as in Poirazi and et al modified by Naomi Lewin et.al. The extracellular space was modeled as a cylindrical shell surrounding each compartment with a volume 15% of the intracellular compartment. The initial intracellular concentrations of Na⁺, K⁺, Cl⁻, Ca²⁺ and HCO₃⁻ were based on the intracellular and extracellular concentrations described in Smirnov et al. The concentrations of Na⁺, K⁺, Cl⁻ and Ca²⁺ were allowed to fluctuate in both the intracellular and extracellular compartments, except where specified. The results showed that blocking the Cl⁻ importer Na⁺-K⁺-Cl cotransporter 1 (NKCC1) is significantly reducing firing rate so NKCC1 blockers such as bumethanide are potential anti-epileptic drugs. Due to these computations, we are experimentally testing bumetanide’s effect on animal subjects. In conclusion combined treatment with bumetanide and phenobarbital after status epilepticus (SE), increase inhibition and maximize the anticonvulsant power of the GABA system and might be useful in the treatment of epilepsy patient.

Keywords: NKCC1, Bumetanide, Temporal Lobe Epilepsy.

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