Reduced Voltage-gated K+ Channel Function in GABAergic NTS Neurons in a Murine Model of Acquired TLE and SUDEP

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Sudden unexpected death in epilepsy (SUDEP) accounts for approximately 17% of epilepsy-related deaths. Altered voltage-gated K+ channel function in neurons of the brainstem nucleus tractus solitarius (NTS) and vagal afferent fibers may contribute to SUDEP in genetic epilepsy models; hippocampal voltage-gated K+ channel function and expression is altered in the pilocarpine-induced status epilepticus (SE) model of acquired temporal lobe epilepsy (TLE) in rodents. However, little is known regarding possible changes in voltage-gated K+ channels in NTS neurons during development of acquired TLE. GABAergic NTS neurons receive information via vagal afferent fibers regarding cardiac and respiratory function and serve to integrate, filter, and modulate this information to regulate cardiorespiratory function. In a genetic epilepsy model with a voltage-gated K+ channel mutation, altered NTS neuron function contributed to cardiorespiratory collapse and sudden death after seizures. However, there is a paucity of information regarding epilepsy-related changes in NTS neuron channel function in acquired epilepsy, which affects a greater proportion of the patient population. We hypothesized that voltage-gated K+ channel function in GABAergic NTS neurons is altered in the pilocarpine-induced SE model of TLE. Pilocarpine (282 mg/kg) was administered to 4 week old male mice that express GFP in a subset of GABAergic NTS neurons (FVB-Tg(GADGFP)4570Swn/J; ie. GIN mice) to induce SE and eventual development of TLE. In vitro electrophysiological results show an increase in action potential firing rate and action potential half-width in GABAergic NTS neurons from mice 12 weeks after SE (i.e., TLE mice) compared to age-matched controls. Upon application of 4-AP (5mM), action potential firing rate and half-width in GABAergic NTS neurons from control mice was increased to levels similar to that in neurons from TLE mice, suggesting that A-type K+ current function may be suppressed following TLE development. Characteristics of the A-type K+ current were therefore assessed in voltage-clamp recordings in GABAergic NTS neurons from control and TLE mice. Preliminary data suggest that peak A-type K+ current is decreased in GABAergic NTS neurons from TLE mice compared to controls, consistent with the increase in action potential firing and half-width in TLE mice. These results suggest voltage-gated K+ channel function is reduced in the NTS of mice with acquired TLE, which contributes to increased neuronal activity and may also increase SUDEP risk.