Sudden unexpected death in epilepsy and functional remodeling of vagal complex activity in a mouse model of temporal lobe epilepsy

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Background: Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in individuals with refractory epilepsy and has been associated with disturbances in cardiorespiratory function and autonomic nervous system (ANS) imbalance. GABAergic neurons of the nucleus tractus solitarius (NTS) of the brainstem dorsal vagal complex are essential modulators of parasympathetic tone. Studies of genetic models of epilepsy suggest that ANS dysfunction coincides with SUDEP susceptibility, but this has not been investigated in models of temporal lobe epilepsy (TLE), the most common epilepsy type.

Purpose/Hypothesis: Due to the paucity of research surrounding ANS dysfunction in association with TLE and SUDEP, this study investigated cardiac function and activity of GABAergic NTS neurons in the vagal complex in the pilocarpine-induced status epilepticus (pilo-SE) model of TLE. We tested the hypotheses that: (1) Mice that survive SE are at risk of sudden death; (2) these mice display cardiac abnormalities indicative of ANS dysfunction; and (3) GABAergic NTS neuron activity is increased post-SE.

Methods: Pilocarpine (281 mg/kg) was administered to 5-6 week old mice to induce SE and eventual development of TLE. Mice were split into 3 groups to assess survival rates, in vivo electrocardiography (ECG), and in vitro electrophysiology of GABAergic NTS neurons at several times post-SE. ECG recordings took place 24 hours prior to treatment, 24 hours post-treatment, and at 6 and 12 weeks after treatment. For electrophysiological recordings from identified GABAergic NTS neurons, coronal brainstem slices were taken at 1, 6, and 12 weeks post-SE. Results: Pilocarpine-treated mice had a 27% survival rate (versus 100% for vehicle-treated controls) 150 days post-SE. Heart rate was increased and heart rate variability was decreased by 12 weeks post-SE relative to age-matched control mice. Significant increases in spontaneous action potential and EPSC frequency ($p<0.05$) were detected 1, 6, and 12 weeks post-SE. Miniature EPSC frequency was increased relative to controls at 6 and 12 weeks post-SE, but not at 1 week. Blockade of ionotropic glutamate receptors significantly reduced spontaneous action potential frequency to levels similar to controls at 6 and 12 weeks post-SE.

Conclusions: These results suggest long-term changes in cardiac function develop in conjunction with increased synaptic excitability of GABAergic NTS neurons after pilo-SE, which could contribute to autonomic dysregulation, cardiorespiratory collapse, and SUDEP. Future studies will determine if increased excitability of GABAergic NTS neurons underlies increased susceptibility to depolarization block and spreading depression in the NTS of mice with TLE.