Seizures, spreading depolarizations and sudden death

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Appendix

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SUMMARY

In this thesis, animal models are developed and characterized to study the mechanisms and potential lethal outcome of spontaneous seizures and spreading depolarizations (SDs).

In **Part I**, two new familial hemiplegic migraine (FHM) mouse models are described. Spontaneous SDs occurred in a subset of mice expressing the FHM3-related L263V mutation in α1 subunits of voltage-gated $Na_V1.1$ sodium channels (**Chapter 2**). These events invariably spread from the visual to the motor cortex. A similar caudal-to-rostral spreading pattern was noted for spontaneous SDs in mice expressing the FHM2-related T345A mutation in α2 subunits of the Na^+/K^+ adenosine triphosphatase pump (**Chapter 3**). These SDs were found to originate mostly from the hippocampus in markedly regular intervals with a diurnal rhythm. Despite increased hippocampal excitability as evidenced by SD susceptibility, seizure expression was in fact decreased. NMDA receptor and sodium channel modulation differentially affected SD initiation and propagation in these animals. As opposed to previous studies that induced SDs via an external trigger, these findings allow differentiation of SD initiation and propagation mechanisms.

In **Part II**, disease mechanisms of sudden death in the presence (**Chapters 4 and 5**) or absence (**Chapter 6**) of epilepsy are described. Fatal seizures, occurring in mice expressing a homozygous S218L missense mutation in the α1A subunit of $Ca_V2.1$ P/Q-type $Ca2^+$ channels, were associated with global neuronal suppression and respiratory arrest that coincided with changes in diffusion-weighted MRI signal in the brainstem, which preceded cardiac arrest (**Chapter 4**). Further studies of neuronal activity in the brainstem's regions critical for respiratory functioning show that suppression of neuronal activity in these regions occurred during fatal seizures, as well as during non-fatal seizures associated with prolonged apnea (**Chapter 5**). Such suppression of neuronal activity was caused by brainstem SD, and death could be prevented by timely respiratory resuscitation. Importantly, prevention of seizure-related SD using NMDA receptor antagonists also prevented fatal apnea. In **Chapter 6**, events of sudden apnea are described that occurred in the absence of seizure activity in an infant with a homozygous $SCN1A^{L263V}$ missense mutation. Similar non-seizure apneic events occurred in mice carrying the same mutation, which were associated with a large brainstem DC-shift. Sudden suppression of neuronal activity occurred during the DC-shift, which was associated with fatal apnea onset. These neuronal dynamics – brought about by gain-of-function effects in sodium channel functioning – could be prevented by sodium channel blockade, which prevented brainstem DC-shifts and fatal apnea in the mice. Similarly, apneic events in the infant decreased following treatment with a sodium channel blocker. Together, these studies substantiate brainstem SD as a potential mechanism for fatal apnea even in the absence of seizure activity.

In **Part III**, the epileptogenic potential and neuronal dynamics in brain-wide (global) *versus* local $Na_V1.1$ channel ablation are studied in the context of Dravet syndrome, an epileptic encephalopathy. Both hippocampal and focal cortical ablation of *Scn1a*, a gene affected in the majority of Dravet syndrome patients which encodes the α1 subunit of voltage-gated $Na_V1.1$ sodium channels, was sufficient to induce spontaneous seizures in mice (**Chapter 7**). Global knock-out of *Scn1a* resulted in an early decrease in theta-gamma cross-frequency coupling which only persisted in mice that developed spontaneous seizures (**Chapter 8**). Decreases in theta-gamma cross-frequency coupling – associated with impaired functioning of inhibitory interneurons in modeling experiments – preceded seizures following local ablation of *Scn1a*. As such, these data suggest theta-gamma cross-frequency coupling as an early indicator of epileptogenesis in Dravet syndrome.