

A Cardiac Sodium Channel Mutation Associated with Epinephrine-Induced Marked QT-Prolongation

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May 18, 2020

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Running Title: SCN5A mutation associated with epinephrine-induced LQTS

Words (excluding references): 746

Disclosures: None

Funding: None

Keywords: Long QT Syndrome, Genetics, Variants, Cardiac Arrhythmias, Cardiovascular Diseases

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The hereditary long QT syndrome (LQTS) is an important cause of polymorphous ventricular tachycardia (torsades de pointes) and sudden cardiac death in otherwise young and healthy individuals. Clinically, this condition is caused by delayed ventricular repolarization and manifests as an abnormally prolonged QT interval on the electrocardiogram (ECG). The most common subtypes of LQTS are LQT1, LQT2, and LQT3 (1-10). The life-threatening arrhythmias occur most frequently during exercise in LQT1, upon auditory stimulation or emotional stress in LQT2, and at rest or during sleep in LQT3 (11). Patients with LQT1 have a mutation in the *KCNQ1* gene which codes for the subunit of the slow outward potassium current channel (I_{Ks}) while patients with LQT3 have a mutation in the *SCN5A* gene, which codes for the cardiac voltage-dependent sodium channel (I_{Na}) (12). LQT1-affected individuals are more vulnerable to β -adrenergic modulation than LQT3-affected individuals. Exercise and epinephrine-infusion ECG tests are therefore useful in differentiating between the LQTS subtypes and optimizing therapeutic strategies in order to prevent sudden cardiac death. While beta-blockers have been established as the standard of care for the treatment of the LQT1 and LQT2 subtypes, their use in LQT3 remains controversial (13, 14). A new missense mutation has been recently identified in the *SCN5A*-encoding I_{Na} channels and was found to be associated with sinus node dysfunction and epinephrine-induced QT prolongation (1). This atypical phenotype of LQT3 has so far been observed in only one patient. Whether other mutations exist that can cause a similar manifestation has yet to be determined.

In the current issue of the Journal of Cardiovascular Electrophysiology, Nakajima et al. describe a family with LQT3 that exhibited epinephrine-induced marked QT prolongation. The *SCN5A* V1667I mutation was found to be responsible for this atypical phenotype which resulted in prolongation of the QT interval in the proband as well as in family members carrying the mutation. The *SCN5A* V1667I mutation is a gain of function mutation located in domain IV-segment 5 (DIV-S5) of the sodium channel encoding *SCN5A* gene. To elucidate the pathophysiology of the disease, the authors transfected a human kidney cell line (tsA-201) to induce expression of wild-type and mutated sodium channels and measured the membrane sodium currents (I_{Na}). They showed that *SCN5A* V1667I mutation was associated with larger I_{Na} peak density, depolarizing shift in steady-state inactivation (SSI) leading to increased window current, and accelerated recovery from depolarization. Additionally, an increased hump in the I_{Na} of V1667I mutant cells (V1667I- I_{Na}) was observed during a ramp pulse protocol consistent with increased window current. There was no difference in fast inactivation rate and steady-state activation between the V1667I- I_{Na} and wild-type I_{Na} (WT- I_{Na}). The authors further examined the effects of protein kinase A (PKA) activation on V1667I- I_{Na} to mimic the effect of epinephrine. PKA activation resulted in a less significant hyperpolarizing shift in SSI in V1667I- I_{Na} compared to WT- I_{Na} leading to increased window current. Additionally, V1667I mutation was found to be associated with accelerated recovery from depolarization, and increased hump during ramp pulse protocol in the setting of PKA activation. Chen et al. have also reported the case of an individual with a mutation in *SCN5A* who exhibited marked QT-prolongation after epinephrine infusion (1). However, contrary to the *SCN5A* V1667I mutation described by Nakajima et al, the *SCN5A* V2016M defect was a loss of function mutation causing a decrease in I_{Na} peak density. The clinical manifestations of the *SCN5A* mutations described by Chen et al. and Nakajima et al. are more comparable to individuals with the LQT1 subtype than those with the LQT3 subtype. Therefore, it should be considered whether certain patients with *SCN5A* would benefit from beta-blocker therapy.

Overall, the authors should be commended on their efforts to describe for the first time a family with the *SCN5A* V1667I mutation and show that this mutation is associated with epinephrine-induced marked QT prolongation. The authors have also provided important insight into the electrophysiological properties of the mutant channels and the structure-function relationship of *SCN5A*. Further studies are needed to elucidate the precise molecular mechanisms of PKA activation on WT- I_{Na} and V1667I- I_{Na} . The results of this study have important clinical implications. The efficacy of beta-blockers for the treatment of LQTS has so far only been proven for the LQT1 and LQT2 subtypes, with conflicting results for the LQT3 subtype (13, 14). Given the marked QT prolongation in response to epinephrine infusion in carriers of the *SCN5A* V1667I mutation, certain LQT3 patients may benefit from beta-blocker therapy. Future studies should clarify whether beta-blockers are effective in these patients.

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