Tachy- or Bradyarrhythmias
Implications for Therapeutic Intervention in LQT3 Families
Kathryn A. Glatter, Nipavan Chiamvimonvat

Congenital long-QT syndrome (LQTS) is a group of inherited disorders that is associated with a prolonged QT interval on the ECG. It can be associated with syncope and sudden death due to episodic cardiac arrhythmias, particularly torsades de pointes and ventricular fibrillation. One common familial form is inherited as an autosomal dominant trait (the Romano-Ward syndrome). Much progress toward understanding the molecular mechanisms in congenital LQTS has been made over the past 8 years. Mutations in several ion channel genes have been discovered in different families with LQTS: KCNQ1, HERG, SCN5A, minK, MiRP1 (for review see 6). Indeed, these studies provided the first molecular basis into the pathogenesis of cardiac arrhythmias and, importantly, possible new insights into the more common types of acquired LQTS such as cardiomyopathy, ischemia, as well as drug-induced LQTS.

SCN5A, located on chromosome 3p21-24, encodes the α subunit of cardiac Na+ channels. Mutation analyses have revealed ≈30 distinct mutations of SCN5A associated with LQTS type 3 (LQT3). Mutations of KCNQ1, a gene that encodes for a slowly activating delayed-rectifier K+ channel (IαK), cause LQT1, the most common form of LQTS. Mutations in the minK gene cause LQT5. Mutations in HERG have been linked to LQT2 and represent 45% of the known LQTS defects. This gene encodes α subunits that form cardiac IαK, a rapidly activating delayed-rectifier K+ channel. MiRP1, or minK-related protein 1, putatively coassembles with HERG α subunits to form cardiac IαK channels and has been associated with LQT6. More recently, a mutation in ankyrin-B (also known as ankyrin 2), a member of a family of membrane adapters, has been shown to underlie LQT4. Mutations in SCN5A associated with LQTS often destabilize the channel inactivation gate, leading to a resultant action potential (AP) prolongation, ie, gain-of-function mutations (LQT3). SCN5A mutations also cause familial ventricular fibrillation (Brugada syndrome) and are associated with loss-of-function mutations.

Specific phenotypes have been associated with the three main genetic subtypes of LQT1 (IαK defect), LQT2 (IβK defect), or the HERG mutation), and LQT3 (the Na+ channel mutation). LQT1 appears to be the most adrenaline-sensitive of the subtypes in that episodes frequently occur during exercise, swimming, or with strong emotion, and beta-blocker medications work well at reducing episodes in this subtype. LQT2 is classically associated with auditory stimuli, and these patients respond variably to beta-blockers. LQT3 is relatively rare, representing only 5% to 10% of all LQTS patients. They classically have episodes while sleeping, are believed to have the lowest event rate but highest mortality with events, and may respond well to pacemaker therapy alone. Bradycardia and sinus pauses have been documented in patients with LQT3, which may further predispose patients to lethal tachyarrhythmic events.

In this issue of Circulation Research, Veldkamp et al provide for the first time the possible molecular mechanism for the previously described bradyarrhythmias and occurrence of tachyarrhythmias in association with slow heart rate in LQT3 families. The investigators performed a detailed analysis of the contribution of Na+ channel mutations to sinoatrial (SA) node dysfunction using computer simulations and the previously published models of a rabbit SA nodal cell, as well as a second model described by Zhang et al for the peripheral SA nodal cell. A previously described 1795insD, a C-terminal SCN5A mutation that causes affected individuals to manifest electrocardiographic features of QT-interval prolongation (LQT3) at slow heart rates and distinctive ST-segment elevations (Brugada syndrome) with exercise, was used for the analysis. The mutant 1795insD Na+ channel results in an incomplete inactivation and persistent Na+ current (IβK) as well as a negative shift in voltage dependence of inactivation. It was quite convincingly predicted from the two different SA nodal cell models that persistent IβK per se slows sinus rate by increasing the SA nodal cell AP duration even though the rate of diastolic depolarization (DDR) was increased, and that a negative shift in inactivation per se slows sinus rate by decreasing the availability of the inward current during phase 4 diastolic depolarization with a resultant decrease in DDR. Indeed, at a critical value of persistent IβK, oscillations occurred at the plateau potentials and the model cells failed to repolarize. Importantly, the sinus slowing effects of the two determinants are almost additive. The Figure shows a schematic Venn diagram of the various SCN5A mutations, the resultant phenotypes, and some possible overlaps.

The interpretation of the model cell data are dependent on the premise that some Na+ channels remain available at the moderately depolarized membrane potential in pacemaking cells. In the last three decades, a large body of evidence has accumulated with regard to the ionic mechanisms underlying
mammalian cardiac pacemaker activity. Spontaneous activity in SA node cells results from a characteristic phase of their APs, the slow diastolic depolarization. During this phase, the membrane slowly depolarizes until the threshold for a new AP is reached. The slow diastolic depolarization results from a number of ionic currents, including the hyperpolarization-activated inward current, \( I_{\text{h}} \), an inward T-type \( \mathrm{Ca}^{2+} \) current, \( I_{\text{Ca,T}} \), inward L-type \( \mathrm{Ca}^{2+} \) currents, \( I_{\text{Ca,L}} \), and the acetylcholine-induced \( K^+ \) current, \( I_{\text{acetyl}} \). In addition, a number of studies have reported an important functional role of \( I_{\text{h}} \) in adult SA nodal cells. Veldkamp et al further tested for this possibility using AP clamp experiments to test the contribution of the \( I_{\text{h}} \) during SA nodal automaticity. For 1795insD mutant channels, the upstroke of the AP generated from a number of ionic currents, including the hyperpolarization-activated inward current, \( I_{\text{h}} \), an inward T-type \( \mathrm{Ca}^{2+} \) current, \( I_{\text{Ca,T}} \), inward L-type \( \mathrm{Ca}^{2+} \) currents, \( I_{\text{Ca,L}} \), and the acetylcholine-induced \( K^+ \) current, \( I_{\text{acetyl}} \), in adult SA nodal cells.

Future studies will be needed to further address whether other types of LQT mutations can be associated with SA node dysfunction and how this may further contribute to QT prolongation and the ensuing tachyarrhythmias. For example, \( I_{\text{h}} \) has also been shown to contribute to repolarization and pacemaking in the SA node of mammalian heart. Class III antiarrhythmic methanesulfonanilide drugs such as dofetilide, at concentrations that block \( I_{\text{h}} \) selectively, reduce the spontaneous pacing rate and slow the rate of repolarization of single mammalian SA nodal cells. It will be important to assess whether LQT2 families also show evidence of SA node dysfunction and more importantly the therapeutic implication in the treatment in these patients.

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