Published in final edited form as:

Heart Rhythm. 2009 January ; 6(1): 107–108. doi:10.1016/j.hrthm.2008.10.037.

Restoring Repolarization in LQT3

Alfred L. George Jr., M.D.

From the Division of Genetic Medicine, Departments of Medicine and Pharmacology, and the Institute for Integrative Genomics, Vanderbilt University, Nashville, Tennessee

Congenital long-QT syndrome (LQTS) is a genetically heterogeneous condition of impaired myocardial repolarization that predisposes to episodes of life-threatening ventricular arrhythmia. Approximately 10% of genotype-positive LQTS subjects carry mutations in *SCN5A* encoding the major cardiac voltage gated sodium channel (designated $Na_v1.5$) and this defines the *LQT3* disease subtype. Most commonly, LQTS-associated *SCN5A* mutations confer a gain-of-function behavior at the molecular level characterized by impaired inactivation and increased persistent sodium current.¹ A similar functional phenotype has been observed for mutations in other genes associated with rare LQTS cases including *CAV3*, *SCN4B* and *SNTA1* that encode proteins that interact with $Na_v1.5$.^{2–4} An increased persistent sodium current disrupts the normal physiological balance of inward and outward currents flowing during the plateau phase of the cardiac action potential causing delayed repolarization, prolonged action potential duration, and predisposition to reentrant arrhythmia triggered by early and delayed afterdepolarizations.

Pharmacological targeting of mutant sodium channels has been suggested as a genotype-specific treatment strategy in *LQT3*. Mexiletine and other sodium channel blocking drugs suppress persistent sodium current *in vitro*⁵ and have been observed to correct the QT interval in subjects with *LQT3*.⁶ In mouse models with engineered *LQT3* mutations, mexiletine shortens myocyte action potential duration and is antiarrhythmic.⁷ Ranolazine, a blocker of physiologic plateau sodium current, has also been demonstrated to suppress persistent current *in vitro* for certain *LQT3* mutations.⁸ However, blocking sodium channels in the setting of *LQT3* may sometimes evoke ECG changes of Brugada syndrome raising potential safety concerns.⁹ Further, this strategy may be unsuccessful in some cases due to intrinsic functional differences among mutant channels.¹⁰ Unfortunately, the standard drugs used for treating LQTS, β -adrenergic receptor antagonists, are less efficacious in *LQT3* than in other LQTS subtypes.¹¹ Clearly, additional approaches for treating subjects with *LQT3* are needed.

Activating I_{Kr} in an *LQT3* Model

In this issue of *Heart Rhythm*, Diness, *et al.*,¹² investigate a new paradigm for normalizing repolarization in a cellular model of *LQT3* using I_{Kr} activators. The study tested the hypothesis that activating I_{Kr} can offset the action potential prolonging and arrhythmia promoting effects of the sea anemone neurotoxin ATX-II that causes a type of sodium channel dysfunction similar to *LQT3* mutations. In acutely isolated guinea pig ventricular myocytes, ATX-II caused a 2.5-fold increase in action potential duration at 90% repolarization (APD₉₀) and induced frequent early afterdepolarizations (EAD). Subsequent exposure of ATX-II modified myocytes to either

Address correspondence: Alfred L. George, Jr., M.D., Division of Genetic Medicine, 529 Light Hall, Vanderbilt University, 2215 Garland Avenue, Nashville, TN 37232-0275, Email: al.george@vanderbilt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

of two structurally different I_{Kr} activators (NS3623 or mallotoxin) normalized APD₉₀ and reduced EAD frequency to levels observed in cells that were not exposed to the neurotoxin. Neither I_{Kr} activator had direct effects on the toxin-modified sodium channels, and the concentrations employed were sufficiently low to avoid nonspecific effects on other channels (e.g., NS3623 may inhibit L-type calcium channels at higher concentrations¹³). Therefore, the investigators could conclude reasonably that increased I_{Kr} , mediated by activation of HERG potassium channels, compensated for the action potential prolonging effects of ATX-II.

Extrapolation and Future Directions

Although ATX-II treated guinea pig myocytes provides a suitable *in vitro* system to test new therapeutic ideas, *in vivo* experiments using genetically engineered mice expressing typical *LQT3* sodium channel mutations or *ex vivo* studies for example in canine ventricular wedge preparations will be important next steps for proving the potential clinical value of this strategy.

If this innovative therapeutic strategy succeeds in animal models, then there will be other considerations to address. The first issue relates to which specific I_{Kr} activator should be advanced to eventual clinical testing. Although NS3623 performed well in the *in vitro* assay, there could be concerns raised about the relatively high drug concentrations required for the effect as well as potential for off-target effects on other myocardial channels. Thinking beyond the heart, these compounds need to be tested for their activity on two brain potassium channels (HERG2, HERG3) that have structural relatedness with cardiac HERG to assess the potential for adverse effects involving the central nervous system. Optimization of structure-activity relationships for NS3623 and other I_{Kr} activating compounds will surely be needed to optimize target specificity and affinity.

Further testing might also be considered in cellular or animal models mimicking other LQTS variants caused by genes that confer *LQT3*-like sodium channel dysfunction such as *CAV3*, *SCN4B*, and *SNTA1*. From a broader perspective, one could also postulate that the strategy of counteracting impaired repolarization by I_{Kr} activation may work similarly for other LQTS subsets such as LQT1 or for other congenital arrhythmia susceptibility syndromes such as Timothy syndrome. Expanding the range of potential clinical uses of I_{Kr} activators might help stimulate greater industry enthusiasm for these orphan pharmaceuticals. Restoring normal repolarization in LQTS remains an important goal of therapeutic intervention in this disease. The work by Diness, et al.¹² illustrated a promising new approach that is certainly worth pursuing further.

References

1. Bennett PB, Yazawa K, Makita N, et al. Molecular mechanism for an inherited cardiac arrhythmia. *Nature* 1995;376:683–685. [PubMed: 7651517]
2. Vatta M, Ackerman MJ, Ye B, et al. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. *Circulation* 2006;114:2104–2112. [PubMed: 17060380]
3. Medeiros-Domingo A, Kaku T, Tester DJ, et al. *SCN4B*-encoded sodium channel $\beta 4$ subunit in congenital long-QT syndrome. *Circulation* 2007;116:134–142. [PubMed: 17592081]
4. Ueda K, Valdivia C, Medeiros-Domingo A, et al. Syntrophin mutation associated with long QT syndrome through activation of the nNOS-SCN5A macromolecular complex. *Proc Natl Acad Sci U S A* 2008;105:9355–9360. [PubMed: 18591664]
5. Wang DW, Yazawa K, Makita N, et al. Pharmacological targeting of long QT mutant sodium channels. *J Clin Invest* 1997;99:1714–1720. [PubMed: 9120016]
6. Schwartz PJ, Priori SG, Locati EH, et al. Long QT syndrome patients with mutations of the *SCN5A* and HERG genes have differential responses to Na⁺ channel blockade and to increases in heart rate - Implications for gene-specific therapy. *Circulation* 1995;92:3381–3386. [PubMed: 8521555]

7. Fabritz L, Kirchhof P, Franz MR, et al. Effect of pacing and mexiletine on dispersion of repolarisation and arrhythmias in DeltaKPQ SCN5A (long QT3) mice. *Cardiovasc Res* 2003;57:1085–1093. [PubMed: 12650887]
8. Fredj S, Sampson KJ, Liu H, Kass RS. Molecular basis of ranolazine block of LQT-3 mutant sodium channels: evidence for site of action. *Br J Pharmacol* 2006;148:16–24. [PubMed: 16520744]
9. Priori SG, Napolitano C, Schwartz PJ, et al. The elusive link between LQT3 and Brugada syndrome: the role of flecainide challenge. *Circulation* 2000;102:945–947. [PubMed: 10961955]
10. Ruan Y, Liu N, Bloise R, et al. Gating properties of SCN5A mutations and the response to mexiletine in long-QT syndrome type 3 patients. *Circulation* 2007;116:1137–1144. [PubMed: 17698727]
11. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95. [PubMed: 11136691]
12. Diness JG, Hansen RS, Nissen JD, et al. Antiarrhythmic effect of I_{K_r} activation in a cellular model of LQT3. *Heart Rhythm*. 2008
13. Hansen RS, Diness TG, Christ T, et al. Biophysical characterization of the new human ether-a-go-go-related gene channel opener NS3623 [N-(4-bromo-2-(1H-tetrazol-5-yl)-phenyl)-N'-(3'-trifluoromethylphenyl)urea]. *Mol Pharmacol* 2006;70:1319–1329. [PubMed: 16825484]