KCNQ1 autoantibodies: another way to regulate $I_{KS}$

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This editorial refers to ‘Anti-KCNQ1 K+ channel autoantibodies increase $I_{KS}$ current and are associated with QT interval shortening in dilated cardiomyopathy’ by J. Li et al., pp. 496–503, this issue.

A subset of patients with dilated cardiomyopathy (DCM) have been shown to carry increased levels of autoantibodies against β-adrenoceptors, muscarinic receptors, Na+–K+–ATPase, or troponin I.1–4 There is increasing evidence that these autoantibodies can have important electrophysiological consequences and may contribute to the arrhythmogenic risk of DCM patients.1 In this edition of *Cardiovascular Research*, Li et al.2 identify another potential electrophysiological target of autoantibodies by showing that a subset of patients with DCM has elevated autoantibodies against the extracellular pore region of KCNQ1, the α-subunit of the slowly activating delayed rectifier K+ current ($I_{KS}$). Anti-KCNQ1 autoantibodies, present in ~6% of DCM patients, increased $I_{KS}$ in human embryonic kidney cells, and were associated with shortened QT intervals in seropositive patients. This interesting study adds important new insights to our understanding of the regulation and potential dysfunction of $I_{KS}$.

Although $I_{KS}$ is small under basal conditions in isolated myocytes and contributes little to cardiac repolarization in this setting, it constitutes an important repolarization reserve that can be called upon when repolarization is compromised, for example, due to inhibition of the rapidly activating delayed rectifier K+ current, or due to reduced inactivation of L-type Ca2+ current following spontaneous diastolic Ca2+-release events.6,7 In addition, recent research has highlighted that $I_{KS}$ can be an extraordinarily varied modulator of cardiac repolarization through its ability to respond to a large number of different signals (Figure 1).

In addition to the KCNQ1 α-subunit, the $I_{KS}$ macromolecular complex incorporates KCNE1 β-subunits, which give the current its characteristic slow activation, as well as the A-kinase anchoring protein yotiao. The latter targets protein kinase A, protein phosphatase type-1, phosphodiesterase 4D3, and adenyl cyclase to the channel and plays a major role in $I_{KS}$ activation following sympathetic stimulation.6,8 Association with calmodulin is critical for assembly and gating of $I_{KS}$, and controls its Ca2+-dependent regulation.9 In addition, calmodulin appears to be required for nitric oxide-mediated regulation of KCNQ1 through S-nitrosylation of cysteine 445.9 Similarly, phosphatidylinositol 4,5-bisphosphate (PIP2) is required for physiological $I_{KS}$ function, with PIP2 depletion leading to $I_{KS}$ inhibition.10 Stimulation of α1A-adrenoceptors and/or muscarinic receptors can modulate intracellular PIP2 levels, thereby indirectly affecting the function of $I_{KS}$.

In addition, these receptors can modulate $I_{KS}$ via activation of protein kinase C and subsequent phosphorylation of KCNQ1.10 The $I_{KS}$ channel is also sensitive to changes in cell volume and/or stretch,11 and it has been shown that a second ‘hit’ such as hypertension, which promotes atrial dilatation and stretch, can be required to observe a phenotype such as atrial fibrillation in KCNQ1 mutation carriers.12

The findings by Li et al.5 add another layer to the complex $I_{KS}$ regulation by identifying that $I_{KS}$ amplitude is increased after treatment with sera of DCM patients with elevated KCNQ1 autoantibodies. The elevation of $I_{KS}$ occurred rapidly (within 1 h of incubation with serum) and was not due to changes in KCNQ1 expression, cell membrane targeting, changes in current–voltage relationship or time-constants of activation and deactivation. Although no changes in channel properties were observed at the whole-cell level, there are at least two different mechanisms at the single-channel level that could explain this observation. The first potential mechanism could involve alterations in single-channel conductance. Recently, Werry et al.13 performed a detailed analysis of $I_{KS}$ single-channel gating and showed that $I_{KS}$ channels exhibit multiple subconductance states that are traversed during channel activation.13 As such, KCNQ1 autoantibodies could increase $I_{KS}$ by altering the distribution of subconductance states. In this respect, it is interesting that the autoantibodies bind in the extracellular pore region of KCNQ1. This region, close to K+ selectivity filter, would be ideally suited to change single-channel conductance. In addition, $I_{KS}$ channels can exhibit minute-long dormant (non-conducting) periods.13 Thus, one alternative mechanism for increased whole-cell $I_{KS}$ could be activation of already membrane-targeted but dormant $I_{KS}$ channels by KCNQ1 autoantibodies. Recordings at the single-channel level would be required to assess these possible mechanisms in subsequent studies.

Defects in any of the constituents of the macromolecular complex or in its regulation may alter $I_{KS}$ function and predispose to cardiac arrhythmias.14 Loss-of-function mutations in KCNQ1, KCNE1, or yotiao give rise to long-QT syndrome (type-1, type-5, or type-11, respectively), impairing ventricular repolarization and predisposing to ‘torsade de pointes’ arrhythmias, particularly during increased sympathetic tone. Gain-of-function mutations in KCNQ1 may result in short-QT syndrome type-2, increasing the risk for ventricular tachyarrhythmias by heterogeneous shortening of the effective refractory period.14 In addition, both loss- and gain-of-function mutations in $I_{KS}$ may promote familial atrial fibrillation. However, even in the absence of genetic defects, $I_{KS}$ may contribute to cardiac arrhythmias. For example, $I_{KS}$ is reduced in...
heart failure and a recent study identified an association between KCNE1 expression and the development of post-operative atrial fibrillation. It is unknown whether the autoantibody-induced augmentation of IKs observed in the current study is protective in DCM patients (by augmenting repolarization reserve) or whether the increased IKs predisposes them to the development of an acquired short-QT syndrome or atrial fibrillation. Future long-term follow-up studies in larger and well-defined cohorts would be required to address these clinically important questions.

In summary, the study by Li et al. identifies DCM as an additional pathology in which IKs (dys)regulation may contribute to the arrhythmogenic phenotype. Their findings add KCNQ1 autoantibody-dependent enhancement of IKs to the list of regulatory mechanisms that may influence both atrial and ventricular electrophysiology and function. In general, KCNQ1 autoantibodies may represent a potential novel biomarker and/or therapeutic option that could complement current genetic screening strategies to identify patients at risk.

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