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Calcium-activated potassium current: a novel ion channel candidate in atrial fibrillation

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Atrial fibrillation (AF) is the most common clinical arrhythmia, and an important contributor to cardiovascular morbidity and mortality (Kannel & Benjamin, 2008). Currently available therapeutic options for AF are limited, and there is hope that rapidly developing knowledge about the pathophysiology of AF will lead to newer and better treatment possibilities targeting underlying mechanisms (Nattel, 2002).

A wide variety of mechanistic paradigms have been postulated for AF, with evidence for involvement of both ectopic impulse formation and atrial re-entry (Nattel, 2002). Abnormalities in atrial K^+ channel function have been implicated in AF on the basis of both experimental models and genetic evidence (Andalib *et al.* 2008; Michael *et al.* 2009). In a recent issue of *The Journal of Physiology*, Li *et al.* (2009) provide the first direct evidence implicating the Ca^{2+}-activated K^+ channel (Ca/K channel) in atrial repolarization and AF.

How do K^+ channel abnormalities lead to AF?

The most accepted mechanism by which K^+ channel abnormalities lead to AF is via increased function and acceleration of repolarisation. Since K^+ is at a higher concentration inside the cell than outside, K^+ channel opening causes positively charged potassium ions to move down their concentration gradient (i.e. to leave the cell), with the positive-ion egress bringing the cell back to its resting potential faster after depolarisation. Thus, the cell repolarises faster after firing, abbreviating the cardiac action potential and decreasing the cellular refractory period. Decreased refractory periods allow cardiac impulses to re-enter more easily and cause arrhythmias like AF (Nattel, 2002).

Surprisingly, loss of K^+ channel function may also promote AF. The first evidence came from animal models (Satoh & Zipes, 1998) and then a single nucleotide polymorphism associated with clinical AF was shown to reduce K^+ current by impairing K^+ channel cell-membrane trafficking (Ehrlich *et al.* 2005). Reduced K^+ current delays repolarisation by decreasing the K^+ egress that is responsible for terminating the action potential. Reduced K^+ current can lead to AF by causing early afterdepolarisations (EADs), such as those well-recognised to cause ventricular Torsades de Pointes arrhythmias in long-QT syndrome (Michael *et al.* 2009). Indeed, recent work shows increased AF risk in patients with congenital long-QT syndrome (Johnson *et al.* 2008). EADs cause ectopic beats that can initiate AF in a re-entry substrate or, if repetitive and rapid, sustain AF. Reduced K^+ current could also promote AF via increases in the spatiotemporal heterogeneity of refractoriness that promote re-entry (Ehrlich *et al.* 2005).

The determination of AF-promoting ionic mechanisms in man is difficult because of limited access to human tissue samples. However, AF-promoting genetic abnormalities are instructive because they indicate specific ion channel abnormalities associated with arrhythmia. To date, gain-of-function K^+ channel mutations are much more commonly associated with familial AF than loss-of-function, but there are also some AF-related loss-of-function K^+ channelopathies (Andalib *et al.* 2008).

Ca^{2+}-activated K^+ channels, atrial repolarisation and AF

A variety of Ca/K channels play a crucial role in vascular physiology (Ledoux *et al.* 2006). Ca^{2+} entry via Ca^{2+} channels causes contractile-filament movement in vascular smooth muscle cells, increasing vascular tone. Unopposed, Ca^{2+} entry could cause excessive vasoconstriction. Ca/K channels, which open in response to the same Ca^{2+} entry that causes vasoconstriction, induce cellular hyperpolarisation that reduces Ca^{2+} channel activation, promotes vasodilatation and limits Ca^{2+}-dependent vasoconstriction (Ledoux *et al.* 2006). Ca/K channels are divided into three classes based on their single channel conductance: small ('SK')-, intermediate ('IK')- and big ('BK')-conductance channels. In the 1970s, there were a number of suggestions for a role of Ca/K channels in the heart, but subsequent evidence called this idea into question (Eisner & Vaughan-Jones, 1983).

Until the late 1990s, no convincing evidence for cardiac Ca/K channels was presented. In 1999, Wang *et al.* detected Ca/K currents and SK3 subunits in the H9c2 cell-line derived from rat ventricles (Wang *et al.* 1999). In 2003, Xu *et al.* described substantial Ca^{2+}-activated K^+-current in mouse cardiomyocytes and biochemical evidence for the presence and atrial-selective distribution of SK2 channels in human and mouse hearts (Xu *et al.* 2003). Tuteja *et al.* subsequently detected all three small-conductance Ca/K channel subunits (SK1–3) in mouse hearts, with SK1 and SK2 having an atrial-selective distribution (Tuteja *et al.* 2005).

The first connection between Ca/K channels and AF was presented by Ozgen *et al.* who observed that intermittent burst pacing of pulmonary vein (PV) cardiomyocyte-sleeves (to mimic PV tachycardias implicated in AF) causes progressive PV action-potential shortening due to increased Ca^{2+}-activated K^+ current and increased membrane trafficking of SK2 (Ozgen *et al.* 2007). However, the Ozgen study offered only circumstantial evidence for a potential role of Ca/K channels in AF. Now Li *et al.* (2009) have provided direct evidence. In an elegant series of experiments, they showed that mice engineered to lack SK2 have prolonged atrial action potentials, show inducible AF upon programmed stimulation, and demonstrate atrial EADs under appropriate conditions.

Taken together, the Li and Ozgen articles point clearly to a role of Ca/K channels in AF. On the other hand, their observations raise some questions. The Ozgen study implicates increased SK2 function in AF, but the Li study shows that loss of SK2 function promotes AF induction in the mouse. This apparent discrepancy may not be significant, however, because both enhancement and suppression of repolarisation can produce arrhythmogenesis (Michael *et al.* 2009) and both have been implicated in clinical AF (Andalib *et al.* 2008). The Li *et al.*

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study used mice with a generalized SK2 knockout (Li *et al.* 2009). Thus, indirect mechanisms for the AF diathesis (e.g. loss of vascular SK2 causing hypertension and secondary cardiac manifestations) are not excluded. Finally, AF predisposition was demonstrated with premature extrastimulation protocols, which are much less effective in precipitating EAD arrhythmias (as postulated by Li *et al.*) than re-entry, which should have been made less likely by APD prolongation. These issues notwithstanding, the Li and Ozgen studies do suggest potentially important roles of Ca/K channels, long thought to be insignificant in the heart, in atrial repolarization and AF.

Potential clinical applications

AF remains an arrhythmia of great clinical importance with suboptimal therapeutic options. The cumulative evidence for atrial-selective expression of Ca/K channel SK1 and SK2 isoforms from the Chiamvimonvat laboratory (Xu *et al.* 2003; Tuteja *et al.* 2005; Li *et al.* 2009) raises the possibility that drugs targeting such channels may prevent AF without ventricular proarrhythmic risk. There is hope that better mechanistic understanding may lead to improved AF therapy (Nattel 2002), and evidence for a role of Ca/K channels should lead to additional research that may provide new pathophysiologically relevant insights. Finally, the knowledge that Ca/K channels may contribute to cardiac disease should direct broader study into the role of such channels in determining heart disease risk and as possible targets for preventive therapy. New insights gained by studies like those of Li *et al.* can only help to improve our understanding of AF pathophysiology, prevention and management.

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