Physiological remodelling of potassium channels in the heart

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This editorial refers to ‘Enhanced cardiac PI3Kα signalling mitigates arrhythmogenic electrical remodelling in pathological hypertrophy and heart failure’ by K.-C. Yang et al., pp. 252–262, this issue.

The failing heart undergoes a process of pathological electrical remodelling that is characterized by maladaptive alterations in ion channel expression and function.1,2 This shift in phenotype manifests as electrical instability which increases the occurrence of arrhythmic sudden death. Indeed, it is estimated that of the ~300 000 annual deaths related to heart failure,3 up to 50% are the result of sudden cardiac death, most likely from ventricular tachycardia and fibrillation.2

Thus, a better understanding of the cellular and molecular mechanisms underlying electrical remodelling is vital to developing therapeutic strategies to prevent lethal arrhythmias. Yang et al.3 describe a thought-provoking series of experiments exploring a signalling pathway underlying adaptive, ‘physiological’ electrical remodelling. The clinical impact of this work is that it provides important clues into ways in which the balance of physiological and pathological signalling can be controlled to prevent sudden cardiac death.

The aetiology of pathological electrical remodelling is complex and incompletely understood, partly because of the diverse diseases that lead to heart failure and variations in the severity or duration of disease. Nevertheless, chronic ventricular dysfunction is consistently characterized by inhibition of repolarizing K+ currents and prolongation of action potential duration.1,2 Furthermore, delayed repolarization contributes to intracellular Ca2+ dysregulation, development of afterdepolarizations, and increased dispersion of refractoriness, which are important substrates for the genesis of sustained arrhythmias.1° Recent experimental data indicate that signalling pathways associated with pathological hypertrophy participate in down-regulating cardiac K+ channels, particularly those carrying the transient outward current (Ito). In particular, pro-hypertrophic agonists such as angiotensin II or endothelin-1 decrease mRNA and protein abundance of Kv4.x α-subunits (Kv4.3 in human, Kv4.2 and Kv4.3 in rodents) that carry Ito in cardiomyocytes.5,6 The signalling mechanisms underlying these changes partly involve stress-activated kinases such as apoptosis signal-regulating kinase-1 (ASK1) and its main targets, p38 and c-Jun N-terminal kinase (JNK).5 Activation of ASK1 is mediated by receptor-stimulated NADPH oxidase and generation of reactive oxygen species,7 thus implicating oxidative stress as a key participant in remodelling. However, the transcriptional events underlying Kv channel down-regulation are not well defined, although it has been proposed that decreased mRNA stability is involved.5

A parallel pathway associated with pathological electrical remodelling involves the Ca2+-sensitive phosphatase calcineurin and the transcription factor nuclear factor of activated T-cells (NFATc3).8–10 This pathway is activated by sustained elevation in [Ca2+]i, which stimulates calcineurin to dephosphorylate NFATc3 and promote its translocation to the nucleus.8 In mice with myocardial infarction or chronic infusion of the β-agonist isoproterenol, down-regulation of several repolarizing K+ currents (Ito, I_kslow1, I_kslow3) was shown to be prevented by calcineurin inhibition or by genetic knockout of NFATc3.9 A pivotal role for Ca2+ in Kv channel remodelling is further supported by experiments in canine myocytes where high-frequency activation of Ca2+ transients by rapid pacing was shown to activate calcineurin and NFATc3, down-regulate Kv4.3 mRNA and protein, and decrease Ito density.10 In this study, Ito down-regulation was also inhibited by blockers of calmodulin kinase II (CaMKII), suggesting that there is cross-talk between CaMKII and calcineurin pathways.10 Thus, growing evidence indicates that ASK1–p38–JNK and Ca2+–CaMKII–calcineurin–NFATc3 pathways mediate pathological remodelling of K+ currents in the heart. It should be noted, however, that down-regulation of Kv channel expression does not simply parallel the development of hypertrophy. For example, rapid pacing of myocytes down-regulates Kv4.3 channels without significant change in cell morphology.10 Moreover, experimental models of diabetic cardiomyopathy exhibit characteristic down-regulation of Kv channel mRNA and protein but little evidence of hypertrophy.11

The present work by Yang et al.4 features a different form of electrical remodelling that contrasts markedly with that observed with pathological stressors. Specifically, ventricular myocytes from mouse hearts with constitutive activation of the lipid kinase phosphoinositide 3-kinase α (caPI3Kα) have increased current amplitudes and increased cell size (measured by whole-cell capacitance) compared with myocytes from wild-type mice, but K+ current densities between the

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two groups of cells are not significantly different. This illustrates that Kv channel expression in caPI3Kα mice increases in proportion to myocyte hypertrophy, which differs from pathological remodelling where channel expression is typically decreased.4–10 Nevertheless, these experiments highlight the importance of pro-survival signalling through PI3Kα in regulating ion channel expression in the heart.

It is well known that PI3Kα is activated following binding of growth factors (e.g. insulin, IGF1, EGF) with receptor tyrosine kinases.11 Activated PI3Kα stimulates the serine/threonine kinase Akt by increasing the formation of phosphatidylinositol-3,4,5-trisphosphate from membrane lipids.13,14 In the heart, the IGF1–PI3Kα–Akt cascade participates in adaptive, physiological hypertrophy that is distinct from the interstitial fibrosis, myocyte apoptosis, and depressed ventricular performance seen in pathological hypertrophy.12 As for electrical remodelling, the precise mechanisms by which IGF1–PI3Kα–Akt signalling controls Kv channel expression are not clear. Targets of Akt that may regulate Kv channel expression include the Forkhead family of transcription factors with putative binding sites on Kv channel genes.15 It is also possible that Akt may regulate the transcription of the accessory subunit KChIP2, which influences Kv4 channel assembly, phosphorylation and membrane stability,2 or the activities of microRNAs that have recently been shown to regulate translation of delayed rectifier K+ channels.1

The experiments by Yang et al.4 also point to a clinically relevant paradigm wherein it is possible to shift pathological to physiological electrical remodelling by stimulating physiological pathways or inhibiting pathological pathways. For example, stimulating physiological pathways by constitutive activation of PI3Kα preserves K+ current densities and QT interval in mice after transverse aortic constriction or in transgenic mice with heart failure.4 In rat models of pathological electrical remodelling, our laboratory has shown that depressed Ito density in ventricular myocytes is reversed by IGF15 or by an insulin mimetic whose effect to up-regulate Ito density is blocked by a PI3K inhibitor.16 Hence, these studies suggest that it is possible to ‘de-remodel’ Kv channels in the diseased heart by directly or indirectly stimulating the IGF1–PI3Kα–Akt pathway. Moreover, we have reported that in myocytes from rat hearts with chronic infarction, pharmacological inhibition of p38 or JNK up-regulates Ito density to normal values,15 suggesting that the ASK1–p38–JNK pathway may be an effective target to prevent pathological electrical remodelling.

Yang et al.4 and a previous report from this laboratory17 additionally present a novel therapeutic approach to mitigate arrhythmogenic electrical remodelling through exercise training. It was shown that swim training of wild-type mice stimulates PI3Kα and Akt in the heart similar to caPI3Kα transgenic mice without training.17,18 Moreover, hearts from swim-trained mice exhibit adaptive hypertrophy, but as with caPI3Kα mice, the increase in myocyte size is associated with up-regulated K+ currents. As such, there are no significant differences in ECG parameters, in particular the QT interval.17 More importantly, perhaps, is the finding that swim training of mice with dilated cardiomyopathy mitigates down-regulation of repolarizing K+ currents in ventricular myocytes and QT interval prolongation in the intact heart.4 These novel findings identify exercise training as a potential therapeutic tool to prevent arrhythmogenic electrical remodelling in the diseased heart. Indeed, exercise has been shown to reduce cardiovascular morbidity and mortality in patients with heart failure.19 Certainly, the numerous metabolic and neuro-humoral factors affected by exercise training make it challenging to fully understand this therapeutic approach, but the reports by Yang et al.4,17 offer important insights into the fundamental mechanisms controlling cardiac ion channel function that hold promise in the treatment of lethal arrhythmias in patients with heart failure.

Conflict of interest: none declared.

References