Ion channelopathies: What have they taught us about arrhythmias and anti-arrhythmic therapy?

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The efficient pumping of blood by the heart requires the co-ordinated activity of the billions of cardiac myocytes that make up the heart. This is achieved by an electrical communication system the centrepiece of which consists of voltage-gated ion channels. Over the last decade the molecular identity of most (if not all) the voltage-gated ion channels in the heart has been elucidated. More importantly it has also been found that mutations in some of these channels (most notably the cardiac sodium channel, SCN5a, and the delayed rectifier potassium channels, KvLQT1 and HERG) result in a marked increase in the risk of lethal cardiac arrhythmias, the so-called "cardiac ion channelopathies". Determination of the mechanisms underlying the increased risk of arrhythmias in patients with these mutant channels has taught us a great deal about the molecular basis of arrhythmias. This is perhaps best illustrated in the case of loss-of-function mutations in the HERG K^+ channel and the increased risk of arrhythmias initiated by premature beats (see e.g. Lu *et al.*, 2001). Understanding the cardiac ion channelopathies has also provided insights into why so many drugs developed to be anti-arrhythmic turned out to be "pro-arrhythmic". For example most Class III anti-arrhythmics inhibit the HERG K^+ channel resulting in a "drug-induced long QT syndrome" (Vandenberg *et al.*, 2001). The big challenge now is to utilise the knowledge we have gained from understanding cardiac ion channelopathies to develop more effective anti-arrhythmic therapies.

One of the major issues that has yet to be fully addressed with respect to the role of ion channels in the genesis of cardiac arrhythmias is the heterogeneity of ion channel expression. This heterogeneity of electrical activity is most clearly illustrated by the differences in the shape and duration of cardiac action potentials recorded from cells in different regions of the heart. One consequence of this heterogeneity is that any drug that modulates ion channel activity will have different effects in different regions of the heart and by altering the delicate balance of inward and outward currents has the potential to be pro-arrhythmic. However, before we can understand the specifics of such postulated pro-arrhythmic mechanisms we need to know much more about the spatial patterns of ion channel expression in the heart and how they are affected by disease processes (see e.g. Wong *et al.*, 2000).

Lu, Y., Mahaut-Smith, M.P., Varghese, A., Kemp, P.R., Huang, C.L.H. & Vandenberg, J.I. (2001) *Journal of Physiology*, 537(3):843-51.

Vandenberg, J.I., Walker, B.D. & Campbell, T.J. (2001) *Trends in Pharmacological Sciences*, 22(5):240-6

Wong, K.R., Trezise, A.E.O. & Vandenberg, J.I. (2000) *Biochemical and Biophysical Research Communications*, 278(1):144-9.