Taming the beast: targeting the L-type calcium channel to reduce cardiovascular morbidity and mortality

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Cardiovascular disease is the world's no. 1 killer responsible for premature death and disability on an unprecedented scale. It is an economic burden that costs Australia $7.5 billion annually. As a result of the increase in obesity and type II diabetes is it anticipated that a second epidemic of cardiovascular morbidity and mortality is imminent and the burden will increase. However the mechanisms leading to the morbidity and mortality remain poorly understood. Calcium is essential to cardiac excitation and contraction. The main route for calcium influx is the L-type Ca^{2+} channel ($Ca_v1.2$) and mice that are homozygous null for the $Ca_v1.2$ gene are embryonic lethal. Acute changes in Ca^{2+} influx through the channel contribute to arrhythmia and sudden death, and chronic increases in intracellular calcium through the channel contribute to pathological hypertrophy and heart failure. We study the role of the L-type Ca^{2+} channel in health and disease. Present work from my group is providing evidence for the induction of arrhythmias by the channel during acute hypoxia. By studying direct regulation of the purified human $Ca_v1.2$ protein in liposomes, we identified the cysteine responsible for the response. Using the same approach we have also identified the critical serine involved in the "Fight or flight" response that has clarified an area of controversy for more than 40 years. Oxidative stress leads to chronic activation of the L-type Ca^{2+} channel as a result of persistent glutathionylation and this leads to the development of hypertrophy. We find that activation of the channel alters mitochondrial function (and energetics) on a beat-to-beat basis *via* movement of cytoskeletal proteins. We use this response to "report" mitochondrial function in models of cardiomyopathy and to test efficacy of therapy to reverse cardiomyopathy.