Does two-pore channel-one play a role in the response of the heart to beta-adrenergic signalling?

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Introduction: Nicotinic acid adenine dinucleotide phosphate (NAADP) is a calcium-mobilizing messenger that acts via two-pore calcium channels (1). NAADP and two-pore channel-2 (TPC2) have been identified as important mediators of acute and chronic beta-adrenergic signalling in the heart (1). While recent evidence has shown a potential role for two-pore channel-1 (TPC1) in protecting the heart from ischaemia-reperfusion injury (2), its role in the absence of disease remains to be determined. The aim of this study was to explore the contribution of TPC1 to the effects of beta-adrenergic stimulation in ventricular myocytes.

Method: Transgenic mice lacking TPC1 expression ($TPC1^{-/-}$; on a C57BL/6;129P background; $Tpnc1^{T159}$ line) were generated as previously described (3). Ventricular myocytes enzymatically isolated from age-matched $TPC1^{-/-}$ mice and wild type (WT) control littermates were electrically field stimulated (1-2 Hz, 36℃). Cell contraction was measured from a video image of the cell using an edge detection system. In separate experiments, ventricular myocytes were loaded with fluo-5F-AM and calcium transients imaged using Nipkow spinning-disk confocal microscopy. Cells were superfused with isoprenaline (3 or 10 nM), which has been demonstrated to recruit NAADP as an intracellular messenger (1,4). Data are presented as mean±SEM. Comparisons were made using unpaired two-tailed Student's t-test or one-way ANOVA with Dunnett's post-hoc test, as appropriate.

Results: Application of isoprenaline (3 nM, 3 min) resulted in a significant increase in the mean contractile amplitude of ventricular myocytes from both WT (n=5) and $TPC1^{-/-}$ (n=5) mice (P<0.001 vs baseline). Contractile amplitude in the presence of 3 nM isoprenaline did not differ between the two groups (increases of 114±27% in WT vs 124±19% in $TPC1^{-/-}$; P>0.05). Similarly, isoprenaline (10 nM, 3 min) significantly increased calcium transient amplitude in ventricular myocytes from both WT (n=5) and $TPC1^{-/-}$ (n=5) mice (P<0.01 vs baseline). The effect of isoprenaline on calcium transients in myocytes from $TPC1^{-/-}$mice was numerically larger than that in myocytes from WT mice, but this was not statistically significant (increases of 139±29% in WT vs 222±34% in $TPC1^{-/-}$; P>0.05).

Conclusions: TPC1 is not responsible for mediating the actions of isoprenaline on excitation-contraction coupling in mouse ventricular myocytes.

References:

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