Calcium release from inositol 1,4,5-trisphosphate receptors influences cardiac pacemaker function in mouse sino-atrial node

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It has been found that Inositol 1,4,5-trisphosphate receptors (IP_3Rs), which function as inositol 1,4,5-trisphosphate (IP_3)-gated Ca^{2+} channels, are expressed in working cardiac myocytes (Nosek *et al.*, 1986). In atrial cells, accumulated evidence shows that IP_3R signalling is involved in arrhythmic activity (Li *et al.*, 2005; Woodcock, Kistler & Ju, 2009). However, there is little direct evidence whether IP_3Rs expression in adult mammalian sino-atrial node (SAN), the origin site of generating rhythm in the heart. In current studies, we quantified the level of the expression of IP_3Rs in the SANs by using a new cell direct qPCR technique. We find that both centre and peripheral SANs expression of IP_3Rs. We also studied the effect of IP_3R agonist, such as endothelin-1, IP_3-butyryloxymethyl ester (IP_3-BM), and antagonist 2-aminoethoxy diphenylborate (2-APB), on intracellular Ca^{2+} of spontaneously firing sinoatrial node preparations. In the presence of 10 nM endothelin-1, the resting $[Ca^{2+}]_i$ was increased by 36 ± 13 % (n = 5; $P < 0.05$) and the firing rate was increased by 20 ± 8 % ($P < 0.05$). The results were similar when IP_3-BM was used. IP_3R antagonist 2-APB reduced intracellular Ca^{2+} and slowed the firing rate. However, such effects were only seen in wild type but not in IP_3R2 knock out mice. The localisation of IP_3R2s and IP_3 induced Ca^{2+} sparks also further support that that IP_3Rs are involved in cardiac peacemaking through the release of Ca^{2+} from the intracellular Ca^{2+} stores that are near subsarcolemmal membrane.

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