Ca^{2+} influx through store-operated Ca^{2+} channel in mouse sinoatrial node

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In both excitable and non-excitable cells, the depletion of intracellular Ca^{2+} stores causes a flux of Ca^{2+} into the cells and refills the Ca^{2+} store to its original level. The inward Ca^{2+} flux resulting from depletion of Ca^{2+} store is through the store-operated cation channels (SOCCs). There is growing evidence that SOCCs play an important role in muscle cell signalling (for review see Gailly, 2002).

In previous studies, we found that intracellular Ca^{2+} stores are involved in cardiac pacemaking (for review see Ju & Allen, 2001). To examine if store–operated Ca^{2+} entry is present in cardiac pacemaker tissue and its possible role in regulating heart rate, sinoatrial node (SAN) tissue was dissected from mouse right atria of the heart and loaded with the Ca^{2+} indicator indo-1 AM. In the presence of extracellular Ca^{2+} ($[Ca^{2+}]_o$), cyclopiazonic acid (CPA), a selective sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) inhibitor, significantly increased resting $[Ca^{2+}]_i$ and gradually reduced the amplitude of $[Ca^{2+}]_i$ transients. Incubating SAN in Ca^{2+} free solution caused a substantial decline in resting $[Ca^{2+}]_i$ and stopped pacemaker activity. Reintroduction of Ca^{2+} (1.8 mM) to the perfusate in the presence of CPA evoked a striking increase in resting $[Ca^{2+}]_i$, a characteristic of SOCC activity. The Ca^{2+} influx in response to reintroduction of $[Ca^{2+}]_o$ was 7.1 ± 3.2 fold greater in the presence of CPA than in its absence ($p < 0.03$, $n = 11$), which suggested that the Ca^{2+} influx was dependent on the SR store depletion. It is known that the Na^+-Ca^{2+} exchanger exists in cardiac pacemaker tissue. After a period of incubation in zero Ca^{2+} solution, the reintroduction of Ca^{2+} could also activate the reverse mode of Na^+-Ca^{2+} exchanger and increase Ca^{2+} influx. To test this possibility, we applied Na^+-Ca^{2+} exchanger inhibitor KBR -7943. We found that in the presence of KBR -7943, there was still a significant rise of $[Ca^{2+}]_i$ in response to the depletion of SR the Ca^{2+} store. Moreover, gadolinium (100 μM), a known SOCC inhibitor, significantly inhibited 72 ± 8% of Ca^{2+} influx in the present of CPA ($P< 0.01$, $n = 4$).

Recent studies have suggested that SOCCs might be related to the transient receptor potential canonical (TRPC) gene family. We examined SAN mRNA expression of the seven known mammalian TRPC isoforms by RT-PCR. mRNA for TRPC1, 2, 3, 4, 6 and 7 was detected in SAN, whereas that for the TRPC5 was not. These results suggest that cardiac pacemaker tissue exhibits store-operated Ca^{2+} activity which may be due to expression of TRPCs in these cells.

Gailly P. (2002) *Biochimica et Biophysica Acta* **1600**, 38-44.
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