Role of intracellular Ca^{2+} in sinoatrial node pacemaking

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A specialized group of cells in the heart, known as the sinoatrial node (SAN), generates a pacemaker current that drives rhythmic beating of the heart. It is known that release and uptake of Ca^{2+} by the sarcoplasmic reticulum (SR) contributes to the cardiac rhythm under resting and stimulated conditions (Lakatta *et al.*, 2003; Imtiaz*et al.*, 2010). During adrenergic stimulation an increase in both release of Ca^{2+} through the ryanodine receptors (RyR2) and uptake by SERCA accelerates heart rate. Transgenic animals lacking adrenergic stimulation of the SERCA with intact RyR2 lose adrenergic-stimulated increase in heart rate (Luo *et al.*, 1994). This suggests that RyR2 alone has no significant role in adrenergic-stimulated increase in heart rate. However, in contradiction, knock-out mice lacking adrenergic stimulation of SERCA are able to produce half the increase in heart rate compared to wild type animals, thus indicating RyR2 has a role in accelerating heart rate (Kushnir *et al.*, 2010; Shan *et al.*, 2010). Thus, the relative contributions and mechanisms of SR uptake and release during adrenergic stimulation are not well understood. Furthermore, the contribution of other sources and sinks of Ca^{2+}, such as the store-operated Ca^{2+} entry (SOCE) to SAN rhythm generation is not well understood. We have used mathematical modelling to investigate the relative contributions of RyR2, SERCA and SOCE in setting resting and adrenergic stimulated SAN rhythm.

The main results of our study are: 1) Our simulations agree with the experimental data in the literature on knock-out and transgenic animals and provide insight into mechanisms underlying the contradictory observations: a) Adrenergic-stimulation of RyR2 alone (compared to normal full stimulation) caused only half the increase in SAN frequency because of lower store load and reduced efficacy of sodium-Ca^{2+} exchange current (I_{NCX}); b) Adrenergic-stimulation of SERCA alone also caused only half the increase in SAN frequency. This is because unstimulated RyR resulted in reduced SR excitability resulting in delayed release of Ca^{2+} from the RyR2, which reduced SR contribution to the late diastolic phase. 2) The relative timing of Ca^{2+} entry through store-operated Ca^{2+} channel determines the effectiveness of SOCE in accelerating SAN frequency.

The results of this investigation indicate that SAN dynamics emerges due to symbiotic interaction between ionic channels, Ca^{2+} uptake and release, and store-operated Ca^{2+} entry.

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