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Atrial myocytes demonstrate the diversity of cardiac calcium signalling

Comment on: Hohendanner F, et al. Cytosolic and nuclear calcium signaling in atrial myocytes: IP3-mediated calcium release and the role of mitochondria. Channels 2015; 9(3):129–38; PMID: 25891132; http://dx.doi.org/10.1080/19336950.2015.1040966

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Atrial myocytes show a wider diversity of physiological calcium (Ca^{2+}) signals than their ventricular counterparts. A study by Hohendanner and colleagues[1] examines the fine tuning of Ca^{2+} signals within atrial myocytes.

Beating mammalian hearts require the repetitive firing of action potentials from the pace-making sino-atrial node, and the coordinated contraction and relaxation of many millions of cardiac myocytes as action potentials sweep through the atrial and ventricular chambers. When an action potential reaches a myocyte within the atrial or ventricular chambers it causes their cell membrane (the sarcolemma) to depolarise, and thereby triggers a rapid, transient, Ca^{2+} signal. Subsequently, the Ca^{2+} signal causes the actin and myosin fibres to engage, and thus elicits myocyte contraction.[2]

The depolarisation-evoked Ca^{2+} signals are caused by the interplay of different types of Ca^{2+} channels. Specifically, sarcolemmal depolarisation triggers voltage-activated Ca^{2+} channels, allowing Ca^{2+} to enter from the external medium. This Ca^{2+} entry triggers the opening of other Ca^{2+} channels known as ryanodine receptors (RyRs), which sit on the sarcoplasmic reticulum, by a process known as Ca^{2+}-induced Ca^{2+} release (CICR).

Action potentials cause both atrial and ventricular myocytes to contract by evoking sarcolemmal depolarisation and Ca^{2+} signals, but with differences. Mammalian ventricular myocytes respond to an action potential with a Ca^{2+} signal that arises simultaneously across the whole cell. With atrial myocytes from many mammalian species action potential-evoked Ca^{2+} signals are not simultaneous, whole-cell events. Rather, they occur as Ca^{2+} waves that arise at the edge of a myocyte and propagate in a centripetal manner inside the cell[3]. A critical difference between ventricular and atrial myocytes is that the former cells have distinctive thin (100 – 200 nm) sarcolemma invaginations called transverse tubules (T-tubules) that convey action potentials deep into the cells.[4]

In terms of T-tubule expression, mammalian atrial myocyes are much more diverse than their ventricular counterparts. Some species express extensive T-tubules in their atrial cells. Whereas, others have no T-tubules, a few dispersed T-tubules, or a less organised series of sarcolemma invaginations that run transversely and axially.[5] In those atrial myocytes that do not have sarcolemma invaginations, action potential-evoked Ca^{2+} signals will solely arise at the edge of the cells and propagate inwards. So, to understand the regulation of atrial contraction, it is important to determine what controls the propagation of centripetal Ca^{2+} waves.

Hohendanner et al. used rabbit atrial myocytes, which do not express T-tubules and therefore rely entirely on centripetal Ca^{2+} waves. They observed that centripetal Ca^{2+} wave propagation was faster at the cell periphery than in the cell centre. This two-speed Ca^{2+} wave propagation was due to mitochondria (**Fig. 1**). By sequestering Ca^{2+}, mitochondria dampen CICR and inhibit Ca^{2+} wave propagation. Their observations provoke a number of intriguing questions; what purpose would mitochondrial Ca^{2+} uptake serve? Why dampen the propagation of a Ca^{2+} wave when it is needed to trigger contraction?

Firstly, mitochondrial respiration is regulated by the concentration of Ca^{2+} within the mitochondrial matrix. So, by sequestering Ca^{2+} mitochondria can match cellular activity and energy production. Secondly, the ventricular chambers, which are larger and stronger muscles, are responsible for the bulk of blood pumping. The atrial chambers enhance the filling of ventricular chambers with blood, and are particularly important during periods of exercise. It has been demonstrated that the extent of the inward centripetal Ca^{2+} wave propagation modulates the contraction of atrial myocytes. So, by dampening Ca^{2+} wave propagation, mitochondria serve to limit contraction, and conserve energy, when forceful contraction is not needed, but their dampening effect must be overcome when stronger contraction is required.

One way in which the dampening effect of mitochondrial Ca^{2+} uptake can be overcome is to activate additional Ca^{2+} channels during Ca^{2+} wave propagation. Hohendanner *et al* demonstrated that inositol 1,4,5-trisphosphate receptors ($InsP_3Rs$) augment Ca^{2+} signalling within atrial myocytes. To trigger the specific opening of $InsP_3Rs$, Hohendanner *et al* used photolytic uncaging of $InsP_3$. They found that depolarisation-evoked Ca^{2+} transients were larger following uncaging of $InsP_3$ inside an atrial myocyte. In essence, $InsP_3Rs$ act to boost CICR as a Ca^{2+} wave passes by.

Although $InsP_3$ enhanced centripetal Ca^{2+} wave propagation in atrial myocytes, uncaging $InsP_3$ did not trigger Ca^{2+} waves by itself unless mitochondrial Ca^{2+} uptake was blocked. This observation alludes to another function of mitochondrial Ca^{2+} uptake;

preventing arrhythmic Ca^{2+} signals. As described earlier, a beating heart requires the coordinated activation of Ca^{2+} release following myocyte depolarisation. However, $InsP_3Rs$ can activate solely upon the binding of $InsP_3$, and unlike RyRs don't have to wait for cellular depolarisation to trigger CICR. $InsP_3Rs$ can therefore release Ca^{2+} during periods when a myocyte should be silent. Promiscuous Ca^{2+} release in the heart is dangerous, as it disrupts myocyte beating[6]. Atrial myocytes use $InsP_3Rs$ as a means to boost Ca^{2+} signals and thereby enhance contraction, but need mitochondrial Ca^{2+} uptake to prevent $InsP_3Rs$ from triggering arrhythmic Ca^{2+} waves.

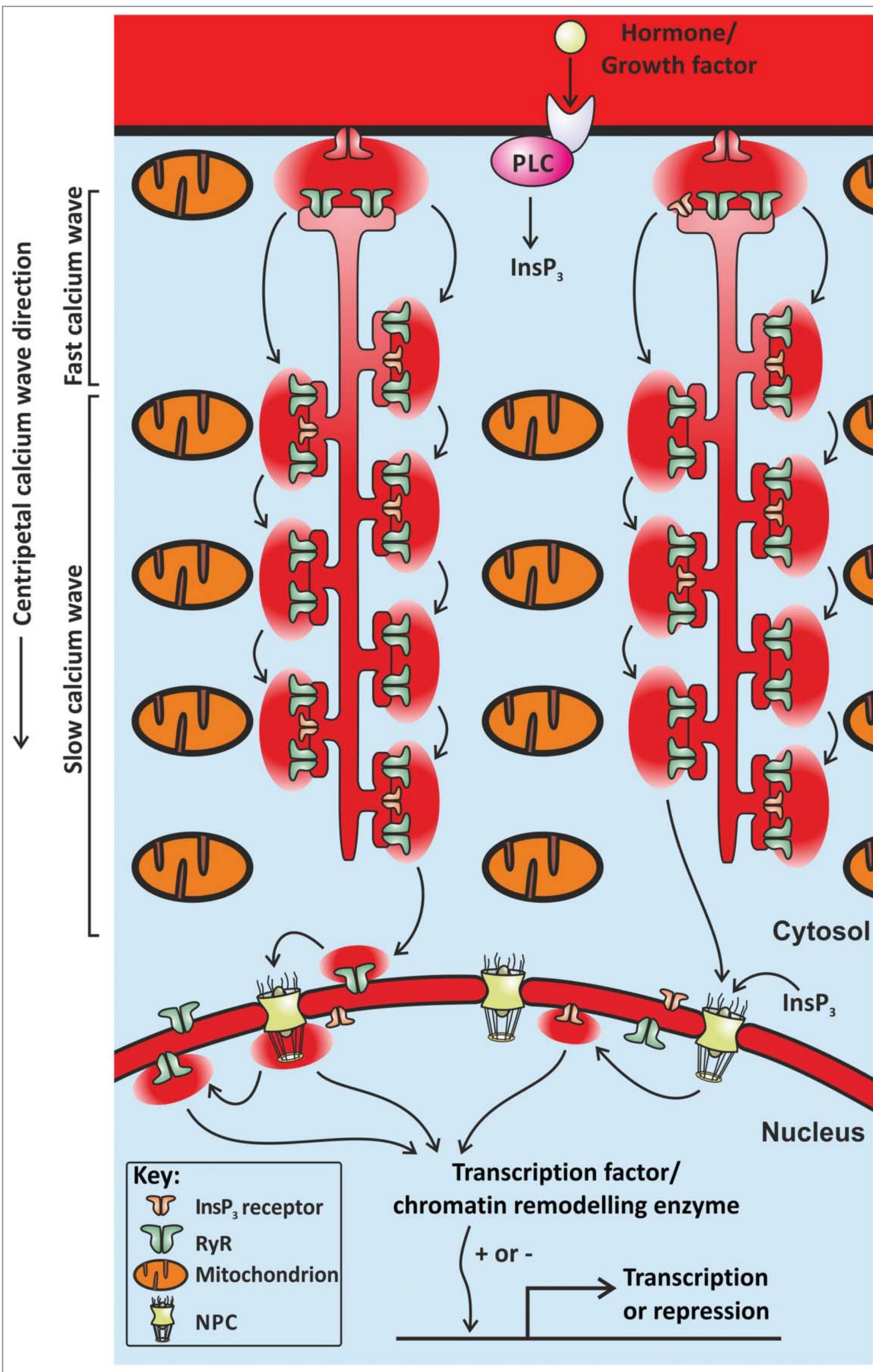

Figure 1. The Figure shows an illustration of part of an atrial myocyte. The arrows denote the movement of Ca^{2+} ions as a centripetal wave. The Ca^{2+} wave propagates via CICR between neighbouring clusters of RyRs. In the presence of $InsP_3$, Ca^{2+} wave propagation is boosted by the opening of $InsP_3Rs$. Both Ca^{2+} and $InsP_3$ can pass through nuclear pore complexes (NPC), and trigger nucleoplasmic Ca^{2+} signals that influence gene transcription. Mitochondria sequester Ca^{2+} ions, and thereby retard Ca^{2+} wave propagation.

The responses to uncaging of $InsP_3$ observed by Hohendanner *et al* were not the same throughout an atrial myocyte. The nucleus was more responsive to $InsP_3$ than the remainder of the cell. Uncaging $InsP_3$ evoked mini Ca^{2+} waves that were restricted to the nucleus. This nuclear restriction was also due to the Ca^{2+} uptake by mitochondria. $InsP_3$ is highly diffusible inside cells and can pass through nuclear pore complexes, thereby triggering nucleoplasmic Ca^{2+} signals. Any Ca^{2+} escaping through nuclear pores would be sequestered by perinuclear mitochondria, thus making the nucleus an autonomous Ca^{2+} signalling domain. It is likely that nuclear Ca^{2+} signals caused by $InsP_3Rs$ will modulate myocyte gene expression, and that the particular genes will be different to those affected by the centripetal Ca^{2+} waves that also invade the nucleoplasm.

Atrial myocytes are amazing cells in which to study Ca^{2+} signalling because of their ability to show diverse responses. Their regular structure and geometry belies a Ca^{2+} signalling toolkit with multiple interacting components to enable discrete subcellular and whole-cell Ca^{2+} signals that are highly plastic and suit particular physiological needs.

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