IP_3 and Ca^{2+} signals in the heart: Boost them or bust them?

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Cardiac muscle Ca^{2+} signaling and excitation-contraction coupling rely on a relatively small Ca^{2+} influx via voltage-dependent L-type Ca^{2+} channels, which is amplified by a severalfold larger Ca^{2+} release from the sarcoplasmic reticulum (SR) via ryanodine receptor Ca^{2+} release channels (RyRs). The Ca^{2+}-induced Ca^{2+} release mechanism (CICR) is driving this signal amplification. Besides the RyRs, inositol trisphosphate receptors (IP_3Rs), a type of Ca^{2+} release channels with many similarities to the RyRs, are also present in cardiomyocytes. But they are vastly outnumbered by the RyRs (ratios of 1:50 to 1:100). While IP_3Rs seem important and more abundant during early cardiac development, their relative expression level declines later, as the SR matures and the number of RyRs increases. Why mother nature is perpetuating the presence of the IP_3Rs at a low density in cardiac muscle has remained a mystery. Several hypotheses have been tested in experimental studies, but the puzzle remains incompletely solved and the role(s) of the IP_3Rs is not yet clearly defined. In cardiomyocytes, particularly in atrial cells where $InsP_3Rs$ are more abundant, a modulatory function of $InsP_3Rs$ on CICR has been recognized (Mackenzie *et al.*, 2002). IP_3Rs may indeed participate in Ca^{2+} signaling, secondary to acute or chronic stimulation of membrane receptors linked to the phospholipase C (PLC) - IP_3 signaling pathways, such as endothelin (ET) or angiotensin (AT) II receptors (Horn *et al.*, 2013). Recently, it has been found that IP_3Rs located in the nuclear envelope are involved in excitation-transcription coupling, thereby participating in the control of gene expression programs. During several pathological conditions, chronic activation of these pathways may engage in cell growth, hypertrophy and the initiation of dedifferentiating gene programs (Nakayama *et al.*, 2010). One notable cardiac condition in which overexpression of IP_3Rs has been observed is the development of cardiac hypertrophy and failure (Harzheim *et al.*, 2009). In these and related diseases, IP_3Rs could represent a key element of a slowly developing positive feed-back loop, whereby their maintained activation (in the nucleus) leads to an increase of their own cellular expression via excitation-transcription coupling. How potential Ca^{2+} signaling complications arising from this constellation could be avoided by spatially targeting the IP_3R expression and by finely tuning their activity can be conceptualized based on findings published in the present issue of *The Journal of* Physiology (Hohendanner *et al.*, 2014).

In an elegant functional study a wide array of state-of-the art methods was combined (e.g. IP_3 measurements with FIRE, an IP_3 affinity trap, photorelease of IP_3, etc.) to define how IP_3R and RyR mediated Ca^{2+} release orchestrates Ca^{2+} signaling in atrial and ventricular myocytes isolated from normal and heart-failure (HF) rabbits. The first astonishing finding was that in the absence of any IP_3 generating stimuli (i.e. at basal cellular IP_3 levels) and in sharp contrast to the behavior of ventricular myocytes, the Ca^{2+} transients recorded from HF atrial myocytes were markedly larger than those from control cells. More detailed analysis of this unexpected observation revealed that it was predominantly due to larger and faster centripetal Ca^{2+} signal propagation, mostly depending on boosted Ca^{2+} release

via IP_3Rs located throughout the cell, with a possible contribution by reduced mitochondrial Ca^{2+} uptake. The next surprising observation was made when IP_3 levels were experimentally elevated above basal, as it might occur in-vivo (e.g. by photolysis of caged IP_3 or by ATII). While normal atrial myocytes responded with a slightly increased Ca^{2+} transient amplitude, the HF cells exhibited dramatically reduced Ca^{2+} signals combined with slowly rising diastolic Ca^{2+} concentrations. The reduced amplitudes were particularly evident after prolonged exposure to elevated IP_3 levels, and appeared to be caused by a larger SR Ca^{2+} leak, manifest as a higher frequency of Ca^{2+} puffs and arrhythmogenic Ca^{2+} waves, and a corresponding decline of intra SR Ca^{2+}.

The strikingly divergent behavior of the atrial myocyte Ca^{2+} signaling system under conditions of constitutively low versus stimulated IP_3 concentrations is dazzling. These results reveal a new dimension of atrial myocyte Ca^{2+} signaling modulation by IP_3. While in HF atrial cells the overexpressed IP_3Rs may contribute to their inotropy at basal IP_3 levels, acute stimulation of IP_3 generating pathways may be pro-arrhythmogenic (by increasing the propensity for Ca^{2+} waves) and in the long run curtail atrial Ca^{2+} signaling, by maintaining an SR Ca^{2+} leak ultimately lowering its Ca^{2+} load.

It is well established that patients with HF have elevated levels of circulating ATII. Therefore, the findings of the present study are potentially therapeutically relevant, both for the atrial mechanical performance (atrial kick) and for atrial arrhythmias. However, the effects of cytosolic IP_3 seem to be vastly different, if not opposite, in atrial myocytes after remodeling of their Ca^{2+} signaling during HF. Thus, it will be crucial to define the role of IP_3 not only in isolated cell preparations, but to translate these findings to the more complex situation and neurohumoral environment of the organ and even patient, where cytosolic IP_3 levels may vary. Such studies seem to be needed to obtain an integrated view of atrial Ca^{2+} signaling during HF with all of its complexities. This knowledge would appear to be a important pre-requisite to design mechanisms based therapeutical strategies.

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