Letter to the Editor

Reply: Does the adenosine A2A receptor stimulate the ryanodine receptor?

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In our paper on the expression and function of the adenosine A2A receptor (A2AR) in human atrial myocytes [1], we show that agonist stimulation of this receptor induces a protein kinase A (PKA)-dependent increase in the frequency of calcium sparks and spontaneous calcium waves. We therefore investigated whether A2AR stimulation affected the L-type calcium current, sarcoplasmic reticulum (SR) calcium uptake, or SR calcium release, as these mechanisms are known to be modulated by PKA-dependent phosphorylation [2–4]. Since only the fast (SR calcium release-dependent) time constant for ICa inactivation was affected by A2AR stimulation, we proposed that a PKA-mediated increase in ryanodine receptor (RyR) opening may account for our results.

However, according to the letter to the editor by Venetucci et al. [13], an increase in time-averaged Ca2+ efflux from the cell is inconsistent with a simple stimulation of the RyR, whereas our observations are compatible with an A2AR-mediated increase in sarcolemmal calcium entry. Venetucci et al. therefore suggest that calcium entry at rest, through a mechanism recently described by their laboratory [5], could account for our results. In favour of this proposal, previous studies that have documented SR calcium loading at rest in different types of myocytes [6–8], and store-operated calcium entry (SOCE) has recently been reported to be more prominent in neonatal than adult rabbit ventricular myocytes [7].

Before we accept this proposal, however, we must examine the premises for ruling out a simple A2AR-mediated stimulation of the RyR. In this regard, Venetucci et al. reason that time-integrated calcium influx and efflux must match (at steady-state) and, based on their observations in ventricular myocytes, they assume that spontaneous calcium release occurs when the SR calcium load reaches a threshold. Their observations in ventricular myocytes may, however, not be directly applicable to atrial myocytes, since it has been shown that the expression of SERCA in the human heart is higher in the atrium than in the ventricle while the opposite is true for phospholamban [9]. According to this observation SR calcium reloading would be expected to be faster in atrial than ventricular myocytes, and consequently a big change in the calcium wave frequency may be associated with a small change in SR calcium loading in atrial but not in ventricular myocytes.

Secondly, and perhaps more importantly, it is implicit from the argumentation of Venetucci et al. that the threshold for SR calcium release is time independent. Refractoriness of the ryanodine receptor has, however, been described and referred to as adaptation [10] or inactivation [11]. This phenomenon implies that the threshold for spontaneous SR calcium release decreases with time from the preceding release. Indeed, a recent study that measured SR calcium loading in situ [12] found that calcium release from the SR was dramatically increased after a 7 s rest period although SR calcium loading did not change during the rest period. Thus, our observations may indeed be compatible with a simple A2AR-induced shortening of the time for the RyR to recover from inactivation, without a significant change in SR calcium loading. This would also be in accordance with the A2AR-dependent shortening of the fast ICa inactivation, observed with repetitive stimulation at 0.5 Hz. In contrast, a slow SOCE-like calcium entry is expected to contribute minimally to SR calcium loading on a physiologically relevant time scale [7].
Thus, we do consider it feasible that A2AR stimulation induces a PKA-dependent increase in RyR opening, but we also find it necessary to document an A2AR-dependent modulation of RyR phosphorylation, and we are currently investigating whether A2AR stimulation modulates phospholamban and RyR phosphorylation.

References


