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Letter to the Editor

Does the adenosine A_{2A} receptor stimulate the ryanodine receptor?

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A recent paper in *Cardiovascular Research* from Hove-Madsen and colleagues [1] has investigated the role of the adenosine A_{2A} receptor in human atrial myocytes. Elegant confocal images show that this receptor is localized at the level of the Z line in the myocyte. Their paper then proceeds to address an important physiological question; the role of this receptor. No effect was found on the amplitude or voltage-dependence of the L-type Ca current. However agonists of the adenosine A_{2A} receptor increased the frequency of both Ca sparks and Ca waves, phenomena that result from Ca induced Ca release (CICR) from the sarcoplasmic reticulum (SR). There was no change in either the amount of Ca extruded from the cell during each Ca wave or the SR Ca content (as assessed by the integral of the caffeine evoked Na–Ca exchange, NCX, current). Based on these observations the authors concluded that binding of agonist to the adenosine A_{2A} receptor results in an increase of RyR opening and that this effect may be mediated by phosphorylation of the RyR.

It is instructive to compare these results and conclusions with the findings of previous work in ventricular myocytes. Here a stimulation of the RyR with caffeine produces an increase in the frequency of Ca waves [2]. This is, however, accompanied by a decrease of both the SR Ca content and the amount of Ca that leaves the cell during each wave. Our interpretation of this result (see [3] for review) is that caffeine increases the open probability of the RyR. This results in a higher frequency of Ca waves and thence a greater efflux of Ca from the cell on NCX. This greater efflux decreases SR Ca content. Since Ca waves now occur from a lower Ca content, the Ca released on each wave and thence Ca efflux from the cell is less than in control. We found that the time-averaged Ca efflux activated by waves (calculated as the frequency of the waves multiplied by the amount of Ca leaving the cell per wave) was unaffected by RyR stimulation [2].

Such a constancy of Ca efflux per unit time is expected on theoretical grounds for manoeuvres that only affect the RyR. In the steady state the time-averaged Ca efflux from the cell must equal the average influx. Therefore, if a given manoeuvre only affects the RyR and has no effect on the influx of Ca into the cell then it will have no effect on the time-averaged efflux. It might be argued that these considerations are based entirely on ventricular cells and may not be applicable to atrial cells. However the data of Hove-Madsen et al show an increase in time-averaged Ca efflux from the cell and this result is inconsistent with a simple stimulation of the RyR.

If the data do not fit the hypothesis of an effect on the RyR, what other explanation can account for them? We suggest that an increase of Ca influx into the cell could account for the experimental data. We have previously [3] compared the effects of manoeuvres that affect the RyR with those that increase the Ca influx into the cell. An increase of Ca influx results in an increased frequency of Ca waves. However the amplitude of these waves does not change. Furthermore there is no change of SR content [4]. These results can be explained as follows. We assume that a Ca wave occurs when the Ca content of the SR has reached a threshold level. During a wave some of the Ca will be pumped out of the cell. Ca entry into the cell will be required to refill the SR back to the threshold level [5]. An increase of Ca influx will accelerate the refilling process and thereby increase the frequency of waves. It is noteworthy that the effects of increasing Ca influx (increased frequency of waves with no change in either the amount of Ca pumped out of the cell per wave or of the SR Ca content) are the same as reported by Hove-Madsen et al for the action of adenosine agonists. There is considerable uncertainty as to the nature of the Ca influx

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into a resting cell [6] but it is interesting to speculate that it may be sensitive to adenosine agonists.

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