Letter to the Editor

Can changes of ryanodine receptor expression affect cardiac contractility?


Cardiac Physiology Unit, Manchester University, 1.524 Stopford Building, Oxford Road, Manchester M13 9PT, UK

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Yamamoto et al. [1] have shown in their recent article that the expression of cardiac ryanodine receptors is decreased in dogs subjected to heart failure induced by rapid-pacing. This agrees with previous work showing that in some models of failure down regulation of the RyR is observed [2,3]. As well as a decrease in the number of RyRs, it has also been suggested that there may be a decrease in the functional coupling between Ca entry into the cell and the opening of the RyR [4,5]. The purpose of this letter is to question the idea that changes in the expression or properties of the RyR are involved in changes of contractility observed in cardiac hypertrophy or failure. The argument below is based on both experimental and theoretical considerations [6].

We have examined the effects of manoeuvres which alter the open probability of the RyR. For example caffeine is known to increase the open probability of the RyR [7]. Consistent with this, the application of low concentrations (<1 mM) of caffeine increases the magnitude of both the systolic Ca transient and the contraction. However this potentiation is completely transient. In the steady-state in the presence of caffeine, the magnitude of contraction is the same as in control [8,9]. Similar results are seen with the compound 2,3-butanedione monoxime (BDM) which also increases the open probability of the RyR [10] and produces a purely transient potentiation of systolic Ca [11]. Correspondingly the local anaesthetic tetracaine which decreases the open probability of the RyR [12] produces a transient depression of contraction [13]. It has recently been pointed out that our previous work was performed under unphysiological conditions such as low temperature [14]. However Fig. 1 shows that, even when studied at 37°C at reasonably fast (2 Hz) stimulation, low concentrations of caffeine still produce a purely transient increase of the systolic Ca transient.

The transient nature of these responses can be explained as follows. Initially the cell must be in a steady state with respect to Ca fluxes. This means that, on each beat, that amount of Ca which enters the cell via the calcium current must be pumped out of the cell (largely on Na-Ca exchange). The equality of these fluxes has been demonstrated experimentally [15]. We now consider the effects of adding agents such as BDM or caffeine which potentiate RyR opening. These will initially produce a larger systolic Ca transient. However this larger transient will produce a greater degree of activation of the Na-Ca exchange and consequently a greater Ca efflux than was the case under control conditions. Since Ca entry has not changed, the cell will therefore no longer be in Ca flux balance but will lose Ca. As a result, s.r. Ca content will decrease, as is experimentally observed [8] and this, in turn, will decrease systolic Ca. This will continue until the decrease of s.r. Ca content balances the potentiation of the RyR. In other words, in the steady state, a potentiated RyR in association with a decreased s.r. Ca content will produce exactly the same size Ca transient as in the control. In this condition

![Fig. 1. Effects of exposure to a low concentration of caffeine (0.5 mM) on systolic [Ca²⁺]. The trace shows a record of F3 fluorescence (a measure of [Ca²⁺]). The cell was voltage clamped (perforated patch technique). The membrane potential was held at −40 mV and 100 ms duration depolarizing pulses applied to 0 mV at 2 Hz.](image-url)
the Ca efflux will be the same size as in the control and therefore a steady-state can be regained. In the case of agents such as tetracaine which decrease RyR open probability the same Ca transient is produced by an increased s.r. Ca content. This requires that a decrease in the number of open RyR can be compensated for by an increase of s.r. Ca content.

Given that agents which interfere with the RyR produce no steady-state change of the Ca transient, it seems unlikely that changes of contractile function in heart failure or hypertrophy are due to the observed changes of RyR expression. Thus, while changes of RyR expression may occur, it is likely that any changes in contraction are due to other factors. For example many studies of either experimental [16,17] or clinical [18,19] heart failure find a decrease in the expression and/or activity of the s.r. Ca-ATPase which would lead to a decrease in systolic \([Ca^{2+}]_i\).

References


