Life, Sudden Death, and Intracellular Calcium

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Since the original studies of Ringer,1 calcium (Ca\textsuperscript{2+}) has become almost synonymous with contraction in the heart. Two papers in the current issue of Circulation Research focus on other roles of this cation.1 Wu and Bers2 show that Ca\textsuperscript{2+} in the nuclear envelope is in a store that is functionally interconnected with the sarcoplasmic reticulum (SR), a result that may have implications for the role of calcium in controlling gene transcription.2 The other area and the main focus of this editorial is the role of Ca\textsuperscript{2+} ions in arrhythmogenesis. Liu et al3 present important data concerning the occurrence of arrhythmias in a mouse expressing a mutant SR Ca\textsuperscript{2+} release channel (ryanodine receptor [RyR]). To discuss this result, we will first briefly summarize current concepts in the area.

It is now known that most of the calcium that activates contraction comes from an intracellular store (the SR) and is released through the RyR. Release occurs through the process of calcium-induced calcium release. This depends on the fact that the probability of the RyR being open is increased by an increase of cytoplasmic Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]i). The entry of a small amount of Ca\textsuperscript{2+} into the cell through the L-type Ca\textsuperscript{2+} current thereby triggers much more release from the SR. It has been appreciated for a long time that such a Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release mechanism is inherently prone to positive feedback as the Ca\textsuperscript{2+} released will tend to further activate the RyR. Both theoretical4 and experimental5 studies have shown that this positive feedback is avoided by the fact that a single L-type channel and associated RyRs act as a functional unit that under normal conditions does not influence other units. Under these conditions if Ca\textsuperscript{2+} is released in one region of the cell there is no tendency for the release to spread to other regions. The release of Ca\textsuperscript{2+} from a single unit is measured as a “Ca\textsuperscript{2+} spark.”5 However, if the cell is overloaded with Ca\textsuperscript{2+} then release in one part of the cell propagates throughout the cell as a wave, a result shown to be caused by Ca\textsuperscript{2+} sparks initiating waves.6 It has long been known that cellular Ca\textsuperscript{2+} overload produces Ca\textsuperscript{2+} waves that activate Ca\textsuperscript{2+} extrusion on the electrogenic Na-Ca\textsuperscript{2+} exchange8 and this leads to delayed afterdepolarizations (DADs).9,10

Ca\textsuperscript{2+} waves seem to occur when the Ca\textsuperscript{2+} content of the SR exceeds a certain threshold.11 In many studies (including those reviewed above) it is the SR Ca\textsuperscript{2+} content that is increased to above normal levels to generate waves (Figure B). However, waves can also be produced by maneuvers that increase the open probability of the RyR and thereby decrease the threshold concentration (Figure C). An experimental example of this is the application of low concentrations of caffeine.12,13 In addition, it has also been suggested that in heart failure phosphorylation of the RyR can lead to its dissociation from the accessory protein FKBP12.6, and mice with reduced FKBP12.6 show increased incidence of arrhythmias.14 Panel C, which is taken from experimental data in which RyR opening is potentiated with caffeine,12 shows a decrease of SR content. This occurs because the greater Ca\textsuperscript{2+} release from the SR results in more efflux from the cell. If a similar decrease of SR Ca\textsuperscript{2+} content occurs with the mutant RyR mouse, then there will be implications for cardiac contractility. In addition, it is important to know what happens to the open probability of the RyR when it is activated by higher cytoplasmic Ca\textsuperscript{2+} as occurs in systole.

Recent genetic studies have shown that some familial cases of catecholaminergic polymorphic ventricular tachycardia are related to mutations in the RyR.15,16 When such RyRs are expressed in heterologous systems, then the mutations show increased spontaneous Ca\textsuperscript{2+} release caused by a sensitization to intra-SR Ca\textsuperscript{2+}.17 The important advance produced by Liu et al is that they have studied this mutation by expressing it in mouse hearts. One important result is that the transgenic mice show DADs even under control conditions, following a train of stimuli, whereas the normal mice do not. However, no extra systoles are seen even in the transgenic animals. This is presumably because the DADs occur after too long a delay to be seen before the next stimulated beat and are therefore only seen at the end of a train of stimulation. The cellular model therefore mimics the intact human in showing that RyR mutation only produces arrhythmias in the presence of catecholamines. An unanswered question concerns why catecholamines are required to produce extra systoles. In particular, does this result from phosphorylation of the RyR or, alternatively, from an effect on phospholamban to increase SR Ca\textsuperscript{2+} ATPase activity and, thence, SR content or on the L-type Ca\textsuperscript{2+} current to increase cell and therefore SR loading with Ca\textsuperscript{2+}? It would be particularly interesting to know whether other maneuvers that increase cellular Ca\textsuperscript{2+} loading also potentiate the arrhythmogenic effects of this mutation.

As well as the particular mutation studied in the present work, there are many other mutations of the RyR that have been associated with cardiac arrhythmias and a variety of different arrhythmias.18 It will be interesting to discover what features determine the type of arrhythmia that is produced. Other studies have suggested that dissociation of FKBP12.6 from the RyR can be implicated in arrhythmogenic activity. This dissociation can be prevented by the
compound K201 (also known as JTV 519), and this compound has been reported to be antiarrhythmic. However, Liu et al find that this compound has no effect on the cellular arrhythmic effects of the RyR mutation and, furthermore, that FKBP12.6 binding to the RyR is unaffected by the mutation. The overall picture is perhaps that anything that increases FKBP12.6 binding to the RyR is unaffected by the mutation.

Finally, perhaps as a consequence of both its size and its intracellular location, the RyR has come belatedly to the threshold and spontaneous Ca release; Sensitized RyR, the threshold is now decreased. The traces for Ca overload and sensitized RyR are taken from Reference 12.

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None.

**References**

1. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. *J Physiol (Lond)*. 1883;4:29–42.

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