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Fabiato A & Fabiato F. Calcium release from the sarcoplasmic reticulum. *Circ. Res.* **40**:119-29, 1977.
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The hypotheses for the mechanism of Ca^{2+} release from the sarcoplasmic reticulum of cardiac and skeletal muscle are discussed. It suggested that Ca^{2+} release from the mammalian cardiac sarcoplasmic reticulum could be triggered by the increase of free Ca^{2+} concentration, which results from transsarcolemmal Ca^{2+} influx during the action potential. [The *SCI*® indicates that this paper has been cited in over 220 publications since 1977.]

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Four years before the publication of this article, we had developed the preparation termed "skinned single cardiac cell," which is obtained by microdissecting the sarcolemma from a fragment of a single cardiac cell. This was 19 years after Natori[1] had described a similar preparation from the much larger skeletal muscle fiber. The small size of the cardiac preparation made it more difficult to prepare but facilitated changing the ionic composition of the solution at the outer surface of the sarcoplasmic reticulum, because the time required for diffusion in a cylinder is proportional to the square of its radius. This permitted us to make more progress in understanding the mechanism of Ca^{2+} release from the sarcoplasmic reticulum of cardiac muscle than had been made by others using skeletal muscle.

This article supports the hypothesis of Ca^{2+}-induced release of Ca^{2+} from the sarcoplasmic reticulum, which had been originally proposed for skeletal muscle.[2,3] According to the modification of this hypothesis applied to the mammalian cardiac muscle, the small amount of Ca^{2+} that crosses the sarcolemma is insufficient to activate the myofilaments directly but triggers a release of Ca^{2+} from the sarcoplasmic reticulum, which in turn activates the myofilaments.

Although published as a "brief review," the article contains original data. It reports only one step in our progress, which has consisted of testing the same hypothesis with continuously improved techniques during the past 15 years. These methodological improvements have now permitted more insight into the mechanism whereby Ca^{2+} itself controls the gating of the Ca^{2+} channel across the membrane of the sarcoplasmic reticulum.[4-6]

The suggestion that there is no steadfast argument to eliminate a physiological role for the Ca^{2+}-induced release of Ca^{2+} observed in skinned mammalian cardiac cells should not be construed as a conclusion that this is necessarily the mechanism of the physiological excitation-contraction coupling, which remains a major stumbling block of muscle physiology. Thus, there are many more years of full-time experimental work in perspective for us, or rather for one of us, since Françoise Fabiato interrupted her physiological work soon after the publication of this article, when the number of our children equaled the number of our publications.

This commentary gives us an opportunity to express our gratitude to the American scientific community for many marks of support and encouragement while we were consistently failing to obtain positions in our own country.

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2. **Bianchi C P & Shanes A M.** Calcium influx in skeletal muscle at rest, during activity, and during potassium contracture. *J. Gen. Physiol.* 42:803-15, 1959. (Cited 385 times.)
3. **Frank G B.** Effects of changes in extracellular calcium concentration on the potassium-induced contracture of frog's skeletal muscle. *J. Physiology—London* 151:518-38, 1960. (Cited 180 times.)
4. **Fabiato A.** Rapid ionic modifications during the aequorin-detected calcium transient in a skinned canine cardiac Purkinje cell. *J. Gen. Physiol.* 85:189-246, 1985.
5. ----------. Time and calcium dependence of activation and inactivation of calcium-induced release of calcium from the sarcoplasmic reticulum of a skinned canine cardiac Purkinje cell. *J. Gen. Physiol.* 85:247-89, 1985.
6. ----------. Stimulated calcium current can both cause calcium loading in and trigger calcium release from the sarcoplasmic reticulum of a skinned canine cardiac Purkinje cell. *J. Gen. Physiol.* 85:291-320, 1985.

