ESSAYS ON APS CLASSIC PAPERS

Ca-induced Ca release: lessons regarding cell models

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This essay looks at the historical significance of an APS classic paper that is freely available online:

Fabiato A. Calcium-induced release of calcium from the cardiac sarcoplasmic reticulum. Am J Physiol Cell Physiol 245: C1–C14, 1983 (http://ajpcell.physiology.org/cgi/reprint/245/1/C1).

Ca entering the cell through L-type channels in the sarclemma is known to activate ryanodine receptors regulating Ca release and reload channels in the SR. The process of filling the SR requires ATP. By shutting down release of Ca from the SR, the cell is able to more efficiently fill this compartment using minimum energy. The entire process of surging intracellular Ca concentration is far more efficient than a simple influx of Ca from the extracellular space through L-type Ca channels. This is one of the pivotal mechanisms of cardiac function and regulation of EC coupling. Our understanding of the mechanisms of Ca-induced Ca release has allowed us to understand much of the pharmacology that changes the level and sensitivity of EC coupling in the cardiac myocyte. Many drugs work through actions on SR Ca release rather than ion influx via Ca channels. In fact, the SR is also a critical player in the rapid

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Fig. 1. Alexandre Fabiato. Courtesy of Dr. Alexandre Fabiato.
uptake of Ca to initiate sarcolemmal relaxation via the SR Ca-ATPase.

Many anesthetic agents act by reducing Ca flux through L-type channels and reducing the amount of Ca stored in the SR. Similarly, positive inotropic agents regulate the force of contraction partially through regulation of Ca from the SR or in combination of intracellular Ca levels via channels. Pathophysiological alterations in the SR uptake and release may represent focus points in the basis of cardiovascular disease. Our understanding of the mechanisms of Ca-induced Ca release has served as a cornerstone with respect to defining the mechanism of EC coupling and the effects of intracellular Ca. This is truly one of the pivotal physiological findings within the physiological literature regarding cardiac function.

REFERENCES
1. Fabiato A. Calcium-induced release of calcium from the cardiac sarcoplasmic reticulum. Am J Physiol Cell Physiol 245: C1–C14, 1983.