Perspectives on Ryanodine Receptor Adaptation

The purpose of the Perspectives in General Physiology is to provide a forum where scientific uncertainties or controversies can be discussed in an authoritative, yet open manner.

The Perspectives are solicited by the editors—often based on recommendations by the advisory editors or members of the editorial board, who may be asked to coordinate the process. To frame the issue, two or more experts will be invited to present a brief point of view on the problem, which will be published consecutively in *The Journal*. The comments and opinions expressed in the Perspectives are those of the authors and not necessarily those of the Editors or the Editorial Board. The Perspectives will be accompanied by a few editorial paragraphs that introduce the problem—and invite the submission of comments, in the form of letters-to-the-editor, which will be published in a single, predetermined issue (usually four months after publication of the Perspective). After the letters-to-the-editor have been published, further responses will be limited to full manuscripts.

In this issue of *The Journal*, R. Sitsapesan and A. J. Williams (The National Heart and Lung Institute, UK), M. Fill, A. Zahradníková, C.A. Villalba-Galea, I. Zahradník, A.L. Escobar, and S. Györke (Loyola University, Institute of Molecular Physiology and Genetics, Slovak Republic, and Texas Tech University), and G.D. Lamb, D.R. Laver, and D.G. Stephenson (La Trobe University, Australia) provide different insights into the controversies relating to ryanodine receptor (RyR) adaptation.

The central problem is to understand how individual RyRs are regulated and, specifically, how Ca^{2+}-induced Ca^{2+} release (CICR) is controlled. There is agreement that the control of RyR function, at least as it pertains to CICR, is a local property; but, there is considerable disagreement about the underlying self-regulatory mechanism(s) that would cause RyR activity to terminate. A central issue of dispute is whether RyRs can adapt to the local $[Ca^{2+}]$, where adaptation means that a step $[Ca^{2+}]$ increase, to <1 μM, causes a biphasic activation pattern in single RyRs, with rapid activation, followed by a slow decrease in channel open probability (P_O)—and, importantly, that the receptor can be reactivated by a further increase in $[Ca^{2+}]$. The latter characteristic is a defining feature of adaptation (Györke, S., and M. Fill. 1993. *Science*. 260:807–809). Therefore, adaptation differs from the desensitization observed in many ligand-activated channels because the adapted RyR is not locked into a Ca^{2+}-refractory state, but can be reactivated by further increases in $[Ca^{2+}]$.

There is agreement that the regulation of RyRs is complex, and that it remains an unresolved issue. Part of the uncertainties arise from the complex kinetic behavior of RyRs, which display multiple gating modes and a complex inactivation pattern that occurs at a relatively high $[Ca^{2+}]$ (>1 μM) and reflects a complex interplay between Ca^{2+} (or P_O) and voltage. When RyRs inactivate, they close to an apparently absorbing state after activation by Ca^{2+}. But, gating cannot be restored just by removing Ca^{2+}, it is necessary to change the membrane potential as well. Adaptation clearly is not inactivation; but, the operational distinction among different channel states remains unresolved. In addition, there is disagreement about how the central experiments should be interpreted. Some authors question the existence of adaptation, and note that flash photolysis–induced release of Ca^{2+} produces an initial spike in $[Ca^{2+}]$ that precedes the step and, therefore, complicates the analysis of the results. Indeed, there are distinct differences in the results obtained when $[Ca^{2+}]$ is increased by rapid perfusion, where there is little evidence for an adaptation-like biphasic activation (Schiefer, A., G. Meissner, G. Isenberg. 1995. *J. Physiol.* 489:337–348), as opposed to what is seen with flash photolysis-induced $[Ca^{2+}]$ increases. But, as is apparent from the present contributions, a major issue pertaining to the regulation of Ca^{2+}-induced Ca^{2+} release remains in contention.

Letters-to-the-editor related to these Perspectives will be published in the April 2001 issue of *The Journal of General Physiology*. Letters-to-the-editor should be received no later than February 1, 2001, to allow for the editorial review. The letters may be no longer than two printed pages (approximately six double-spaced pages) and will be subject to editorial review. They may contain no more than one figure, no more than 15 references, and no significant references to unpublished work. Letters can be submitted electronically, by sending a formatted text file as an attachment to an e-mail to the editorial office "jgp@rockvax.rockefeller.edu". Figures must be submitted in hard copy (they can be faxed so that they are received in the editorial office by the February 1 deadline).

Olaf Sparre Andersen
Editor
The Journal of General Physiology