Nitric Oxide and the Ryanodine Receptor Ca-Release Channel

To the Editor:

I have read with interest the recent review on the role of S-nitrosylation in cardiovascular signaling, in which Lima et al. provide a very useful digest on the current status of research in this important but burgeoning field of cardiovascular physiology. On the other hand, I believe that one of the many functions of a scientific review, especially when summarizing the status of a field with a certain degree of ambiguity, is to promote further progress. This is, perhaps, best achieved if all the available data relevant to the field are summarized and discussed, even those that seem to be contradictory to the intended conclusion of the review. Although the review in question cites almost 200 works, it still falls short in summarizing all applicable data.

The Ryanodine Receptor Ca-release channel (RyR) is a key component of a signaling mechanism, which itself directly controls cardiac function and, at the same time, serves as an effector site of changes in the intracellular milieu. Thus, it is of vital interest to understand how the RyR is affected by NO. Interestingly, S-nitrosylation activates RyR2 (one of the cardiac isoforms of RyR1), whereas several lines of evidence would allow us to draw a different conclusion. Although the biochemistry of S-nitrosylation is still somewhat obscure, it is generally accepted that nitric oxide (NO), either directly or via some intermediate, S-nitrosogluthathione, NO+, or ONOO−, for instance, brings on various cellular signals, including cardiac regulation. Thus, it is of vital interest to understand how NO (directly or indirectly) affect RyRs.

Our group has been the first to address the question whether NO alters the kinetic properties of either the skeletal or the cardiac isoforms of the RyR, and we have—contrary to the conclusion of Lima et al.—found that NO, instead of activating RyR, reduces the activity of both isoforms. Importantly, as we have also observed that NOS activity copurifies with RyR in sarcoplasmic reticulum (SR) preparations, it was possible to test the effects of NO that were generated from L-arginine via the sarcoplasmic reticulum (SR) preparations, it was possible to test the effects of NO that were generated from L-arginine via the SR. These results and should shed light on the picture in regard to both the RyR and the mechanism of NO action on RyR(s).

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_Circ Res._ 2010;107:e1
doi: 10.1161/CIRCRESAHA.110.221887

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/107/1/e1

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