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 cardiac regulation. Thus, it is of vital interest to understand how cardiac RyR isoforms of the RyR, and we have—contrary to the conclusion of Lima et al—found that NO, instead of activating RyR activity. In their review, Lima et al simply conclude that “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-nitrosoglutathione, NO+, ONOO-, for instance), brings on nitrosylation of protein thiols. Thus, it is appropriate to see all available data on 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 NOS reaction in situ, and again found that NO decreased RyR activity under the influence of functioning NOS. In addition, using confocal microscopy, we have found that NO (in a cGMP-independent mechanism) suppressed spontaneous Ca-release events in isolated cardiac myocytes, which was clearly due to an NO-induced decrease in RyR activity. In a different approach, Gonzalez et al found that in NOS1-deficient myocytes RyR2 is indeed hypo-nitrosylated, but at the same time they obtained no evidence for decreased RyR2 activity. As an alternative, they found a Ca leakage from SR as a consequence of hypo-nitrosylation, which was, at the same time, likely due to a leak through RyR2.

These examples clearly demonstrate that the physiological consequences of S-nitrosylation of RyR(s) are far from being a closed problem. Instead, many new questions should be addressed in order to clarify the physiological role of S-nitrosylation processes in the heart (and vasculature). By going through the relevant literature, it seems evident that both the reactivity of protein thiols and the fate of NO in the cell should be extremely sensitive to changes in the intracellular milieu (pO2, pH, the concentration of small redox molecules, including but not restricted to reactive oxygen species, GSNO, etc…). Thus, it seems likely that systematic investigations of S-nitrosylation of RyR(s) that mimic physiologically appropriate changes in the intracellular milieu will lead to very exciting new results and should shed light on the picture in regard to both the role and the mechanism of NO action on RyR(s).

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