Reply to Meszaros: S-Nitrosylation of the RyR in Health and Disease

To the Editor:

Protein S-nitrosylation has been implicated in most major functions of nitric oxide (NO) in the cardiovascular system, and accumulating evidence indicates potential causal roles for aberrant S-nitrosylation in disease.1,2 In our recent review,2 we attempted to summarize current understanding of the roles of protein S-nitrosylation in multiple aspects of vascular and cardiac function, including the role of S-nitrosylation in regulating the function of the cardiac form of the Ca2+-release channel known as the ryanodine receptor (RyR2).

In his letter commenting on our review,3 Meszaros points out that we omitted reference to early work from his laboratory4,5 that described an inhibitory effect of exogenous or endogenously generated NO on RyR1 of skeletal muscle and RyR2 of cardiac muscle. Although our review focused on the best-established current view of the role of S-nitrosylation in RyR function, our discussion of that role would have been more complete with inclusion of the work of Meszaros et al.4,5

Initial interest in the role of NO in regulating the RyR through cGMP-independent, protein thiol-based mechanisms originated in the suggestion that NO derived from NO synthase (nNOS) in skeletal muscle sarcolemma would S-nitrosylate proteins of the sarcoplasmic reticulum and thereby “… promote Ca2+- release and force production.”6 The first direct measurement of RyR S-nitrosylation (assessed both in vitro and in vivo), carried out in conjunction with rigorous quantification of thiol content and oxidation state, suggested an excitatory effect on RyR2.7 Subsequent analyses, and in particular those in which S-nitrosylation has been assessed directly, have reported consistently that both RyR1 and RyR2 are activated rather than inhibited by S-nitrosylation (see, for example, References 8 to 12 and reviews in References 1 and 2).1,2,8–12 Although we cannot resolve the discrepancy between the observations of Meszaros et al.4,5 and other studies, it is worth noting that S-nitrosylation was not demonstrated directly by Meszaros et al. In addition, the disparity may perhaps reflect a difference in NOS isoform involved (eNOS in studies by Meszaros versus nNOS in other studies; see References 13 and 14 for differential influence of eNOS and nNOS on RyR2).13,14

Recent work emphasizes that dysregulated S-nitrosylation of RyR1 and RyR2 is implicated in a number of pathophysiological conditions in which the consequences of altered S-nitrosylation do not follow simply from direct regulation of RyR activity. Indeed, Gonzalez et al.15 (referred to by Meszaros3) reported that genetic elimination of nNOS, which colocalizes with RyR2 in cardiac sarcoplasmic reticulum,13 results in hypo-S-nitrosylation of RyR2 and diastolic Ca2+- leakage. However, leakage was caused by thiol oxidation7 consequent on suppressed S-nitrosylation rather than by removal of an inhibitory influence of S-nitrosylation on Ca2+- flux through RyR2. Conversely, Bellinger et al.16 reported that strenuous exercise in mice and humans is associated with gradual hyper-S-nitrosylation of RyR1 that is accompanied by depletion of FKBP12, resulting in leaky channels that impair exercise tolerance. Finally, Durham et al.17 found that enhanced S-nitrosylation of RyR1 in mice with a malignant hyperthermia point mutation in RyR1 is associated with Ca2+- leak and contributes to the observed malignant hyperthermia and central core disease phenotype. Thus, we certainly agree with Meszaros that “… the physiological consequences of S-nitrosylation of RyR(s) are far from being a closed problem.”

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