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EDITORIAL COMMENT

From Contractile Enhancement to Pathological Hypertrophy

Angiotensin II–Induced Nox2-Mediated Reactive Oxygen Species*

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Reactive oxygen species (ROS) are produced primarily in mitochondria as by-products of oxidative phosphorylation. However, enzymes also actively produce ROS (1). The NADPH oxidase (nicotinamide adenine dinucleotide phosphate oxidase, or Nox) family proteins are unique in that they are dedicated to producing superoxide and H_2O_2. Nox2, also known as $gp91^{phox}$, and Nox4 are the major Nox isoforms in the heart. Both Nox2 and Nox4 form a heterodimer with $p22^{phox}$ at either plasma or intracellular membranes, whereas Nox2 also associates with cytosolic activators, $p47^{phox}$, $p67^{phox}$, and Rac1/2, for its full activation. In the healthy heart, ROS are promptly eliminated by powerful intracellular antioxidant mechanisms, including superoxide dismutase (SOD), catalase, and peroxiredoxin (2). However, excessive accumulation of ROS, caused by either up-regulation of ROS-producing enzymes or down-regulation of antioxidants under myocardial stress, induces myocardial injury and promotes heart failure. Nox proteins are often up-regulated in response to stress, and they function cooperatively with other ROS-producing mechanisms, thereby promoting mitochondrial "ROS-induced ROS release" to exacerbate overall oxidative stress in many pathological conditions in the heart (3).

Importantly, however, increasing lines of evidence suggest that the Nox family proteins also play physiological or adaptive roles in some conditions. For example, stretch-induced production of ROS (X-ROS) by Nox2 at the junctional sarcoplasmic reticulum (SR) mediates mechano-chemo transduction by sensitizing the ryanodine receptor (RyR2) in healthy cardiomyocytes (4) (**Figure 1A**). The physiological level of ROS produced by either Nox2 or Nox4 is required for HIF-1α activation, which is essential for cardiomyocytes to survive during ischemia/reperfusion (5). Generally, these cellular functions are mediated by a limited amount of ROS, which are produced locally and modulate their targets post-translationally, thereby acting as signaling molecules.

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ANGIOTENSIN II–INDUCED NOX2-ROS

In this issue of the *Journal*, Zhang et al. (6) reported an unexpected function of Nox2-mediated ROS in the heart. Using transgenic mice with cardiomyocyte-specific overexpression of Nox2 (Tg-CM-Nox2), the authors studied the short-term effects of a subpressor dose of angiotensin II (Ang II) on contractile function in the heart and the cardiomyocytes therein. Whereas Tg-CM-Nox2 showed no obvious cardiac phenotype at baseline, the transgenic mouse heart exhibited significantly increased contractility with more rapid calcium (Ca^{2+}) reuptake and enhanced Ca^{2+} release in

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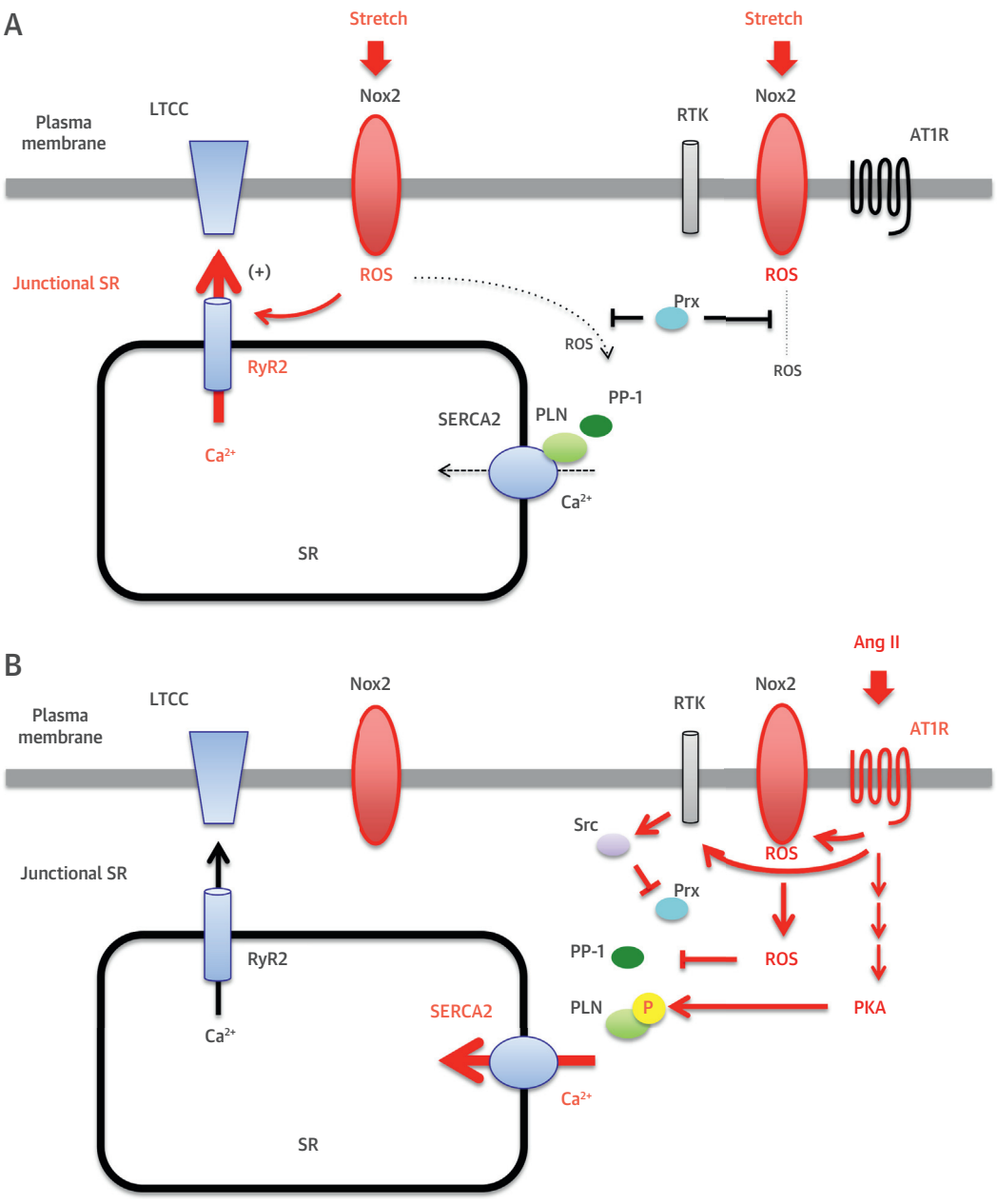
FIGURE 1 Speculated Mechanisms Underlying Nox2-ROS–Mediated Contractile Enhancement



(A) Stretch-induced production of reactive oxygen species (ROS) from nicotinamide adenine dinucleotide phosphate oxidase (Nox2) at the junctional sarcoplasmic reticulum (SR) enhances calcium (Ca^{2+}) sensitivity by sensitizing the ryanodine receptor (RyR2) in healthy cardiomyocytes. Stretch-induced Nox2-ROS may not reach phosphatase-1/phospholamban (PP1/PLN) because of the action of antioxidants, such as peroxiredoxin (Prx). **(B)** Angiotensin II (Ang II) type 1 receptor (AT1R) may activate Nox2 located far apart from the junctional SR. Alternatively, stretch and Ang II may activate distinct populations of receptor tyrosine kinases (RTKs), which in turn lead to inactivation of Prx located in distinct subcellular spaces. Thus, Ang II–induced Nox2-ROS, but not stretch, can suppress PP-1 activity, thereby enhancing phosphorylation of PLN and SERCA2 activation. LTCC = L-type calcium channel; P = phosphorylation at Ser-16; PKA = protein kinase A; SERCA2 = sarcoplasmic reticulum Ca^{2+}-ATPase 2.