All Oxidase Roads Lead to Angiotensin, Too

Lilach O. Lerman, Amir Lerman

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ree radicals and other oxygen- or nitrogen-derived reactive species formed during cellular metabolism and respiration, like superoxide (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), and nitric oxide (NO), are important second messengers and fundamental mediators in biological processes, redox signaling, and cellular growth. However, over the past 2 decades it has become clear that reactive oxygen species (ROS) in particular are also important participants in a number of pathological processes, including cardiovascular and kidney diseases. In fact, increased production of ROS has been proposed as a common pathomechanism by which cardiovascular risk factors affect the vessel wall to induce and amplify vessel and organ injury.

Several possible enzymatic sources of ROS have been identified in blood vessels and other tissues, such as nicotinamide adenine dinucleotide (phosphate) oxidase (NAD(P)H oxidase), xanthine oxidase (XO), and uncoupled nitric oxide synthase. NAD(P)H oxidase has long been considered one of the most important sources of ROS in the vessel wall. One of its most potent stimulants is angiotensin II. In turn, NAD(P)H oxidase mediates several downstream effects of angiotensin II like inflammation, endothelial dysfunction, collagen deposition, and vascular hypertrophy.

Nevertheless, an important role in the pathogenesis of cardiovascular disease has also been ascribed to XO. This ROS-producing enzyme is generated by the posttranslational modification of xanthine dehydrogenase, catalyzes the oxidation of purines to uric acid, and in the process reduces molecular oxygen and generates the free radical superoxide (Figure). In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Landmesser et al contribute to our understanding of the mechanisms regulating XO by showing that angiotensin II upregulates its expression and stimulates production of superoxide from XO in cultured bovine and human aortic endothelial cells.

Previous studies have reported that angiotensin receptor antagonist decreased plasma XO activity in hypercholesterolemia. However, activation of XO by angiotensin II appears to be cell type-specific, because it was not observed in human vascular endothelial cells in vitro, and may be related to differential tissue distribution of these enzymes. In cardiac fibroblasts, the membrane-associated NAD(P)H oxidase is the predominant source of ROS generation by angiotensin II, and in patients with coronary artery disease it contributes around 60% while XO contributes around 25% of superoxide anion production.

Another important finding in the study by Landmesser et al is that NAD(P)H oxidase activates XO, an interaction previously suggested to involve hydrogen peroxide. The ability of angiotensin II to activate both enzymes, and of NAD(P)H oxidase to subsequently further activate XO, underscores the important role of angiotensin II in cardiovascular pathophysiology. The importance of this interaction is that it could represent a feed forward mechanism of self-propagation of oxidative stress, by which vascular damage would be amplified during exposure to risk factors. Alas, this process may be partly self-limiting by negative feedback regulation of ROS, which decrease AT1 receptor mRNA expression through intracellular release of calcium and inactivation of p38 MAP kinase.

The relevance of these pathways to human disease is underscored by the elevated expression of both NAD(P)H oxidase and XO observed in humans with coronary artery disease. It is not unlikely that NAD(P)H oxidase and XO mediate different effects of angiotensin II like inflammation, endothelial dysfunction, collagen deposition, and vascular hypertrophy.

Importantly, Landmesser et al translated their in vitro observations to a clinical study. They demonstrated that in patients with coronary artery disease acute inhibition of the endogenous XO activity significantly improved peripheral endothelial function, an effect that was markedly attenuated after 4 weeks of chronic AT1 receptor blockade. Although allopurinol and losartan similarly reduced XO activity, losartan led to greater improvement of endothelial function. These results may have several implications. Firstly, they further support the interaction between angiotensin II and the XO pathway established in vitro. Secondly, endothelial dysfunction is an independent marker for cardiovascular events, and several therapeutic interventions, such as statins and angiotensin-converting enzyme inhibitors, improve endothelial function beyond their intended primary effect. These obser-

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Atherosclerosis Chronic kidney disease.

Xanthine oxidase as a downstream mediator of angiotensin II. Systemic or local activation of the renin–angiotensin system induces upregulation of NAD(P)H oxidase in the vessel wall. Consequently as well as directly, angiotensin II can also upregulate expression of xanthine oxidase, and thereby modulate the levels of uric acid and amplify generation of reactive oxygen species. The ensuing superoxide anion reacts with nitric oxide, decreases its bioavailability, and forms noxious peroxynitrite (ONOO−), a sequence that fosters vasoconstriction, endothelial dysfunction, and cardiovascular events.

Disclosures

None.

References


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