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Oxidative Stress

The Curse That Underlies Cerebral Vascular Dysfunction?

Frank M. Faraci, PhD

Complex structural and functional changes occur within the blood vessel wall with disease. In peripheral blood vessels, increasing evidence suggests that oxidative stress plays a major role in producing many of these changes.^{1,2} Oxidative stress occurs as the result of an imbalance between generation of reactive oxygen species (ROS) and antioxidant defense mechanisms. Such stress may occur as a result of increased enzymatic or nonenzymatic generation of superoxide anion (the precursor for multiple ROS and reactive nitrogen species [RNS]) or decreased expression or activity of antioxidant enzymes that tightly regulate subcellular levels of ROS (Figure).³ Although our overall understanding of the importance of oxidative stress in the cerebral circulation lags substantially behind work on blood vessels outside of the brain, there has been an emerging focus into this area. This editorial highlights some recent key findings in relation to cerebral vascular oxidative stress.

Does oxidative stress occur within the cerebral circulation? In models of angiotensin II-dependent hypertension,^{4,5} hyperhomocysteinemia,⁶ insulin resistance,⁷ diabetes and/or metabolic syndrome,^{8,9} inflammation,¹⁰ ischemia with reperfusion,¹¹ and subarachnoid hemorrhage,¹² there is evidence for increased levels of superoxide within the wall of cerebral blood vessels. Thus, oxidative stress in the vasculature appears to be a common feature in diverse models of cerebral vascular disease and injury. These findings are important because they were obtained using models of major risk factors for cardiovascular disease and stroke. Many of these same risk factors have also been linked with vascular cognitive impairment and Alzheimer disease.¹³

There are many reasons why vascular oxidative stress is potentially important. Nitric oxide (NO), a potent vasodilator, is a major mediator of endothelium-dependent relaxation and thus regulator of tone in large arteries and microvessels of the brain.¹⁴ NO reacts extremely efficiently with superoxide, resulting in loss of NO bioavailability (Figure). Superoxide-mediated impairment of NO signaling and endothelial regulation of vascular tone continues to be a major focus of basic research. The study of endothelium-dependent responses is a very useful experimental endpoint but is also important as an independent predictor of clinical events.¹⁵

In all the models of vascular disease listed, superoxide-mediated endothelial dysfunction recently has been described.⁴⁻¹⁰ In addition to impairing NO-mediated responses that are under control by the endothelium, superoxide (or other ROS) impair neurovascular coupling⁴ and vasodilation mediated by activation of potassium channels, an additional mechanism of vasodilation.¹⁶

Vasoconstrictor mechanisms may also be affected by oxidative stress. For example, activity of rho kinase is thought to be a key mediator of vasoconstrictor responses through effects on calcium sensitization.¹⁷⁻¹⁹ Activity of rho kinase may be increased in cerebral blood vessels during disease.^{8,20} The precise cause for this increase is not certain but may be a consequence of loss of inhibitory effects of NO on rho kinase or direct effects of ROS to promote activity of rho kinase.⁸ Increased activation of rho kinase is potentially important as it may predispose vessels to vasoconstriction or vasospasm.

The consequences of oxidative stress and loss of NO-mediated signaling extend beyond the regulation of vascular tone. For example, chronic loss of endothelium-derived NO produces increases in cross-sectional area of the vessel wall (hypertrophy) of cerebral arterioles (Figure).²¹ Such structural changes may have functional consequences because vascular hypertrophy may impair maximal vasodilator capacity. ROS may produce hypertrophy by inactivating NO or through direct activation of signaling cascades involved in growth of vascular muscle. Preliminary studies indicate that deficiency in the CuZn isoform of superoxide dismutase (CuZn-SOD), a key antioxidant within blood vessels,³ increases vascular superoxide, impairs NO-mediated signaling, and produces marked hypertrophy of brain microvessels.^{22,23} Alterations in the extracellular matrix and vascular structure may also occur as a consequence of ROS-induced activation of matrix metalloproteinases.^{11,24} Increases in activity of matrix metalloproteinases can potentially produce increases in vascular permeability,²⁴ vascular remodeling, and perhaps aneurysm formation (Figure).

Increased vascular growth, altered vascular structure, or other changes in the vessel wall may be mediated by activation of redox-sensitive kinases and transcription factors, including nuclear factor- κ B, activator protein-1, and hypox-

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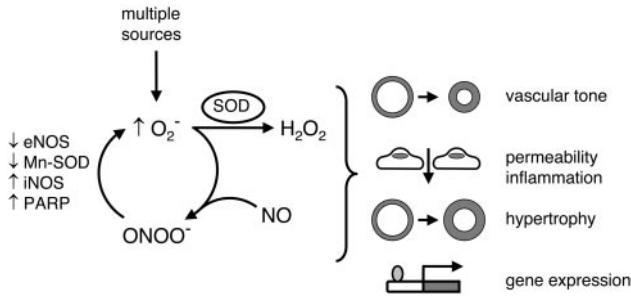
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Schematic illustration of some of the major effects of oxidative and nitrosative stress on the vasculature. Superoxide (O_2^-) is produced from molecular oxygen by a variety of sources. O_2^- can directly produce injury or can be converted by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2). H_2O_2 is an important signaling molecule but can also produce injury by forming hydroxyl radical (not shown). Superoxide can react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$). This extremely efficient reaction results in a decrease in NO bioavailability and impaired NO-mediated signaling. In addition, $ONOO^-$ may produce additional increases in superoxide as a result of effects on endothelial NO synthase (eNOS uncoupling), Mn-SOD, inducible NO synthase (iNOS), and poly (ADP-ribose) polymerase (PARP). The resulting changes include endothelial dysfunction, increases in vascular tone, increases in permeability and inflammation, as well as reductions in maximum vasodilator capacity, vascular remodeling, and alterations in gene expression.

ia-inducible factor-1 α (Figure).^{25,26} Although relatively little is known regarding effects of ROS on gene expression in vascular cells, examples of such effects are beginning to emerge. Overexpression of CuZn-SOD attenuates expression of inducible NO synthase (iNOS) in endothelium and adventitia of cerebral arteries after subarachnoid hemorrhage.²⁷ Superoxide-dependent expression of iNOS is potentially important because iNOS has emerged as a key mediator of endothelial dysfunction.^{28,29} The underlying vascular gene clusters that are activated or suppressed by oxidative stress remain to be identified. In this regard, future application of redox proteomics³⁰ to blood vessels of the brain may also be insightful.

A major question in understanding and potentially combating oxidative stress therapeutically relates to defining sources of ROS. In peripheral blood vessels, there has been much interest recently regarding the role of NAD(P)H oxidases as sources of superoxide.^{1,2} To date, there is very little known regarding the importance of this enzyme complex versus other sources of superoxide (mitochondria, other oxidases, etc) within the cerebral circulation. Recent work has provided evidence that NAD(P)H oxidase is expressed and is an important source of ROS in cerebral blood vessels during hypertension and diabetes, in response to angiotensin II, and after SAH.^{4,12,31–33}

The interaction of NO with superoxide results in formation of the RNS, peroxynitrite. Vascular dysfunction may also result as a consequence of nitrosative stress. It is becoming increasingly apparent that peroxynitrite is not simply a marker of nitrosative stress but is a mediator of cellular injury (Figure). Detrimental effects of peroxynitrite include activation of poly (ADP-ribose) polymerase (another mediator of vascular dysfunction) and matrix metalloproteinases, as well as expression of iNOS.^{3,11} Formation of peroxynitrite can

further amplify oxidative stress via nitration and inactivation of the mitochondrial isoform of SOD (Mn-SOD), and possibly by promoting the uncoupling of NO synthase, a circumstance in which the enzyme produces superoxide rather than NO (Figure).^{2,3}

In summary, changes in structure and function of cerebral blood vessels occur in a variety of disease states, and recent studies suggest that oxidative stress plays a major role in mediating at least some of these changes (Figure). The importance of specific ROS and RNS, as well as the contribution of the multiple sources of ROS within the cerebral vasculature, are poorly defined. Finally, it is important to remain cognizant that relatively low concentrations of ROS function as signaling molecules^{30,34} and may be involved with normal regulation of cerebral vascular tone and structure. We are only beginning to understand the total impact of ROS and RNS within the cellular elements of the cerebral vascular wall.

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