NO solution for a radical problem: a TAL story

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Even before the endothelium-derived relaxing factor (EDRF) was known to be nitric oxide (NO), it was recognized that it could be inactivated by the radical superoxide (O$_2^-$) (16). Once the EDRF was identified as NO, the chemistry underlying this phenomenon was obvious. Both NO and O$_2^-$ are radicals, and rapidly react with one another to form the strong oxidant peroxynitrite, which ultimately degrades to nitrite and nitrate (depending on other factors available in the reaction) (9). This simple chemical reaction between NO and O$_2^-$ has turned out to have enormous implications in biology and human pathophysiology. Oxidative inactivation of NO and formation of peroxynitrite play a role in endothelial dysfunction, ischemiareperfusion injury, neurodegenerative diseases, phagocytic killing of foreign organisms, cellular damage in sepsis, and many other states (2). In vessels, common conditions, such as hypercholesterolemia, diabetes, hypertension, cigarette smoking, and hypertension, promote a modest increase in O$_2^-$ production and oxidative inactivation of NO (4). This is thought to promote vasoconstriction, increase systemic vascular resistance, and raise blood pressure.

Beyond this effect of superoxide in the vessel, it is now apparent that it can contribute to hypertension in other organs. One important site is the central nervous system, where O$_2^-$ production in the circumventricular organs promotes sympathetic outflow and hypertension. Indeed, intracerebroventricular injection of an adenovirus expressing superoxide dismutase reduces hypertension in experimental animals (23), while deletion of a form of superoxide dismutase in these tissues induces hypertension (12).

Another site where the interaction between NO and O$_2^-$ seems to play a critical role in modulating blood pressure is the kidney, and in particular the medullary thick ascending limb (mTAL) (14). Several recent papers, including the study by Hong et al. (7) in an issue of the American Journal of Physiology-Renal Physiology, have emphasized how the balance of NO and O$_2^-$ is regulated in the mTAL and how this modulates and is affected by sodium reabsorption. These prior studies showed that O$_2^-$ stimulates activity of the Na-K-Cl cotransporter and that NO inhibits this transporter. These authors also showed that O$_2^-$ can stimulate protein kinase C (likely the alpha isoform), which in turn stimulates the Na-K-Cl cotransporter and promotes sodium and chloride absorption (3, 5, 6, 15, 17).

Hong et al. (7) further investigate how the mTAL produces O$_2^-$. Using isolated segments of the mTAL, these authors show that flow markedly stimulates O$_2^-$ production. The authors proved that the NADPH oxidase was the source by using the pharmacological inhibitor apocynin and by performing studies in p47phox$^{-/-}$ mice. Unlike their prior paper, which showed that O$_2^-$ stimulated PKC activation, they now show that PKC is activated by flow and that PKC is upstream of NADPH oxidase activation. Using a dominant-negative form of PKC-$\alpha$, the authors were able to identify this subunit as the likely suspect in flow activation of the NADPH oxidase. These data are compatible with recent studies showing that diabetes, angiotensin II, and oxalate also stimulate mTAL superoxide production in a PKC-dependent fashion (18, 20, 21).

The current findings of Hong et al. and several of their prior studies emphasize various similarities between the mTAL and the vascular endothelium. Like the endothelium, mTAL epithelial cells express NO synthases and NADPH oxidases (13, 14). Both cell types are flow responsive, and PKC is one of many mediators of downstream signaling events. In both cell types, flow simultaneously stimulates NO and O$_2^-$ production, and the balance between these two is tenuous and critical in the ultimate response. In the endothelium, excessive superoxide stimulates vasoconstriction and inflammation, while in the mTAL, O$_2^-$ stimulates sodium reabsorption. By reducing bioactive NO, superoxide can modulate tone of the adjacent vasa recta, and thereby affect interstitial Starling forces that promote sodium uptake into the vasculature. Thus, in both the endothelium and the renal medulla, excessive O$_2^-$ favors blood pressure elevation.

An important message to be taken from the impressive body of work in this area is how prone this system is to production of O$_2^-$ in a “feed-forward” fashion. Sodium, pressure, and flow in the mTAL lumen stimulate O$_2^-$ production (1, 5, 8, 10). This activates the Na-K-Cl cotransporter, which further stimulates O$_2^-$ production. Superoxide in turn can activate PKC, which promotes NADPH oxidase activation and more O$_2^-$ production (5). These interactions seem to represent a vicious cycle that promotes sodium reabsorption and ultimately hypertension.

One begins wonder how hypertension is avoided given the propensity for sodium reabsorption and O$_2^-$ production to promote one another in the mTAL. An obvious answer is via production of NO, which puts a brake on this cycle; however, other factors are likely involved. Because NO is often reduced in pathophysiological conditions, it is interesting to consider how pharmacological approaches might interrupt the vicious cycle described above. Agents like Tempol, other superoxide dismutase mimetics, and apocynin might reduce O$_2^-$, but are not clinically available. Statins, by inhibiting geranylation of the small G protein Rac, can block NADPH oxidase assembly and activity. Statins also increase NO synthase expression and NO production (22). The novel $\beta$-adrenergic antagonist Nebivolol also seems to favorably increase NO production and to decrease NADPH oxidase activity in the mTAL (19). Other agents that stimulate NO production, such as tetrahydrobiopterin and perhaps l-arginine, might also be effective (11). Finally, a low-sodium diet, by reducing the amount of sodium presented to the distal nephron, could also reduce mTAL O$_2^-$ production (10).
This area of research also provides some insight into why common clinical conditions, such as obesity, atherosclerosis, diabetes, and insulin resistance, are often associated with hypertension. These conditions promote oxidative stress and reduce bioavailable NO and would therefore favor the viscous cycle described above. Thus, the specialized cells of the mTAL represent an attractive target for treatment of hypertension. Future studies are needed to understand how the feed-forward production of O2- in these cells can be interrupted.

REFERENCES