Mitochondrial Dysfunction and Mitochondrial-Produced Reactive Oxygen Species
New Targets for Neurogenic Hypertension?

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Over the past 10 to 15 years, a vast collection of studies have provided evidence indicating that reactive oxygen species (ROS), particularly superoxide (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$), contribute to the pathogenesis of cardiovascular diseases, such as heart failure and hypertension. Griendling et al$^1$ first demonstrated that NADPH oxidase present in the vasculature is a primary source of the elevated ROS levels. Since these initial studies, NADPH oxidase–derived ROS in the kidney,$^2$ heart,$^3$ and brain$^4$ have been linked to the development and progression of numerous cardiovascular-related diseases. More recently, however, mitochondria have also been identified as important sources of ROS in controlling cardiovascular function. Considering that mitochondria are the primary source of ROS in most cells during normal respiration because of the leaking of electrons from the electron transport chain (ETC), perhaps it should not be all that surprising that mitochondrial-produced ROS are involved in pathophysiological conditions of the cardiovascular system.

To date, most of the evidence linking mitochondrial dysfunction and mitochondrial-produced ROS to the pathogenesis of cardiovascular diseases comes from studies on the peripheral renin-angiotensin system.$^5$ For example, using a model of cardiac ischemic reperfusion injury, Kimura et al$^6$ reported that angiotensin II (Ang II)–induced preconditioning is mediated by mitochondrial-produced ROS. The authors further demonstrated that Ang II–induced NADPH oxidase–derived ROS lie upstream of mitochondrial-produced ROS, thus, implicating a ROS-induced ROS mechanism. Similarly, it was demonstrated recently that, in aortic endothelial cells, Ang II–induced NADPH oxidase activation leads to an increase in mitochondrial ROS production, as well as mitochondrial dysfunction, as determined by a decrease in mitochondrial membrane potential and mitochondrial respiration.$^7$ Together, these studies and others (detailed elsewhere$^5$) clearly illustrate a role for mitochondrial-produced ROS and mitochondrial dysfunction in peripheral tissues in the pathogenesis of cardiovascular diseases, primarily those associated with increased Ang II signaling. However, in the central nervous system, the contribution of defective mitochondria and mitochondrial-produced ROS in cardiovascular diseases has been mostly overlooked.

In the present issue of Hypertension, Chan et al.$^8$ studying neurogenic hypertension, provide new evidence that, indeed, mitochondrial dysfunction and the subsequent production of mitochondrial-localized ROS in the central nervous system, particularly the rostral ventrolateral medulla (RVLM), play a critical role in cardiovascular function. More specifically, they report a decrease in ETC complex I and complex III activity accompanied by an increase in mitochondrial-produced ROS, particularly O$_2^-$ and H$_2$O$_2$, in the RLVM of spontaneously hypertensive rats (SHRs). Direct RVLM administration of coenzyme Q$_{10}$, a mitochondrial electron transporter and antioxidant, restored electron transport capacity, decreased mitochondrial-localized ROS production, and significantly reduced mean systemic arterial pressure and sympathetic neurogenic vasomotor tone in SHRs. Using mitochondrial ETC inhibitors rotenone and antimycin A, Chan et al$^8$ provide further evidence that mitochondrial dysfunction in the RVLM results in mitochondrial-produced ROS, which, in turn, induce changes in cardiovascular function. In normotensive Wistar-Kyoto rats or prehypertensive SHRs, RVLM administration of rotenone or antimycin A significantly elevated mitochondrial H$_2$O$_2$ production, as well as mean systemic arterial pressure and power density of vasomotor activity. Similar to its action in hypertensive SHRs, coenzyme Q$_{10}$ markedly attenuated the augmented cardiovascular responses induced by ETC inhibition in normotensive animals. These data indicate that diminished mitochondrial ETC activity and the subsequent production of ROS in the RVLM contribute to the SHR hypertensive phenotype.

To address the hypothesis that a cytoplasm-to-mitochondria ROS-induced ROS mechanism in the RVLM is involved in neurogenic hypertension, Chan et al$^8$ used an intracerebroventricular (ICV) Ang II infusion model. ICV Ang II infusion results in an increase in sympathetic tone and blood pressure, at least in part, via NADPH oxidase activation in the RVLM.$^9$ Compared with ICV infusion of artificial cerebrospinal fluid, Ang II infusion decreased ETC complex I through III activity while increasing mitochondrial-produced H$_2$O$_2$ in the RVLM. Inhibition of NADPH oxidase via p22$^{phox}$ antisense significantly attenuated the Ang II–induced increase in mitochondrial H$_2$O$_2$ levels, thus implicating a ROS-induced ROS mechanism initiated by NADPH oxidase–derived ROS. Similar to the SHR experiments, RVLM administration of coen-
zyme $Q_{10}$, inhibited the Ang II–induced increase in mitochondrial-produced ROS, mean systemic arterial pressure, and sympathetic vasomotor tone. Together, these studies strongly suggest that increased sympathetic tone and the pathogenesis of neurogenic hypertension are mediated by mitochondrial ETC dysfunction and an ensuing increase in mitochondrial-produced ROS in the RVLM.

In an attempt to further support the ROS-induced ROS hypothesis, Chan et al.\(^8\) used adeno-viral-mediated gene transfer to overexpress 3 different antioxidants, copper/zinc superoxide dismutase (SOD1), manganese superoxide dismutase (SOD2), and catalase in the RVLM of SHRs. Previously, this group demonstrated that SOD1, SOD2, or catalase overexpression in rats also present in mitochondria,\(^11\) and, thus, it is possible that interpretations should also be considered. For example, SOD1 is a mitochondrial ETC dysfunction and an ensuing increase in mitochondrial-produced ROS in the RVLM.

In summary, Chan et al.\(^8\) report a role for mitochondrial-produced ROS in brain angiotensinergic signaling by reporting that overexpressing SOD2, the mitochondrial-targeted isoform of SOD, in the brain significantly attenuates the cardiovascular responses induced by ICV administration of Ang II. However, this earlier study failed to identify a potential source of Ang II–induced mitochondrial-produced ROS in central neurons. More recently, Nozoe et al.\(^13\) also showed that SOD2 overexpression in the brain, notably, the RVLM, attenuates the acute pressor response of Ang II microinjected into the RVLM. Similar to Chan et al.\(^8\) Nozoe et al.\(^13\) suggest that Ang II signaling in neurons involves a ROS-induced ROS mechanism, which starts with NADPH oxidase–derived ROS and ends with mitochondrial-produced ROS. However, in contrast, Nozoe et al.\(^13\) report that Ang II does not alter the activity of ETC complexes. This discrepancy is likely attributable to the fact that Nozoe et al.\(^13\) measured the acute effect of Ang II (1-hour stimulation) on ETC complex activity in cultured PC-12 cells, whereas Chan et al.\(^8\) measured complex activity in vivo in RVLM tissue after 5 days of ICV Ang II infusion. As discussed earlier, the fact that rotenone or antimycin A, 2 ETC inhibitors, microinjected into the RVLM increased mitochondrial-localized ROS, mean systemic arterial pressure, and sympathetic tone strengthens the conclusion by Chan et al.\(^8\) that, in neurons, damaged ETC complexes are a source of mitochondrial-produced ROS. Nevertheless, further experiments, perhaps using genetic strategies to inhibit ETC activity in central neurons, are required to corroborate this conclusion.

In summary, Chan et al.\(^8\) report a role for mitochondrial dysfunction and mitochondrial-produced ROS in the central nervous system in the pathogenesis of neurogenic hypertension. The data indicate that impaired ETC complexes are a source of mitochondrial-localized ROS and that NADPH oxidase–derived ROS may mediate the impairment of the ETC (Figure). Additional studies are required to examine the downstream mechanism(s) by which mitochondrial-produced ROS include redox-sensitive transcription factors (TF) and/or ion channels (broken-line arrows).

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**Figure.** Proposed Ang II signaling pathway in RVLM neurons involving mitochondrial dysfunction and mitochondrial-produced ROS. Chan et al.\(^10\) provide evidence indicating that Ang II stimulation of neurons in the RVLM increases NADPH oxidase–derived ROS, which, in turn, damage mitochondrial ETC complexes leading to an increase in mitochondrial-produced ROS (solid-line arrows). Additional experiments using mitochondrial-targeted antioxidants, such as SOD2, are needed to determine the downstream signaling events mediated by mitochondrial-produced ROS. Possible targets of mitochondrial-produced ROS include redox-sensitive transcription factors (TF) and/or ion channels (broken-line arrows).
ROS increase sympathetic tone and drive the development of hypertension. Such studies should use mitochondrial-targeted antioxidants, including SOD2, and focus on the redox sensitivity of neuronal ion channels, as well as redox control of transcription factors (Figure). The results of these future experiments may strengthen the conclusions by Chan et al⁸ and may help distinguish damaged ETC complexes and mitochondrial-produced ROS as novel therapeutic targets in neurogenic hypertension.

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