R eview

The article by Yang et al\(^1\) in this issue of *Hypertension* is noteworthy in that it makes significant contributions in 2 areas. First, the authors describe an approach using retroviral constructs to achieve long-term (up to 5 months) expression of a human heme-oxygenase 1 (HO-1) gene in the liver, kidney, and vasculature of rats in vivo. They also demonstrated that they could knockdown endogenous HO-1 activity in rats by administration of a retrovirus containing a rat HO-1 antisense construct. The second major advance in this study is that it provides new information that further highlights the importance of the HO/CO system as a key modulator of vascular tone in vivo. They found that overexpression of the human HO-1 gene in the rat attenuates the pressor response to intravenous administration of angiotensin II and that knockdown of endogenous HO-1 activity potentiates the pressor response to angiotensin II.

**Gene Therapy Approaches in Hypertension Research**

The completion of the sequencing of the human, rat, and mouse genomes now provides an unprecedented opportunity for the discovery of new genes, pathways, and drug targets for the treatment of hypertension and associated end-organ damage. Unfortunately, an examination of the publicly available genome databases (eg, LocusLink, Online Medelian Inheritance in Man [OMIM], the Human Genome Organization [HUGO], and the Genome Database [GDB]) reveals that only \(\approx 5000\) of the 30 000 predicted human genes have any inferred function. The challenge is now to attach function to the genome and to identify the genes and pathways involved in human disease. Most of the progress to date has been generated using targeted gene knockout in mice.\(^2\)–\(^4\) While this approach has proven to be extremely valuable to confirm the actions of known genes, it has been less effective in defining the function of the newly discovered genes. One of the problems is that it is difficult to develop phenotyping protocols broad enough to identify all the functional consequences associated with knockout of a gene without prior knowledge of the function or organ systems to study. The gene knockout approach has also run into problems with the failure to produce obvious phenotypes and genomic background effects.\(^5\) The emergence of adenoviral vectors for transient gene therapy\(^6\) and now retroviral vectors to achieve long-term expression of constructs in vivo as described in this study\(^1\) offers a number of advantages for future functional genomics studies. First, viral constructs can be produced to enhance or knockdown the expression of any gene. Viral-driven gene therapy can be applied to any species. This is especially relevant to workers using rats, in which a large number of well characterized inbred models of hypertension and associated end-organ damage are available. Given these advantages, it is likely that viral-driven gene therapy approaches as well as other related knockdown techniques (RNAi) will become as commonplace as traditional pharmacological tools to unravel the contribution of different genes and pathways to the pathogenesis of hypertension and other complex diseases.

**Heme Oxygenase/Carbon Monoxide in the Control of Vascular Tone**

The other major contribution of the study by Yang et al\(^1\) is that it emphasizes the critical role of HO and CO in the control of vascular tone. In the past 5 years, this field has exploded; nearly 500 articles have been published this year alone. It is now apparent that HO is expressed in blood vessels and tissues throughout the body and that CO serves as an important endogenous mediator of vascular tone.\(^7\)–\(^11\) It is a potent vasodilator that has multiple effects on vascular smooth muscle. These actions include activation of guanylyl cyclase,\(^9\)–\(^11\) direct activation of \(K^+\) channels,\(^11\) inhibition of the formation of NO\(^12\) and P450 metabolites of arachidonic acid,\(^10\)\(^11\) stimulation of the formation of prostacyclin,\(^14\) and downregulation of the expression of CYP4A and cyclooxygenase 2 enzymes.\(^13\) The study by Yang et al\(^1\) indicates that overexpression of HO attenuates the pressor response to angiotensin II. This finding suggests that angiotensin II increases the production of CO and that CO modulates the vasoconstrictor response to angiotensin II. More work is needed to understand the mechanisms by which HO-1 and CO alter the vasoconstrictor response to angiotensin II. CO could be formed and act at the level of vascular smooth muscle cells to directly oppose the actions of angiotensin II. However, because HO-1 is highly expressed in the brain and the nervous system, it is just as likely that locally generated CO may influence baroreflex responses to exogenous administration of angiotensin II. Regardless of the mechanism involved, this article is important in that it further defines the role of HO and CO in the control of vascular tone and the regulation of blood pressure.

**References**

Gene Therapy and Heme Oxygenase Coming of Age
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