Induction of Heme Oxygenase
Can It Really Reverse Hypertension?

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Carbon monoxide (CO), produced within the body as a product of the catabolism of heme by the enzyme heme oxygenase (HO), has been reported to be a local vasodilator. One of its possible pathways is to stimulate guanylyl cyclase to produce cGMP as a second messenger. The parallel to NO, another gaseous signaling molecule that also works through cGMP-mediated pathways (although more potent), is obvious. In fact, the vasodilator actions of these 2 may be integrally linked. Both are endothelium derived. NO stimulation of cGMP may facilitate CO-mediated dilation of resistance vessels through calcium-activated potassium channels. However, the HO–CO story has not received the same interest and attention as NO, nor is it as generally well understood by those who work outside the field. In the present issue, we are presented with a provocative study by one of the well-established laboratories within the field of HO–CO. Wang et al focus on HO in the genetic model of hypertension, the spontaneously hypertensive rat (SHR). They report that 3 weeks of administration of hemin, the oxidation product of heme, produced a profound 80-mm Hg decrease in blood pressure that was sustained completely for 9 months after ceasing treatment (a duration in a rat’s life, which roughly translates into 17.5 human years). Although this is a remarkable, hopeful, and possibly profound observation, the study probably raises more questions than it answers.

First, it is important to point out that this sustained decrease in blood pressure and reversal of hypertension is an unprecedented result. The potential importance of this observation is that a single 3-week treatment regimen induced a protracted reduction in blood pressure, long after treatment had ceased. To put this in perspective, treatment of virtually all forms of hypertension in humans, as well as animal models, typically requires a constant drug regimen in which hypertension was already well established, treatment had no antihypertensive action. Effective treatment is a long-term habitual, physical, and financial commitment, not always embraced or fully understood by many patients. The authors provide us with a rather optimistic and ebullient extrapolation of their results into human antihypertensive therapy. Although we can only hope they are ultimately proved right, some healthy perspective and further inquiry would seem in order.

First, keep in mind that these results were obtained in SHRs. This is an animal model of genetic hypertension, derived from a small fraction of a large population selected by an extreme phenotype of blood pressure. It is not a model of human essential hypertension, and to suggest that it ignores the complexity and unknown etiologies of the human condition. Hypertension in SHRs has a unique but well-characterized etiology involving altered salt balance, an enhanced sympathetic contribution, and, to a lesser extent, angiotensin-mediated components, none of which are addressed in the present work. However, the predictable progression of hypertension in these rats without the need for any external stimulus or manipulation makes them a very useful experimental model of the overall disease process.

In the present study, hemin treatment was initiated at 12 weeks of age. That is a young adult in which the rapid onset of hypertension had just concluded. Administration of hemin decreased blood pressure by 80 mm Hg over 2 weeks while having no effect on normotensive controls. The authors report that in previous studies involving younger SHRs (4 weeks old), hemin was only transiently or not at all effective, whereas in older SHRs (20 weeks) in which hypertension was already well established, treatment had no antihypertensive action. Hypertension in SHRs has been classically characterized by initial onset of sodium-positive sodium balance between 3 and 10 weeks of age, during the rapid increase in blood pressure. Interestingly, the protocol of Wang et al began right at the end of this period, presumably when pressure natriuresis had been reset, achieving a sodium balance to normalize renal function. One might then expect that the effectiveness of inducing HO would somehow lie in targeting this renal mechanism so that HO presumably plays some undefined role in reversing the positive sodium balance and altered renal function. Unfortunately, the present study only focuses on the mesenteric vasculature as a generalized index of increased peripheral resistance. The other question that begs an answer is, if the kidney in the untreated SHR requires an elevated pressure to maintain renal equilibrium, how does hemin treatment, which drops renal perfusion pressure by 80 mm Hg, also manage to keep the kidney functioning in an apparently normal fashion for 9 months? Studies of renal histology have not indicated the development of obvious renal lesions until 6 to 7 months of age, despite the early onset of increased...
blood pressure and cardiac hypertrophy, suggesting that inherent changes in renal function precede any chronic structural adaptation. However, no index of renal function, proteinuria, or even comparative renal histology at the extended observation period of 9 months is provided in this work.

Previous studies suggest that hemin administration may well upregulate the HO–CO system in the kidneys of SHR and that heme induction may alter renal cytochrome P-450 and 20-HETE production in the SHR kidney. However, despite these provocative observations focusing on the kidney as a target of the antihypertensive actions of HO, in the present study we are only told of normal serum creatinine and urea levels and reversal of eutrophic inward remodeling of the mesenteric arteries (which could be secondary to the drop in blood pressure, independent of how it was reduced). It should also be noted that there may well be other important effects of HO induction not really considered in the present work. Although CO may affect cGMP, its vasodilator effect in mesenteric and cerebral vessels seems to be linked to calcium-activated potassium channels, which may interact with NO-stimulated cGMP or may act in the mesenteric vasculature in a totally cGMP-independent fashion. Also, bilirubin is the primary product of HO degradation of heme, and it is known to be a potent antioxidant. Reactive oxygen species have been implicated as a major factor in all of the forms of hypertension. The present study found a small but significant increase in bilirubin, suggesting that this could also have a significant contribution to the hypertensive response to HO induction. The reader is left lacking more pertinent information and a more focused explanation of possible mechanisms that might more logically address the authors’ remarkable results.

Ndisang and Wang found previously that hemin treatment was not effective in 4- or 20-week-old SHRs but did transiently decrease blood pressure in 8-week-old SHRs. The decrease was associated with increased HO-1 and guanylyl cyclase activity not seen at the other ages. The effectiveness of subcutaneous administration of hemin also seems to be because of the duration of administration rather than the amount, because durations of 4 and 13 days were ineffective in producing the complete or sustained lowering of blood pressure that was observed when it was given over 21 days. Thus, the effectiveness of this therapeutic regimen was not only limited to a particular age or stage of the development of hypertension in SHR but also to a well-defined duration of treatment to evoke the necessary induction of both expression and activity of HO. The rationale for such a focused and defined window of opportunity is not at all clear. Their observation that basal HO expression (although not activity) in 12-week-old SHR was more than twice that seen in normotensive controls even before hemin treatment could be a key. Hemin doubled expression again, and this did result in increased HO activity. This increased expression in the untreated SHRs, particularly at this age, may be a clue as to why hemin activation was so effective in increasing HO for such a prolonged duration, in that SHR may uniquely have a more reactive enzyme system that can be readily (and apparently irreversibly) enhanced. The authors do note this observation, but the contribution of this characteristic to their results remains unresolved.

It is of particular interest that, whereas there has been a good deal of work studying the antihypertensive effects of HO and CO in SHRs, especially by the current authors, very little seems to have been done in other models of hypertension. Botros et al have reported that HO induction before and throughout the onset of 2K,1C renovascular hypertension in the rat attenuates the onset of hypertension by interfering with the angiotensin-mediated increase in blood pressure. However, Johnson et al reported that HO induction resulted in prohypertensive CO-mediated endothelial dysfunction in deoxycorticosterone acetate-salt hypertensive, rats which is not apparent in SHRs under the same conditions. Thus, whereas there seems to be some level of consensus as to the upregulation of HO and an antihypertensive role for CO in the genetic rat model SHR, a useful extrapolation to other animal models of hypertension is not readily apparent in the literature, and in some cases CO may be a prohypertensive factor.

So, as is typical in science, things are never as simple as we would like them to be. However, that does not undermine a really provocative and important result presented by Wang et al. The dramatic and sustained total reversal of hypertension long after treatment ceased provides an exciting platform from which more detailed experiments may clarify how and when certain therapies may be more effective. The extrapolation to treatment of human hypertension may not be resolved as quickly as the authors clearly would like it to be, but understanding any mechanism by which a model of genetic hypertension can be “cured” is certainly a very positive and hopeful step in understanding this deadly and all-too-common disease.

Disclosures

None.

References
