NO and CO have got to GO for enhanced chemoreceptor sympathoexcitation in heart failure

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ARTERIAL CHEMORECEPTORS LOCATED in the carotid body are an important defense mechanism against systemic hypoxemia. Activation of arterial chemoreceptors increases alveolar ventilation and sympathetic outflow to most vascular beds. During acute exposures to hypoxia, the sympathoexcitatory responses to chemoreceptor activation are important in counteracting the direct vasodilator effects of hypoxemia and preventing falls in blood pressure that might compromise blood flow to hypoxic tissues.

However, chronic activation of arterial chemoreceptors could conceivably lead to deleterious, chronic elevations in sympathetic outflow. The carotid body chemoreceptors have been shown to play an important role in the chronic sympathoexcitation observed in a rabbit cardiac pacing model of chronic heart failure (CHF) (13). Ding et al. (2) present evidence that endogenous modulators that inhibit carotid body chemoreception are reduced during CHF in the rabbit. Since these modulators normally attenuate the response of the carotid body chemoreceptors to hypoxia, their reduction could contribute to enhanced chemoreceptor afferent discharge and, thereby, the elevated sympathetic outflow observed in CHF.

Previous work by Li and Schultz (7) and Schultz and Sun (13) showed that renal sympathetic nerve responses to graded hypoxia are enhanced in anesthetized rabbits with CHF compared with sham rabbits and suggest that nitric oxide (NO) is involved in this process. Ding et al. (2) extend these observations and determine the effect of NO and carbon monoxide (CO) on the renal sympathetic nerve response to graded hypoxia in conscious, unanesthetized rabbits with CHF. The use of a conscious preparation provides a major interpretive advantage. These studies provide important new information related to the role of CO and NO in chemoreceptor-evoked sympathoexcitation in conscious, unanesthetized animals.

Ding et al. (2) found that the enhanced renal sympathetic nerve activity (RSNA) induced by exposures to graded levels of hypoxia in CHF rabbits was attenuated by systemic administration of an NO donor or a CO-releasing molecule. In normal (sham) animals, systemic administration of an NO donor or a CO-releasing molecule had no effect on the renal sympathetic nerve response to hypoxia.

Ding et al. (2) also found that NO synthase (NOS) inhibition (the NOS inhibitor did not distinguish between the various isoforms of NOS), as well as inhibition of heme oxygenase (HO, the enzyme that produces CO), augmented the renal sympathetic nerve responses to hypoxia in sham, but not CHF, rabbits. Simultaneous administration of either NO donors and CO releasers or NOS and HO inhibitors resulted in additive effects indicating independent mechanisms of action.

Together, the results suggest that NO and CO systems are active in the normal rabbit, inasmuch as their inhibition leads to enhanced renal sympathetic nerve responses to hypoxia. However, in the normal animal, their contribution to hypoxia-evoked sympathoexcitation may be maximal, inasmuch as NO donors and CO liberators are without effect. The failure of NOS and HO inhibitors to alter the renal sympathetic nerve response to hypoxia in CHF suggests that these systems are functionally downregulated and no longer modulate chemoreceptor-induced changes in RSNA, so that their inhibition has no discernable effect.

Ding et al. (2) examined some of the proteins that regulate NO and CO synthesis. Western blot analyses indicated reduced expression of the neuronal and endothelial isoforms of NOS in carotid bodies isolated from CHF rabbits. Immunostaining for HO-2 was also reduced in glomus cell clusters in the carotid bodies of CHF rabbits. The changes in protein levels in CHF were consistent with the physiological responses, suggesting that alterations in the expression of synthetic enzymes might mediate the reduced inhibitory role of NO and CO in CHF rabbits.

An excellent technical aspect of these studies, and one that makes them rather unique in this field, is the use of pharmacological techniques to normalize drug-induced changes in blood pressure. Since the systemic administration of NO and CO drugs can have effects on blood pressure, the approach of Ding et al. (2) enables examination of the hypoxia-RSNA relationship in the absence of confounding baroreceptor influences and pressure-induced changes in carotid blood flow. The caveat is that, depending on the ability of these drugs to penetrate the central nervous system, one cannot definitively assign the site of action to the peripheral chemoreceptors. Schultz and Sun (13) reported that NOS inhibitors enhance the hypoxia-evoked discharge of single carotid body afferent fibers in CHF, so it is reasonable to assume that, at the very least, some component of the changes reported in the study of Ding et al. (2) occur at the level of the carotid body chemoreceptors.

The study of Ding et al. (2) represents an important step in an ongoing evaluation of the role of the arterial chemoreceptors in chronic pathophysiological states. It is the first demonstration in a conscious, unrestrained animal that both NO and CO inhibit the renal sympathetic nerve response to systemic hypoxia and that the absence of a functional role for these inhibitory modulators could contribute to enhanced hypoxia-induced sympathoexcitation in CHF.

Their study, combined with previous work by them and others, has lead Ding et al. (2) to propose a model of enhanced chemoreception during CHF. Angiotensin AT1 receptors are upregulated on carotid body glomus cells in CHF and contribute to enhanced chemoreceptor and renal sympathetic nerve responses to hypoxia in CHF (8). Enhanced chemoreceptor responses to hypoxia in CHF are mediated, at least in part, by an angiotensin-mediated increase in the sensitivity of glomus
cell K⁺ channels (Kv3.4) to closure during hypoxia (7) and by angiotensin activation of an NADPH oxidase-superoxide signaling pathway (9). Angiotensin-induced oxidative stress can downregulate NOS and NO function (4). In addition to superoxide inhibition of NOS and NO function, NO availability could also be reduced by angiotensin as a result of superoxide-NO interaction to produce peroxynitrite (9). This chain of events could lead to the absence of a demonstrable NO and CO contribution to chemoreceptor regulation of RSNA in the present study. In support of this model, Ding and co-workers were able to eliminate the enhanced chemoreceptor discharge response to hypoxia in CHF rabbits by application to the carotid body of an adenovirus expressing the neuronal isoform of NOS (6).

The study of Ding et al. (2) provides ideas for several potential future directions. Examination of the respiratory responses to arterial chemoreceptor activation in CHF rabbits would be of interest, especially given recent data indicating that much of the sympathoexcitation following acute exposures to hypoxia results from an augmentation of the respiratory component of sympathetic outflow (1). Is any of the increased sympathetic outflow observed in CHF the result of enhanced respiratory drive?

In addition, the arterial chemoreceptors are potential contributors to the chronic sympathoexcitation observed in sleep apnea patients (10, 11) and in rats exposed to intermittent hypoxia, a model of the arterial hypoxemia that accompanies sleep apnea (5). Could a commonality of mechanism exist that explains persistent chemoreceptor activation in CHF and sleep apnea/intermittent hypoxia? Intermittent hypoxia (3) and CHF (14) are associated with increased circulating/plasma renin activity, and the role of oxidative stress in enhanced carotid body chemoreceptor responses to hypoxia has been demonstrated in the intermittent hypoxia model (12). Could activation of angiotensin AT1 receptors on carotid body cells initiate oxidative stress and downregulation of NOS and HO, leading to the enhanced chemoreceptor responses to hypoxia observed in sleep apnea and intermittent hypoxia? However, it is important to recognize that actions at the level of the carotid body are likely only one component of the story, inasmuch as a similar angiotensin-oxidative stress-reduced NO scenario has been described in several central nervous system nuclei involved in the regulation of sympathetic outflow in CHF (14). Therefore, this “common mechanism” might be occurring at multiple sites.

REFERENCES


