Carbon Monoxide in Vasoregulation
The Promise and the Challenge
Flavio Coceani

Less than 10 years have elapsed since the possibility of carbon monoxide (CO) being a novel signaling agent was first discussed. In this time, a wealth of data has accrued supporting this idea and providing the foundation for physiological and pathophysiological schemes. Originating from heme through the action of specific oxygenases (heme oxygenase [HO]), which are both inducible (HO-1) and constitutive (HO-2 and HO-3) in character, CO may be formed at rest and, to a greater degree, on exposure to a host of HO-1–directed stimuli (ie, hypoxia, hyperoxia, shear stress, pyrogens, and metals, among the pertinent ones). It then exerts several effects within and without the vasculature. Blood vessels, in particular, have a complete system for the generation of CO and may dilate under the influence of the agent. Their actual response, however, varies with the vascular bed, and there are also instances of vessels failing unexpectedly to respond. Of relevance here is the recent observation of CO being ineffective on the pulmonary circulation in the fetus and hence on a system reproducing well, with a naturally high resistance, the condition of the hypertensive adult. The issue of apparent inconsistencies in CO action is intertwined with questions about the identity of the target for the compound. By analogy with nitric oxide (NO), the guanylate cyclase/cGMP system is commonly, and perhaps too hastily, regarded as the only messenger for CO inside cells, notwithstanding the relatively low affinity of the enzyme for the agent and the reported unresponsiveness of certain vessels. However, there is evidence implicating a cytochrome P450 (CYP450) hemoprotein and potassium channels as alternative transducing mechanisms. Clearly, all of these mechanisms are not mutually exclusive and may, in fact, complement each other, depending on the site and the prevailing physiological or pathophysiological condition. For example, in the ductus arteriosus, CO relaxation is ascribed to inhibition of the functional complex CYP450/endothelin (ET-1) under normal oxygenation, whereas activation of guanylate cyclase may become the main factor under hypoxia. An even more complicated picture can be visualized when assuming the existence in the tissue of compounds that make guanylate cyclase more susceptible to the action of CO. Should such activator be found, CO would acquire, for potency and versatility, a new functional dimension.

Not only is CO formation conditioned by several stimuli, but it is also liable to self-regulation and regulation by NO. In fact, these 2 messenger systems may interact in a varied manner and ultimately, depending on the condition, influence each other synergistically or antagonistically. Whereas CO inhibits its own synthesis and the synthesis of NO, NO promotes the formation of CO. CO, on the other hand, can also displace NO from heme-binding sites. In brief, CO and NO form an operational unit whose activity and specific arrangement can vary with the functional demands. For example, under hypoxia and the attendant divergent changes taking place in the CO (upregulation) and NO (downregulation) systems, this interaction is expectedly minimal, if present at all. An opposite situation is likely to occur after exposure to pyrogens or hyperoxia when both systems are fully operational.

Progress in this area has had other important consequences and, specifically, brought evidence of the function of hemoproteins as sensing and transducing elements inside cells. In fact, CYP450 hemoproteins have moved beyond their conventional roles of catalysts for biodegradative processes to become key factors for oxygen sensing and a host of arachidonate-linked transformations. In addition, hitherto uncharacterized hemoproteins have been implicated in certain hypoxia-triggered events, including pulmonary vasoconstriction. Analysis of the effect of CO versus oxygen has been critical in defining the operation of these hemoproteins, inasmuch as one could identify the source of the signal in a conformational change when the two agents acted synergistically and in a monoxygenase reaction when they acted antagonistically. Important developments are expected in this field as new tools and methodologies become available. Nanotechnology, to mention one development, may provide the means to monitor and manipulate the changes taking place in hemoproteins when they interact with appropriate ligands. Ultimately, this should lead to a better understanding of physiological and pathophysiological processes involving hemoproteins as a crucial link and, by extension, to the design of new strategies for prevention and treatment of any relevant disease. Pulmonary hypertension is conceivably one such disease. In this connection, it is tempting to speculate that the impact of perinatal hypoxia as a predisposing event for pulmonary hypertension later in life is expressed not only through a structural anomaly, as recently suggested, but also through alterations in a signaling hemoprotein.

In this issue of Circulation Research, Christou et al provide a new perspective on this complex subject by documenting the adaptive and reactive functions of CO in the...
sequence of events triggered by hypoxia and resulting in pulmonary hypertension. The work stems from an operational model, based on investigations from their own and other laboratories, according to which hypoxia promotes the formation of the vasoconstrictor ET-1 via a specific transcription factor (hypoxia-inducible factor-1 [HIF-1]). The same model assumes the concomitant upregulation of HO-1 by the hypoxic stimulus and, hence, the formation of CO, which would modulate the response by dilating the vasculature directly and through interference with HIF-1 DNA binding via messenger cGMP. No effect of CO is expected on the hypoxia-sensing heme moiety, and in this respect, the position of Christou et al. departs from that of others and the general notion in the literature. Christou et al. report that the CO rebound after HO-1 induction may become strong enough to curtail two distinctive effects of hypoxia on the pulmonary vasculature leading to hypertension, namely, constriction and structural remodeling. The practical implications of this finding are obvious and coincide with those of another investigation, allied in rationale and finality, in which suppression of pulmonary hypertension was achieved through the overexpression of prostaglandin I2 synthase. Leaving aside the conceptual interest, legitimate questions would ask whether the approach heralded by these studies is the most appropriate one for pulmonary hypertension and what the limitations of the study are, if there are any. Theoretically, the optimal agent should be selective in its vasodilator and antiproliferative actions and, within the bounds of the pulmonary vascular district, hemodynamic normalization should be achieved through the removal of constrictor ET-1 rather than the enhanced activity of one of the several dilator systems. Failing this, there is the potential for systemic vasodilatation, and there is locally the risk of increasing the blood shunt fraction. In addition, rebound hypertension could occur if the dilator action were to abate below a critical threshold. With this premise, any activation of the CO-based mechanism, whether obtained pharmacologically or with genetic techniques, may be viewed as an adjuvant for the management of hypertension rather than the treatment proper.

Whatever the expected end point for a CO-based treatment of pulmonary hypertension, certain facts inherent to the operation of this agent need to be considered first. CO is known to exert a negative feedback on its own synthesis, and this raises the question of whether any inducer of HO-1 will actually be able to ensure a sustained acceleration in CO formation. It is interesting to note that HO-1 null mutants do not exhibit an exaggerated hypertensive state after 5 to 7 weeks of hypoxia when compared with the wild-type controls, nor do they show signs of a more severe vascular remodeling. Of course, one may claim a compensating action of HO-2 in the mutant. Nevertheless, it would be of interest to ascertain whether the effect of HO-1 induction on pulmonary hypertension, as reported by Christou et al., remains unabated if hypoxia were extended beyond the 1-week period chosen for the present experiments. Another point to be considered concerns the relative stability of CO, at least compared with NO, which is already used therapeutically, with the attendant possibility that the compound originating from an endogenous source may reach multiple targets over a broad area. At this time, the actual impact of these actions cannot be defined easily.

In the end, it is safe to say that several facts need to be evaluated experimentally before one may look at CO as a potential tool for the management of pulmonary hypertension. Nevertheless, there is conceptual importance in the demonstration that CO functions as a defense mechanism in the course of the response of the pulmonary circulation to hypoxia and that its presence could be exploited for therapeutic means.

References


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