What role does the heme—heme oxygenase—carbon monoxide system play in vasoregulation?

G. S. Marks, J. F. Brien, and K. Nakatsu
Department of Pharmacology and Toxicology, Queen’s University, Kingston, Ontario, Canada K7L 3N6

In 1990, we noted to our surprise that when carbon monoxide (CO) was bubbled into a tissue bath containing a rabbit aortic strip precontracted with phenylephrine, the vascular tissue relaxed (7). Perusal of the literature revealed that other investigators had reported on the vasorelaxant effect of CO in vascular smooth muscle preparations from a variety of animal species (7). At this time, the scientific world was excited by the revelation that the gas, nitric oxide (NO), formed endogenously from NO synthase (NOS), had an important physiological role. With this background, we published a paper in 1991 entitled Does carbon monoxide have a physiological function? (7). We suggested that CO, which is formed endogenously from heme catabolism by heme oxygenase (HO) and shares some of the chemical and biological properties of NO, may play a similar role. Three forms of HO have been identified, namely HO-1 (inducible form), HO-2 (non-inducible form), and HO-3 (a newly recognized form), whose role is yet to be clarified. Since publication of our study, a considerable amount of experimental work has been carried out to support the concept that CO has a physiological role (9).

In our original study, we suggested that because CO shared the ability of NO to activate soluble guanylyl cyclase (sGC), CO would exert its physiological effects by activating sGC (7). Our proposal has been criticized because CO is considerably less potent than NO in activating sGC (1). This criticism has been muted by a number of observations; thus a synthetic chemical, YM-1 [3-(5’-hydroxymethyl-2’-furyl)-1-benzylindazole], an NO-independent activator of sGC, potentiates CO stimulation of the activity of this enzyme to a magnitude similar to that achieved by NO (3). The existence of an endogenous functional analog of YM-1 would greatly strengthen the concept of a physiological role for CO (3). The recent observations that bilirubin and biliverdin potentiate the relaxant effects of CO in the guinea pig fundus may be relevant in this regard. Biliverdin and bilirubin are produced by the nitrergic neurons of this preparation concomitantly with CO by HO and might be endogenous functional analogs of the synthetic drug YM-1 (2). Wang et al. (11) showed that in precontracted rat tail artery, CO produced its vasorelaxant effect both by activation of sGC and by opening of high conductance KCa channels. The involvement of KCa channels in CO-induced vasorelaxation has been confirmed by others (5, 12). Further important physiological effects of CO, namely anti-inflammatory and anti-apoptotic effects, have been shown to be due to modulation of the p38 mitogen-activated protein kinase (MAPK) signaling pathway (9). These observations demonstrate that sGC activation is not the only mechanism by which CO can act and that earlier estimates of CO potency on sGC may have been too conservative.

CO is now considered to have a variety of physiological functions in the circulation, namely restraint of platelet aggregation, inhibition of vascular smooth muscle cell proliferation, and a tonic vasodepressor function (9). Exposure of blood vessels from a variety of organs and a variety of species to exogenous CO has been reported to relax blood vessels. It is therefore of considerable interest that Johnson and Johnson (6) have reported in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology that CO promotes endothelium-dependent constriction rather than relaxation of isolated gracilis muscle arterioles. These investigators exposed isolated, pressurized first-order rat gracilis muscle arterioles pretreated with phenylephrine to exogenous CO and a heme precursor, δ-aminolevulinic acid (δ-ALA). Constriction was observed that was found to be dependent on the presence of endothelium. The rationale for using δ-ALA in these studies was to enhance the synthesis of heme, the precursor of CO. The investigators chose to use δ-ALA rather than heme to prevent the possibility of heme contributing to detrimental iron effects on tissues. Of considerable interest was the finding that the CO-induced vasoconstriction observed after CO or δ-ALA administration was converted to dilations when NOS was inhibited by Nω-nitro-L-arginine methyl ester (l-NAME). The present observations and previous reports of CO inhibition of NOS, a cytochrome P-450 type hemoprotein, led Johnson and Johnson to suggest that CO likely promotes endothelium-dependent vasoconstriction by inhibiting endothelial NOS and thus NO formation. In our laboratory, we made similar observations in the intact vascular bed of the rat hindlimb (8). In this preparation, concentration-dependent vasoconstriction (increase in perfusion pressure) was observed after exposure to CO. In the presence of the NOS inhibitor l-NAME, a CO-mediated depressor response of 24 ± 12.8 mmHg was observed. On the basis of the above studies, it appears that there is an interaction between the NOS/NO and HO/CO systems.

Whereas CO has been shown to inhibit NOS, it has recently been shown that NO can inhibit human HO-1.
leading to the suggestion that inhibition of human HO-1 by NO can contribute to the signaling interplay between NO and CO (10). Hartsfield (4) has summarized what is known about the cross talk between CO and NO and concludes that “based on any given system, CO and NO act together in a complex, dynamic and adaptable association.” The study of Johnson and Johnson provides support for this view and suggests that the study of the interaction between the HO/CO and the NOS/NO systems requires further elaboration.

REFERENCES