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Organ Design for Generation and Reception of CO: Lessons from the Liver

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ABSTRACT

Carbon monoxide (CO) is synthesized *in vivo* by heme oxygenase. Although for many years CO had been regarded as potentially toxic waste, recent studies have indicated that it is a signaling molecule with important physiological functions. Nitric oxide (NO), another diatomic diffusible gas, is regarded as an established signaling molecule. Structural similarities between CO and NO have led many investigators to draw analogies between the two gaseous mediators. Whereas the NO signaling system has been well defined as to its receptor molecule, soluble guanylate cyclase, the CO system has been conceived to require further tuning with respect to identifying its receptor molecules and its downstream effectors. Furthermore, there has been little quantitative information to argue for a physiological role of CO *in vivo*. This review, therefore, focuses on recent developments on both physiologic and pathophysiologic roles of CO in the model of isolated perfused liver of rats where endogenous production of CO is actually estimated. This model has revealed that CO acts as an endogenous vasorelaxant in the liver and that effects of CO are at least in part cyclic GMP-dependent. It has also provided answers to many questions of hepatobiliary functions that had not been resolved because of the complexity introduced by the interplay between NO and CO. *Antioxid. Redox Signal.* 4, 633–637.

INTRODUCTION

HEME OXYGENASE (HO) degrades protoporphyrin IXα, giving rise to carbon monoxide (CO), ferrous iron, and biliverdin IXα, which is subsequently reduced to bilirubin through the action of biliverdin reductase (9, 21, 25). Among the three products of HO activity, CO has been studied extensively as a potential neurotransmitter in the brain (12, 23) and as a vasorelaxant in the liver (18, 20). The latter is based on our quantitative determination of CO production, on the enzyme distribution, and on the following observations in rat microcirculation in the perfused liver: elimination of endogenous CO by zinc protoporphyrin IX (ZnPP), a potent inhibitor of HO, caused an increase in vascular resistance that was repressed by supplementing with CO. When differences in local flow rates between *ex vivo* and *in vivo* systems are considered, it appears reasonable to speculate that local concentrations of CO in and around sinusoidal vessels are no less than 1 μmol/L. To our knowledge, little information has been available as to the quantitative estimation of CO generation in neuronal tissues. Furthermore, whether such a vasodilatory action of CO could also occur in other microvascular systems remains largely unknown.

Reception mechanisms for CO-mediated signaling have not been fully understood. Like those of nitric oxide (NO), effects of CO are thought to be mediated by activation of soluble guanylate cyclase (sGC). Our recent studies, however, have suggested that CO could alter vascular tone in the stimulated liver through cyclic GMP (cGMP)-independent mechanisms involving cytochrome P450 monooxygenases. Because NO shares receptor proteins with CO, the biological actions of CO appear to be influenced not only by cell-specific roles of the receptor proteins, but also by endogenous amounts of NO *in situ*. This article summarizes our current understanding of microvascular actions of CO under physiological and pathological conditions in the liver and attempts to compare them with those in other vascular systems.

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DESIGN OF LIVER TO UTILIZE CO FOR REGULATION OF BLOOD FLOW AND METABOLISM

Two isozymes are considered to play a biologically important role in oxidative degradation of heme. HO-1, the first form of the enzyme discovered, is an inducible protein, and is concentrated in tissues that are exposed to degrading red blood cells and to hemolysis and numerous other toxic perturbations. This isozyme is present in spleen macrophages, a putative major cellular component for destruction of aged red blood cells, and in the reticuloendothelial system involving the liver, where Kupffer cells constitute a major cellular component for the HO-1 expression. HO-1 is induced in the liver when stimulated with endotoxin or ischemia/reperfusion (1). By contrast, HO-2 is constitutively expressed and is known to be highly concentrated in neural tissues (16), testicular germ cells (22), and hepatocytes of rodents (4) and humans (10). Because of spontaneous turnover of hemoglobin (Hb) and other heme proteins in the liver, the HO reaction yields a steady flux of CO into individual sinusoids, being in a range of 0.5–0.7 nmol/min/g of tissue. This amount of CO does not block mitochondrial respiration through cytochrome oxidase; under normoxic conditions, a majority of its prosthetic heme is in the ferric form that does not permit CO binding, yet displaying affinity for NO. However, considering that local concentrations of CO *in vivo* are estimated to be no less than 1 μM, this amount may be sufficient to moderately activate sGC and/or to partially inhibit cytochrome P450 monooxygenases that produce a variety of vasoactive substances as a consequence of arachidonic acid (AA) metabolism.

It should be noted that the liver appears to be designed so as to limit generation of NO in this organ. Although quantitative information on local NO generation in the liver has been highly limited, its flux in this organ seems to be at least 2 orders of magnitude lower than that of CO. Maintaining uniform blood flow through capillary networks requires coupling a mechanism for local detection of the flow to a mechanism for modulating microvascular resistance (24). Microvascular flow in many tissues is regulated by NO. In response to local wall shear stress, endothelial cells produce NO that counteracts the vasoconstriction induced by nerve stimulation or hormones. Many studies, however, have failed to demonstrate a role of NO in modulation of the resistance in the liver under unstimulated conditions (18, 19). This is because sinusoids in the liver exhibit low shear stress due to the minimal pressure gradient between portal and central venules. On the other hand, a unique paracrine mechanism can be envisioned for regulation of sinusoidal flow in the liver through the HO-CO system. Hb in erythrocytes serves as a CO-scavenging system that helps exhalation of the gas in the lung. In poorly perfused sinusoids, locally generated CO would accumulate *in situ* and contribute to sinusoidal relaxation, whereas in those exhibiting excessive flow, CO would be washed out with eventual restoration of basal resistance. Because local CO generation is determined by the rate of heme degradation through the HO reaction, such a feedback mechanism could help recovery of blood flow in the locally damaged sites. These data suggest that CO plays a more important role than NO in regulation of the basal vascular resistance in the liver.

When the liver undergoes stress conditions that cause the release of a variety of vasoconstrictors, inducible NO generation may play a more important role to guarantee an ample blood supply. Even under such circumstances, however, induction of HO-1 seems to counteract unnecessary overproduction of NO. Antagonism of NO by the HO-CO system could involve multiple mechanisms: competition for NADPH between NO synthase (NOS) and HO, blockade of the NOS reaction by CO through its binding to the prosthetic heme, and degradation of the heme moiety by HO enzymes. Such potential inhibitory actions of the HO-CO system should remind us of the fact that the hepatocyte is the locus of the urea cycle where arginine (a substrate for NOS) and citrulline (a by-product of the NOS reaction) are integral components. Under circumstances in which hepatocytes overproduce NO, the efficiency of the urea cycle may be reduced due to a possible shunt between arginine and citrulline in a cytosolic compartment where the inducible NOS is expressed. At the same time, NO could diffuse into the mitochondria and thereby limit their respiration (15). A shunt of this kind is clearly undesirable for the efficient elimination of ammonia, one of the most important functions of this organ.

ROLES OF BASAL CO GENERATION IN REGULATION OF BILE EXCRETION

Eliminating endogenous CO production not only causes an increase in sinusoidal tone, but also stimulates bile acid-dependent bile flow (13). When the isolated rat liver is perfused with taurocholate (30 μM), a major conjugated bile acid in rats, perfusion of ZnPP at a concentration (1 μM) that abolishes detectable levels of CO in the venous perfusate results in ~20% increase in bile output. The time course and extent of this choleretic response are correlated with an increase in vascular resistance. This ZnPP-induced choleresis is cancelled by supplementing CO exogenously, and does not occur when taurocholate is removed from the perfusate. Furthermore, the choleretic response is reproduced by administration of HbO_2 (a ferroheme compound that traps both CO and NO), but not of metHb (a ferriheme form that traps NO, but not CO) (7). These data suggest the important role played by endogenous CO in regulating bile acid-dependent bile output.

CO generated through HO-2 in hepatocytes may also affect bile excretion by modulating the contractility of the bile canaliculus (BC) (14). According to analyses in rat cultured hepatocyte couplets using time-lapse videomicroscopy, BCs contract with a periodicity of ~6 min (11, 14). When endogenous CO production is inhibited by ZnPP, the intervals shorten to 3–4 min and intracellular calcium increases (14). Supplementation of CO at micromolar levels reverses these changes. Interestingly, this reversal effect of CO is not accompanied by an increase in cGMP content (2), suggesting that this action of CO is not mediated through activation of sGC and may require other receptor molecules. Like sGC, cy-

tochrome P450 monooxygenases possess ferroheme to which CO could bind. Indeed, several lines of evidence suggest that CO controls BC contractions through its modulatory action on cytochrome P450-mediated calcium mobilization. Firstly, inhibitors of the monooxygenase reaction, such as clotrimazole or metyrapone, mimic the effect of CO on BC contraction and intracellular calcium mobilization (14). Secondly, micromolar levels of CO partially inhibit the monooxygenase activities in cultured hepatocytes. At present, metabolites of AA that are responsible for calcium mobilization in hepatocytes have not been identified.

EFFECTS OF STRESS-INDUCIBLE CO IN BILE REGULATION

Recent studies in our laboratory have suggested that an increase in CO generation alters bile output and biliary constituents through multiple mechanisms. Distinct from its role in the unstimulated liver, CO generated through the inducible HO-1 appears to restore biliary insufficiency in the endotoxemic liver (7). Such restoration of bile excretion by CO results in part from improvement in heterogenous lobular perfusion through its vasodilatory action. In this case, CO appears to exert its vasodilatory actions by inhibiting cytochrome P450 monooxygenases rather than by activating sGC; the HO-1-dependent overproduction of CO does not induce any notable elevation of the tissue cGMP concentration despite causing marked vasorelaxation (7).

CO-elicited choleresis appears to occur not only through a mechanism involving increased sinusoidal perfusion, but also through a direct effect on hepatocytes. We have recently observed that, depending on its concentration, CO supplementation to the perfused liver results in a biphasic alteration in bile output. At up to 4 μM, CO caused choleresis, whereas concentrations greater than 4 μM led to a decrease in bile flow. The CO-induced increase in bile flow paralleled the increased biliary excretion of bilirubin IXα and glutathione that provide the osmotic driving force for choleresis. On the other hand, addition of CO did not affect the amounts of phospholipids or bile acids in the bile. Such an effect of CO was not observed in the Eisai hyperbilirubinemic rats that spontaneously lack mrp2, an ABC transporter responsible for biliary excretion of bilirubin and glutathione (S. Norimizu and M. Suematsu, unpublished observation). Although detailed mechanisms by which CO facilitates mrp2-mediated transport of bile constituents are largely unknown, such an effect of the HO-derived gaseous mediator could assist in regulating the metabolism of the bile pigment generated through the same reaction. In other words, CO appears to stimulate biliary bilirubin excretion during heme detoxification behind the scenes.

CO: A PARTIAL ANTAGONIST FOR SGC?

Recent investigations *in vitro* have shown that NO and CO activate sGC by distinct mechanisms. NO binds to iron of the prosthetic heme and proceeds to break the proximal His-Fe bond, forming a five-coordinated nitrosyl heme complex. This is thought to result in conformational changes leading to a 100-fold increase in the cGMP generation (6, 17). On the other hand, CO, while binding to the heme of sGC with high affinity, forms a six-cordinated heme complex with the His-Fe bond remaining intact. Consequently, the potency of CO to activate the enzyme is far less than that of NO in many systems, although mechanisms that sensitize sGC to endogenously generated CO may exist (*e.g.,* YC-1) (3).

Because of such a discrepancy in the ability of the two gas molecules to activate sGC, the biological actions of CO could differ depending on the local amounts of NO. Recent studies have provided evidence for such a possibility. Contrary to the prediction that CO and NO might work in tandem and bring about an additive or synergistic reduction in systemic blood pressure, transgenic (Tg) mice overexpressing HO-1 specifically in vascular smooth muscle cells showed a significant increase in systemic blood pressure (5). Furthermore, aortic rings isolated from the Tg mice displayed impaired nitrovasodilatory responses through mechanisms involving CO. This CO-mediated impairment of vasorelaxation appeared to be NO-dependent, whereas sGC *per se* remained intact functionally. It is worth noting that basal cGMP content in aortic segments from the Tg mice was significantly reduced as compared with those from the nontransgenic mice despite increased NO production in Tg mice. Treatment with tin protoporphyrin IX, an HO inhibitor, increased the cGMP contents of Tg aortas to levels similar to those in control rings. On the other hand, treatment of Tg mice with N^{ω}-nitro-L-arginine did not bring about any reduction in the cGMP level, presumably because overproduction of CO provides sufficient stimulation for sGC to maintain its basal activity. These observations led us to hypothesize that CO competes with NO for the heme moiety of sGC and functions as a partial antagonist for the enzyme; that is, CO stimulates the enzyme when NO levels are low (*e.g.,* liver microcirculation), whereas it inhibits the enzyme when NO levels are sufficient (Fig. 1). Considering that chronic exposure of cells and tissues to NO stimulates HO-1 synthesis, the results obtained with the Tg mice could explain why chronic administration of nitrovasodilators leads to resistance to the vasodilatory effects of these compounds.

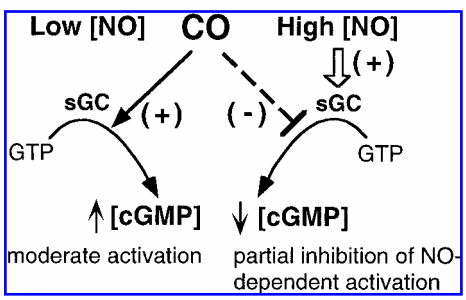

FIG. 1. Double-faced effects of CO on sGC. Action of CO on sGC to produce cGMP could be either facilitative or inhibitory depending on the local NO concentration.

MODULATION OF CYTOCHROME P450 MONOOXYGENASES BY CO

CO may modulate a wide range of organ functions through cytochrome P450-dependent monooxygenase reactions (Fig. 2). Various investigators have recognized the role of the cytochrome P450 monooxygenase pathway in the generation of a novel group of biologically active metabolites. The cyochrome P450 isoenzymes are a superfamily of heme-containing enzymes that serve as terminal electron acceptors of the NADPH-dependent mixed-function oxidase system, which catalyzes the oxidative transformation of endogenous (*e.g.,* fatty acids, steroid, prostaglandins, leukotrienes) and exogenous (*e.g.,* polycyclic aromatic hydrocarbons, anticancer drugs) substrates (8). This enzyme system, in the presence of NADPH and molecular oxygen, is capable of metabolizing AA to a number of oxygenated metabolites. These include four regioisomeric epoxides [5,6-, 8,9-, 11,12-, and 14,15-epoxyeicosatrienoic acids (EET)], which are subsequently hydrolyzed to the corresponding diol derivatives, six regioisomeric *cis-trans* conjugated monohydroxyeicosatetraenoic acids (HETE), and ω and ω-1 alcohol. Thus, biological actions of CO might vary among different organs, and depend on the primary reaction products generated through these cytochrome enzymes.

Our recent experiments using rat cerebral arteries suggest that CO usually acts as a vasoconstrictor in the brain. This is based on the observation that topical application of ZnPP caused dilation of the cerebral arterioles that was reversed by supplementing with CO at micromolar levels. Furthermore, pretreatment with clotrimazole or metyrapone, inhibitors of cytochromes P450, mimicked the vasoconstrictive actions of CO. Because the CO effects were not evident when the preparation was pretreated with the P450 inhibitors, these results suggest that CO could bind to the prosthetic heme of P450 and thereby exert its vasoconstrictive actions (M. Ishikawa, unpublished observation). Such vasoactive properties of CO are obviously opposite of those observed in the liver (7).

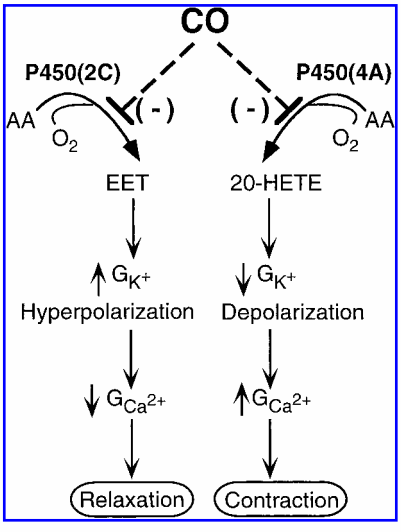

FIG. 2. Inhibitory effect of CO on cytochrome P450 monooxygenases. Action of EET and 20-HETE on membrane K^+ conductance (G_{K+}), membrane potential, membrane Ca^{2+} conductance (G_{Ca+}), and vasomotor tone.

CONCLUDING REMARKS

It has become evident that regulation of HO activity and, therefore, CO production has branched out in multiple directions for a host of physiological processes. The biological activities of the HO-CO system, as well as that of the NOS-NO system, appear to be intimately related to the affinity of the gas molecules for the heme moiety of hemoproteins. Two putative receptor molecules, sGC and cytochromes P450, have been identified among the many hemoproteins and heme-activated enzymes. Although several mechanisms have been postulated to explain the various biological properties of CO, the mutual regulatory interactions between CO and NO noted above prevent us from ascribing, at the present time, simple and individual activities to these gaseous heme ligands, especially *in vivo*. The isolated perfused liver model, however, has unveiled a part of the complicated picture. It is hoped that future investigations will reveal and elucidate the additional layers of complexity.

ABBREVIATIONS

AA, arachidonic acid; BC, bile canaliculus; cGMP, cyclic GMP; CO, carbon monoxide; EET, epoxyeicosatrienoic acids; Hb, hemoglobin; HETE, hydroxyeicosatetraenoic acids; HO, heme oxygenase; NO, nitric oxide; NOS, nitric oxide synthase; sGC, soluble guanylate cyclase; Tg, transgenic; ZnPP, zinc protoporphyrin IX.

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