Carbon monoxide: from silent killer to potential remedy

Nathalie Hill-Kapturczak and Anupam Agarwal
Department of Medicine, Nephrology Research and Training Center, University of Alabama at Birmingham, Birmingham, Alabama

All substances are poisonous, there is none which is not a poison. The right dose differentiates a poison from a remedy.

—Paracelsus

Thoughts that come to mind when the words carbon monoxide (CO) are heard include accidental deaths from malfunctioning home appliances, suicides in closed garages, and assisted suicides (Jack Kevorkian, a.k.a. Dr. Death). In fact, the top 10 sites in a Google search for CO are all related to the toxic effects of this gas. CO is a colorless, tasteless, and odorless gas that, when inhaled, enters the bloodstream and replaces the oxygen on hemoglobin, forming carboxyhemoglobin. Increasing levels of carboxyhemoglobin can result in a wide range of symptoms from mild cognitive impairment including reduction in visual perception and driving performance to more severe effects like headache, weakness, gastrointestinal symptoms, and finally progressive confusion, collapse, and coma. The major exogenous source for CO is the incomplete burning of carbon from solid, liquid, and gaseous fuels. The United States National Ambient Air Quality Standards for CO levels in outdoor air are 9 parts/million (ppm) for 8 h and 35 ppm for 1-h exposure. However, no standards for indoor air CO levels have been agreed upon.

Although the toxicity of CO has been extensively studied, it is now also being explored for its physiological effects and potential therapeutic benefits (9, 19). Since the realization that the poisonous gas, nitric oxide (NO), has a significant biological role in physiology and pathophysiology, CO, which is a structurally similar gas, has gained significant attention as a molecule with many analogous chemical and biological properties (19). Like NO, CO is produced endogenously during cellular metabolism, primarily from the degradation of heme by the heme oxygenase (HO) enzyme system, which comprises two main isoforms, an inducible enzyme, HO-1, and a constitutive one, HO-2 (10). HO-1 is activated in a wide range of injurious settings and serves as an adaptive and protective response (2, 8, 15, 16). The beneficial effects of HO-1 induction are mediated, in large part, through one or more of its reaction products including bile pigments and CO (8, 21). Endogenous CO formation has been measured in several biological systems, and humans have been shown to exhale ~10 ml of CO/day (11).

The intracellular mechanisms for the actions of CO are not completely understood. CO binds to the iron of heme proteins and affects several intracellular signaling pathways, including soluble guanylyl cyclase, mitogen-activated protein kinases (MAPK), particularly p38 MAPK, and the antioxidant enzyme manganese superoxide dismutase (3, 18, 26). CO has been shown to ameliorate inflammation, vascular dysfunction, and transplant rejection in several animal models through its vasodilatory, anti-inflammatory, antiapoptotic, and immunomodulatory properties (reviewed in Ref. 22). Over the last decade, CO has become the subject of intense investigation and is emerging as a potential therapeutic molecule. The clinical use of CO, however, is not without controversy. One major criticism is that while CO administered as a gas is cytoprotective in both in vitro and in vivo cellular and tissue injury models, the concentrations of CO used can lead to hemoglobin saturation, tissue hypoxia, and injury (22, 27).

The recent identification and characterization of CO-releasing molecules (CO-RMs) by Motterlini and colleagues (12) have initiated and will promote further progress in studies of the physiological properties of CO. Most CO-RMs are transition metal-containing carboxyls; however, more recently a boron-based CO-RM (CORM-A1) which does not contain a transition metal has been identified and releases CO at a slower rate compared with transition metal-containing CO-RMs (6, 13). CO-RMs are capable of carrying and delivering CO to biological systems and exert functional effects including blood vessel relaxation, lowering of blood pressure, protection against cardiac and renal ischemia-reperfusion injury, and suppression of endotoxin-induced inflammatory responses (5–7, 23, 28).

In this issue of the American Journal of Physiology-Renal Physiology, Tayem and colleagues (25) have further explored the role of CO, released from a water-soluble, transition metal-containing carboxyl (CORM-3) (4), in cisplatin-mediated renal injury in vitro and in vivo. A major limitation to the anticancer effects of the chemotherapeutic agent cisplatin is its dose-dependent nephrotoxicity, which occurs in about one-third of patients receiving the drug. Previous work has demonstrated that chemical inhibition of HO enzyme activity or genetic deficiency of HO-1 worsens cisplatin-induced renal failure, suggesting that HO-1 has a protective role in this model (1, 24). As HO enzyme activity results in the release of CO and bile pigments, the use of CO-RMs allows for the contribution of CO to be more thoroughly investigated. In this work, LLC-PK1 cells exposed to cisplatin and CORM-3, but not biliverdin, displayed significantly less apoptosis, and this cytoprotective effect was dependent on activation of the cGMP pathway (25). Intraperitoneal administration of CORM-3 but not inactive CORM-3 (iCORM-3) attenuated both structural and functional indexes of renal injury in a rat model of cisplatin nephrotoxicity. CORM-3 treatment even in the presence of tin protoporphyrin, an inhibitor of HO enzyme activity, was able to partially rescue renal function in the cisplatin model (25).

It is possible that a combination of CO with other HO reaction products may further enhance protection. For example, Nakao et al. (14) have recently reported that dual treatment with CO (as an inhaled gas) and biliverdin is superior to either agent alone in a model of ischemia-reperfusion injury in kidney isografts. It would be of interest to evaluate whether CO-RMs alone or in combination with biliverdin would rescue renal
injury in HO-1 knockout mice known to have an increased susceptibility to acute renal injury (17, 20, 24). Nevertheless, the studies by Tayem and colleagues (25) provide a basis for the use of CO-RM as a protective strategy that will be applicable to both ischemia-reperfusion and nephrotoxin-induced acute renal failure. In summary, CO is endogenously formed and has significant physiological functions that could be exploited with the use of CO-RMs as a potential therapeutic agent.

REFERENCES