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Forum Editorial

Emerging Role of Carbon Monoxide in Physiologic and Pathophysiologic States

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ABSTRACT

The discovery of nitric oxide in the 1980s unraveled the novel concept then that an endogenous production of a gaseous substance such as nitric oxide can impart critical physiologic functions in a variety of biological and pathological processes. Interestingly though, we have known for a longer period of time that there exists another gaseous molecule, carbon monoxide (CO), that can be generated endogenously. The heme oxygenase enzyme system generates the majority, if not, all of the endogenous CO. Accumulating data in recent years have lent an intriguing supposition that we need to regard CO beyond the old paradigm that it imparts only toxicity and lethality to organisms. Instead, we need to consider CO, at low physiologic concentration, to play critical physiologic roles in various pathophysiologic states. This forum will review this double-edge sword of CO.
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THE FIRST DETECTION OF A COMBUSTIBLE GAS in the blood was described by Grehant in 1894 (4). This gas was supposed by de Saint Martin and Nicloux to be carbon monoxide (CO) (3, 5). Nicloux and others attempted to show that CO was formed in the body and first asserted that the origins of CO in the body arose via carbohydrate metabolism (6). The proof should have been on the determination of the CO in inspired and expired air simultaneously combined with the measurement of carboxyhemoglobin (COHb) in the blood. Unfortunately, these measurements were not possible with the methods available before 1940. With the onset of the industrial revolution and the invention of the combustion engine, it became urgent to work out methods to measure and determine COHb because it was rapidly discerned that CO levels in the atmosphere were dangerous. It was discovered very early on that the COHb levels in the blood reflected the CO concentration in the alveolar air determined using rebreathing techniques. It was not until 1949 that Sjorstrand, and later Coburn, discovered that endogenously produced CO arose from the degradation of hemoglobin released from senescing erythrocytes (1, 2, 9). CO measurements via COHb or by rebreathing techniques in the 1970s were used by clinicians to determine the life span of erythrocytes and the rate of heme turnover in their patients. Greater than 75% of CO produced in normal humans arises from erythrocyte turnover generated as a by-product of heme metabolism.

In 1969, the source of endogenous CO was discovered. Tenhunen *et al.* described and characterized heme oxygenase as the enzyme responsible for breaking down heme in the body, demonstrating that heme catalysis resulted in the subsequent release of CO and free iron as by-products (10). This enzymatic cleavage also resulted in the production of biliverdin, which was subsequently found to be rapidly converted to bilirubin via biliverdin reductase (7). Certainly the products of heme oxygenase activity have been observed for decades, if not centuries, because unlike most biochemical functions, heme catalysis is color-coded and readily observable. For instance, a hematoma arising from a blow to the body is initially black—the color of heme. Over a number of days, the color changes to green—the color of biliverdin—and finally to yellow—the color of bilirubin. Use of these visual observations can be dated back to the times of Hippocrates, when patients with liver disease presented as hyperbilirubinemic and were recognized because their skin was yellow in color. The generation of CO would also generate a pink skin hue as it bound tightly to hemoglobin.

Similarly, the presence of CO has also been observable well before there were scientific "instruments" by which to test the atmosphere. With the advent of fire, it is not hard to imagine that primitive man, taking refuge in caves, brought their fire inside and learned rapidly that when some co-dwellers did not survive the night, they should be sure next

time to extinguish the flames lest they not awaken to greet the following day. Perhaps they recognized that if they began to turn bright red (from CO's binding to hemoglobin) it was time to get outside for some fresh air. And thus the first CO monitor and/or spectrophotometric assay was created [adapted from Penney (8)].

This forum will address many aspects of CO, including the known toxicity and biochemistry [reviewed by Piantadosi (15)] of CO and recent findings demonstrating antiinflammatory [reviewed by Otterbein (12)] and antiapoptotic effects of CO [reviewed by Soares *et al.* (17)] in a number of inflammatory models in rodents that begin to implicate CO as a functional biological mediator in numerous organ and tissue systems. The role of CO in the cellular response to hypoxic stress [reviewed by Kourembanas (7)], its cross talk with nitric oxide [reviewed by Hartsfield (5)], and signaling network in the central nervous system [reviewed by Koehler and Traystman (6)] represent key elements to the functional role of CO in pathophysiologic states. Clinical investigators have also begun to use CO analysis of the exhaled breath as a biomarker related to increase in levels of oxidative stress resulting in increased implications of CO in human diseases [reviewed by Morse and Sethi (9)]. The analytical detection of CO has also improved both *in vitro* and *in vivo* [reviewed by Marks *et al.* (8)], with potential use in clinical scenarios. These reviews most certainly represent the early segments of a long and fruitful journey of CO research and knowledge.

ABBREVIATIONS

CO, carbon monoxide; COHb, carboxyhemoglobin.

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