EDITORIAL

Carbon Monoxide: Two Sides to the Same Coin

Diego Castillo and Pere Casan

Unitat de Funció Pulmonar, Departament de Pneumologia, Hospital de la Santa Creu i Sant Pau, Facultat de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain.

The Old Side to Carbon Monoxide

Carbon monoxide is the product of the incomplete combustion of organic matter. When any carbon-containing fuel burns with sufficient oxygen, the end product is carbon dioxide and water. When the same chemical reaction takes place with insufficient oxygen, however, the end product is carbon monoxide.

When oxygen enters the lungs, it binds to hemoglobin and is delivered to tissues to be metabolized by mitochondria. Hemoglobin and oxygen form oxyhemoglobin, a molecule that is a model of elegance, harmony, and even beauty. As one physiology professor is reported to have said "we can see the poetry of creation in the hemoglobin molecule."

Hemoglobin, however, also binds to other elements in other ways. With carbon monoxide, it forms a molecule called carboxyhemoglobin, which is a dysfunctional form, much like sulfhemoglobin and methemoglobin. Normal carboxyhemoglobin levels are between 1% and 2% of total blood volume, and are mainly the result of endogenous production. The body has been said to produce 0.4 mL of carbon monoxide every hour. Sjostrand's[1] classical study showed that most endogenous carbon monoxide is an end product of heme catabolism.[2] Although endogenous carbon monoxide is mostly bound to hemoglobin, it also has an affinity for myoglobin and cytochromes. The heme component of hemoglobin is converted by both the inducible and constitutive forms of the heme oxygenase enzyme to equal proportions of biliverdin, iron, and carbon monoxide. The biliverdin is converted to bilirubin, the iron is recycled, and the carbon monoxide binds to hemoglobin, for which it has a high affinity, to form carboxyhemoglobin. Elevated levels of endogenous carboxyhemoglobin are mainly due to hemolytic anemia, although slightly raised levels may also be seen in serious inflammatory diseases.

Correspondence: Dr. D. Castillo.
Unitat de Funció Pulmonar. Departament de Pneumologia. Hospital de la Santa Creu i Sant Pau. Facultat de Medicina.
Sant Antoni M. Claret, 167. 08025 Barcelona. España.
E-mail: dcastillo@santpau.es

Manuscript received November 15, 2005. Accepted for publication November 22, 2005.

Evidently, carbon monoxide can also enter the blood stream from exogenous sources via inhalation. The main sources of ambient carbon monoxide are vehicle and heating emissions in large cities, although faulty gas burning appliances in the home can also be to blame. The normal background level of carbon monoxide in the home is 10 parts per million parts (ppm) of air, although exposure levels can be chronically higher in smokers (up to 400 ppm to 500 ppm in inhaled air during smoking) and acutely higher in cases of poisoning (usually suicide attempts). It is estimated that carbon monoxide is responsible for over 50% of fatal poisonings in the world.[4] Because carbon monoxide has such a high affinity for hemoglobin (200-250 times greater than that of oxygen), it can drastically reduce the blood's capacity to carry oxygen and cause serious health effects. Carbon monoxide poisoning symptoms range from dizziness and headache to death.

A New Side to Carbon Monoxide

Carbon monoxide is not just a toxic gas, however. A number of recent studies have revealed that it is a powerful signaling molecule involved in several physiological processes.

Heme oxygenase was discovered in 1968.[5] Initially this enzyme served to characterize the heme degradation process, and its possible role in other biochemical processes was not contemplated until the early 1980s. It has since been described as a brain neurotransmitter,[6-8] a platelet aggregation inhibitor,[9] a cardiovascular tone modulator,[10-12] a gastrointestinal modulator,[13] an inhibitor of uterine contraction during pregnancy,[14] and a regulator of pancreatic islet hormone secretion.[15]

It is heme oxygenase's ability to protect against injury,[16-18] however, that has attracted the most interest in respiratory medicine. High levels of heme oxygenase-1 and carbon monoxide, measured in both bronchoalveolar lavage specimens and exhaled air, have been reported in animal models with acute lung injury (acute respiratory distress syndrome).[19-21] In a study of intensive care unit patients with acute respiratory distress syndrome, Mumby and colleagues[22] found that heme oxygenase-1 levels in bronchoalveolar lavage

specimens and/or lung tissue specimens were higher in the study group than in the control group. The mechanism by which heme oxygenase-1 provides cytoprotection via the production of carbon monoxide is highly complex and several hypotheses have been proposed. In vitro findings suggest that it may be related to its ability to reduce apoptosis, protein oxidation, and lipid peroxidation.[23] Carbon monoxide has also been attributed similar protective effects against apoptosis[24] as well as the ability to modulate inflammatory activity by inhibiting the expression of proinflammatory cytokines and the overproduction of anti-inflammatory cytokines (mainly interleukin).[25] Since Otterbein and colleagues[26] first used heme oxygenase-1 in vivo in animal models to successfully protect against acute lung injury, a number of other in vivo studies have corroborated their claim that heme-oxygenase-1 might have beneficial effects.[27-29] Subsequent studies focusing on hypoxia-induced changes in the pulmonary vasculature have suggested that heme oxygenase-1 might play a preventive role in hypoxia-induced inflammation, pulmonary hypertension, and hypertrophy of vascular smooth muscle.[30-31] While these particular studies testify to the beneficial effects of heme oxygenase-1 and carbon monoxide, the literature contains many contradictory reports.[32-34] The debate on the clinical application of these molecules is therefore far from over and has undoubtedly been fueled by the fact that carbon monoxide is highly toxic. Its addition to the therapeutic arsenal in the near future is therefore unlikely.[35] Moreover, although results to date have been contradictory, carbon monoxide has also been attributed a major role in controlling breathing in the presence of hypoxia.[36,37]

These findings indicate that carbon monoxide plays an unexpectedly important role as a cellular mediator. Of particular interest is the fact that in many ways carbon monoxide is similar to nitric oxide, a molecule that has been widely studied from pathophysiologic, diagnostic, and therapeutic perspectives and that has even led to a Nobel Prize. Why not, then, envisage an equally brilliant future for carbon monoxide?

The New and the Old

One certainty is that the small amount of carbon monoxide stored in our bodies–that tiny amount of carboxyhemoglobin that is detected in arterial blood gas results and normally never exceeds 1.6% of total blood volume[38]–is much more than a mere indicator of whether a patient is still smoking or not (the old side of carbon monoxide). This molecule now also shows promise as a biological marker that contributes, through its involvement in a range of key cellular activities, to the correct functioning of many biological processes; in the future it may well be used as a marker of various abnormal processes (the new side).

Juxtaposing the old and the new will provide us with a different lens and a new perspective, and help us recognize which pages of history need to be rewritten. Respiratory medicine physicians need to remain alert to this new facet of carbon monoxide and overcome the idea that carboxyhemoglobin is always an enemy to be defeated.

REFERENCES

1. Sjostrand T. Endogenous formation of carbon monoxide in man under normal and pathological conditions. Scan J Lab Invest. 1949;1:201-14.
2. Corburn RF, Williams WJ, Foster RE. Effect of erythrocyte destruction on carbon monoxide production in man. J Clin Invest. 1964;43:1098-103.
3. Necheles T, Rai U, Valaes T. The role of hemolysis in neonatal hyperbilirubinemia as reflected in carboxyhemoglobin values. Acta Paediatr Scand. 1976;65:361-7.
4. Raub J, Mathieu-Nolf M, Hampson N, et al. Carbon monoxide poisoning–a public health perspective. Toxicology. 2000;145:1-14.
5. Tenhunen R, Marver HS, Schmid R. The enzymatic conversion of heme to bilirubin by microsomal heme oxygenase. Proc Natl Acad Sci. 1968;61:748-55.
6. Verma A, Hirsch DJ, Glatt CE, et al. Carbon monoxide: a putative neural messenger. Science. 1993;259:381-4.
7. Maines MD. Carbon monoxide: an emerging regulator of cGMP in the brain. Moll Cell Neurosci. 1993;4:389-97.
8. Ingi T, Cheng J, Ronnett GV. Carbon-monoxide: an endogenous modulator of the nitric oxide-cyclic GMP signaling system. Neuron. 1996;16:835-42.
9. Wagner CT, Durante W, Christodoulides N, et al. Hemodynamic forces induce the expression of heme oxygenase in cultured vascular smooth muscle cells. J Clin Invest. 1997;100:598-96.
10. Mortterlini R, Gonzales A, Foresti R, et al. Heme oxygenase-1-derived carbon monoxide contributes to the suppression of acute hypertensive responses in vivo. Circ Res. 1998;83:568-77.
11. Sammut IA, Foresti R, Clark JE, et al. Carbon monoxide is a major contributor to the regulator of vascular tone in aortas expressing high levels of haeme oxygenase-1. Br J Pharmacol. 1998;125:1437-44.
12. Mortterllini R, Clark JE, Foresti R, et al. Carbon-monoxide-releasing molecules: characterization of biochemical and vascular activities. Circ Res. 2002;90:17-24.
13. Watkins CC, Boehning D, Kaplin AI, et al. Carbon monoxide mediates vasoactive intestinal polypeptide-associated nonadrenergic/noncholinergic neurotransmission. PNAS. 2004;101:2631-5.
14. Acevedo CH, Ahmed A. Hemeoxygenase-1 inhibits human myometrial contractility via carbon monoxide and is upregulated by progesterone during pregnancy. J Clin Invest. 1998;101:949-55.
15. Henningsson R, Alm P, Ekström P, et al. Heme oxygenase and carbon monoxide: regulatory roles in islet hormone release. Diabetes. 1999;48:66-76.
16. Choi AM, Alam J. Heme oxygenase-1: function, regulation, and implication of a novel stress-inducible protein in oxidant-induced injury. Am J Respir Cell Moll Biol. 1996;15:9-19.
17. Villar J, Ribeiro SP, Mullen JB, et al. Induction of the heat shock response reduces mortality rate and organ damage in a sepsis-induced acute lung injury model. Crit Care Med. 1994;22:914-21.
18. Maines MD. Heme oxygenase: function, multiplicity, regulatory mechanisms, and clinical applications. FASEB J. 1988;2:2557-68.
19. Camhi SL, Alam J, Otterbein L, et al. Induction of heme oxygenase-1 gene expression by lipopolysaccharide is mediated by AP-1 activation. Am J Respir Cell Mol Biol. 1995;13:387-98.
20. Liu HL, Zhao JY, Chen L. Changes of carbon monoxide, nitric oxide levels and heme oxygenase system in acute respiratory distress syndrome induced by oleic acid. Zhonghua Yu Fang Yi Xue Za Zhi. 2004;38:240-3.
21. Zegdi R, Fabre O, Lila N, et al. Exhaled carbon monoxide and inducible heme oxygenase expression in a rat model of postperfusion acute lung injury. J Thorac Cardiovasc Surg. 2003;126:1867-74.

22. Mumby S, Upton RL, Chen Y, et al. Lung heme oxygenase-1 is elevated in acute respiratory distress syndrome. Crit Care Med. 2004;32:1130-5.
23. Suttner DM, Sridhar K, Lee CS, et al. Protective effects of transient HO-1 overexpression on susceptibility to oxygen toxicity in lung cells. Am J Physiol. 2000;1999;276:L443-L51.
24. Otterbein LE, Otterbein SL, Ifedigbo E, et al. MKK3 mitogenactivated protein kinase pathway mediates carbon monoxide-induced protection against oxidant-induced lung injury. Am J Pathol. 2003;163:2555-63.
25. Inoue S, Suzuki M, Nagashima Y, et al. Transfer of heme oxygenase 1 cDNA by a replication-deficient adenovirus enhances interleukin 10 production from alveolar macrophages that attenuates lipopolysaccharide-induced acute lung injury mice. Hum Gene Ther. 2001;12:967-79.
26. Otterbein L, Sylvester SL, Choi AM. Hemoglobin provides protection against lethal endotoxemia in rats: the role of heme oxygenase-1. Am J Respir Cell Mol Biol. 1995;13:595-601.
27. Otterbein LE, Mantell LL, Choi AMK. Carbon monoxide provides protection against hyperoxic lung injury. Am J Physiol. 1999;276:L688-L94.
28. Sarady JK, Otterbein SL, Liu F, et al. Carbon monoxide modulates endotoxin-induced production of granulocyte macrophage colony-stimulating factor in macrophages. Am J Respir Cell Mol Biol. 2002;27:739-45.
29. Taylor JL, Carraway MS, Piantadosi CA. Lung-specific induction of heme oxygenase-1 and hyperoxic lung injury. Am J Physiol. 1998;274:L582-L90.
30. Minamino T, Christou H, Hsieh CM, et al. Targeted expression of heme oxygenase-1 prevents the pulmonary inflammatory and vascular responses to hypoxia. Proc Natl Acad Sci U S A. 2001;98:8798-803.
31. Fujita T, Toda K, Karimova A, et al. Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression of fibrinolysis. Nat Med. 2001;7:598-604.
32. Dennery PA, Visner G, Weng YH, et al. Resistance to hyperoxia with heme oxygenase-1 disruption: role of iron. Free Radiac Biol Med. 2003;34:124-33.
33. Clayton CE, Carraway MS, Suliman HB, et al. Inhaled carbon monoxide on acute lung injury in rats. Am J Physiol Lung Cell Mol Physiol. 2001;281:L949-L57.
34. Ghosh S, Wilson MR, Choudhury S, et al. Effects of inhaled carbon monoxide on acute lung injury in mice. Am J Physiol Lung Cell Mol Physiol. 2005;288:L1003-L9.
35. Jin Y, Choi AMK. Cytoprotection of heme oxygenase-1/carbonmonoxide in lung injury. Proc Am Thorac Soc. 2005;2:232-5.
36. Prabhakar NR. Endogenous carbon monoxide in control of respiration. Respiratory Physiology. 1998;114:57-64.
37. Paro FM, Steiner AA, de Paula PM, et al. Central heme oxygenase-carbon monoxide pathway in the control of breathing under normoxia and hypoxia. Respir Physiol Neurobiol. 2002;130:151-60.
38. Casan P, Miralda RM, Sanchis J. Concentración de carboxihemoglobina (COHb) en una población urbana de pacientes no fumadores. Arch Bronconeumol. 1994;30:517-8.