Acute CO poisoning is known to produce both immediate and delayed cellular injury to various regions of the brain. The classical teaching is that CO causes tissue hypoxia (1). It binds very tightly to heme centers of respiratory proteins such as hemoglobin and cytochrome c oxidase, outcompeting O2 (1, 2). Accordingly, CO decreases both the O2 carrying capacity of the blood and O2 utilization by the mitochondria. Toxic exposure to CO also produces an oxidative stress which is secondary to inhibiting mitochondrial respiration: reactive oxygen species (ROS) are released that cause oxidative damage to proteins, lipids, and nucleic acids. In this issue of The Journal Ischiropoulos and co-workers (3) expand on this theme. They describe a possible connection between CO toxicity and increased nitric oxide (NO) production in the brain. Ischiropoulos et al. find that CO exposure leads to perivascular deposits of nitrotyrosine, a marker of peroxynitrite (OONO−). Peroxynitrite is the oxidant formed on NO/superoxide reaction. Thus, NO generation also diverts O2− away from mitochondria. The measurement of peroxynitrite poses a significant problem as it is short-lived. Evidence for its production in vivo rests largely on detection of nitrotyrosine, a stable product of its reaction with proteins. The specificity of this assay in tissues in unknown and its interpretation is complicated by the low-yield of nitrotyrosine under physiological conditions; most of the peroxynitrite is consumed in other reactions. Limitations notwithstanding, nitrotyrosine appears to be a useful marker of NO-related oxidative stress—much as malondialdehyde is a marker of O2−-related stress—to which peroxynitrite undoubtedly contributes. Indeed, extensive protein nitration occurs in a variety of inflammatory diseases including atherosclerosis, ARDS, and arthritis. The immunoradiochemical assay developed by Ischiropoulos and co-workers to quantify nitrotyrosine (3) is an important step forward. The demonstration of an increase in oxidative stress, however, should not be confused with causality.

How does CO increase levels of nitrotyrosine? By binding to heme irons in proteins, CO may competitively displace NO which is normally bound by virtue of its higher affinity. By disrupting mitochondrial electron transport, it will also promote escape of O2−. The simultaneous liberation of NO and O2− would generate OONO−. Such displacement of NO (or release of O2−) from blood-borne hemoglobin might explain the perivascular predominance of nitrotyrosine. Additionally, OONO− formation could arise from activation of N-methyl-D-aspartate receptors when damaged brain cells release glutamate. CO, NO, and O2 may further cycle to exacerbate radical damage (7).

Is OONO− causal in brain poisoning by CO? In weighing the role of NO/O2−, one should not forget that O2− is inevitably displaced from hemes before NO and that aerobic metabolism is inhibited before O2− is released from mitochondria. Accordingly, nitrotyrosine is more likely to be a marker of the lost capacity of hemoglobin to carry O2− or to reverse CO hypoxia by dilating blood vessels. In the final analysis, Ischiropoulos et al. increase our understanding of the biochemical events associated with CO poisoning, but questions regarding the role of NO/O2− remain.

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References


