Carbon Monoxide Protects Against Ventilator-Induced Lung Injury via PPAR-γ and Inhibition of Egr-1.

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Abstract:
Researchers from Pittsburgh, Freiburg, and Boston find that inhaled CO (250 ppm) protects anesthetized mice from lung injury by high-volume positive pressure ventilation via tracheostomy tube (12 ml/kg for up to 8 h). The tidal volumes, about twice those of unperturbed mice, elicited histologically obvious damage and the release of protein and white cells into alveoli. Interleukin-1ß, monocyte chemotactic protein-1, macrophage inflammatory protein-1ß, and heat shock protein-70 appeared in the lung tissue. All the changes were substantially blocked by exogenous CO.

An early change was the increased expression of a pro-inflammatory gene-transcription regulator called “early growth response-1.” CO blocked the induction of the regulator, and mice genetically deficient in the regulator were resistant to high-volume-ventilation lung damage.

The benefits of CO were blocked by GW9662, an inhibitor of an anti-inflammatory gene-transcription regulator called “peroxysome proliferator-activated receptor-γ.” In cultured macrophages, CO increased levels of that vexingly named factor. Anti-inflammatory action of CO may involve up-regulation of that factor, which then blocks expression of early growth response-1.

The receptor which actually binds CO and triggers its anti-inflammatory action is not identified. However, since the transcription of DNA into RNA is involved in CO action, the receptor may prove to be located in the cell nucleus.

Comments:
By means of the newly invented spectroscope, Claude Bernard established in the 1840s that CO competes with O2 for hemoglobin. That was arguably the first molecular mechanism to be shown for a poison. However, the mechanism is more subtle than was first proposed. One molecule of CO not only displaces one O2 from the hemoglobin tetramer; it also tightens O2 binding to the three other sites, inhibiting O2 release to tissues. Furthermore, other heme-proteins react with CO. For instance, CO reacts with the heme of the terminal cytochrome of the mitochondrial electron transport chain, thus blocking oxidative phosphorylation. Otto Warburg thus used CO as a tool to establish cytochrome a3 as the major O2-consuming enzyme of cellular respiration (Nobel prize, 1931). CO was viewed strictly as a poison until 1949, when Torgny Sjöstrand found that it is normally produced in humans during conversion of heme into iron and bilirubin by heme oxygenase.

Keen interest in the physiology and therapeutic pharmacology of CO was prompted by discovery that another endogenously produced “toxic” gas, NO, is of great importance (1998 Nobel to Furchgott, Ignarro, and Murad). Though clinicians administer NO to patients, CO may not likewise prove to become a clinical drug. However, CO demonstrates that ventilator-induced lung injury is remarkably susceptible to pharmacological control. Furthermore, our bodies may treat themselves with CO, in that heme oxygenase-1 was induced (albeit “not enough”) by high-volume ventilation.