The Therapeutic Potential of Gaseous Autacoids

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Editorial

Carbon monoxide (CO) and hydrogen sulfide (H₂S) are small, lipid-soluble gaseous autacoids that modulate numerous physiological processes. Historically, both gases were considered highly noxious environmental hazards having well-defined modes of toxicity: CO binds avidly to hemoglobin reducing the oxygen-carrying capacity of the protein leading to tissue hypoxia while H₂S is a potent mitochondrial poison that blocks cellular respiration. Surprisingly, research conducted in the past couple of decades discovered that CO and H₂S are produced endogenously by mammalian cells and serve as important signaling molecules in the nervous, inflammatory, and cardiovascular systems. Recent experimental studies indicate that these gases act as vasodilators and elicit broad-spectrum anti-inflammatory, antioxidant, growth-regulatory, and cytoprotective effects in animal models of hypertension, inflammation, sepsis, atherosclerosis, transplantation, and ischemia-reperfusion injury [1-4]. These preclinical findings underscore the wide-ranging therapeutic potential of CO and H₂S, and offer novel translational opportunities in treating multiple human diseases.

CO is a colorless, tasteless, odorless gas that is produced primarily from the degradation of heme by a family of enzymes known as heme oxygenase (HO). Molecular cloning identified three isoforms of HO. HO-1 is a ubiquitously distributed and highly inducible isoform that functions in an adaptive manner to limit tissue injury, largely through the release of bile pigments and CO. HO-2 is a constitutively expressed isozyme that is activated by calcium/calmodulin and plays an important role in neurotransmission. A third isoform, HO-3, is nearly devoid of activity and likely represents a pseudogene derived from the HO-2 transcript. In contrast to CO, H₂S is a colorless but flammable gas with the characteristic odor of rotten eggs. H₂S is generated from cysteine by the action of three enzymes: cystathionine-β-synthase (CBS), cystathionine-γ-lyase (CSE), and 3-mercaptoppyruvate sulfur transferase (3-MPST). These enzymes exhibit selective tissue distribution with CBS and 3-MPST responsible for a majority of H₂S synthesis in the central nervous system while CSE, a calcium/calmodulin-sensitive enzyme, is the predominant source in the cardiovascular system. However, H₂S is also formed non-enzymatically from various sulfur-containing compounds. Interestingly, reciprocal regulatory interactions between gaseous autacoids have been identified that may influence their biological activities. In particular, H₂S may stimulate the synthesis of CO by inducing the expression of HO-1 while physiologically relevant concentrations of CO inhibit H₂S production by blocking the activity of CBS [5,6]. Significant cross-talk between these gases and nitric oxide (NO) is also observed. NO stimulates HO-1 gene transcription and CO synthesis whereas CO represses NO formation by attenuating nitric oxide synthase activity [7,8]. Complex functional interactions between NO and H₂S have also been reported with H₂S either amplifying or attenuating the biological actions of H₂S [9]. In addition, NO increases CSE activity and expression while low concentrations of H₂S have been shown to enhance the release of NO.

CO and H₂S elicit many similar physiological actions that may underlie the salutary profile of these gases in various pathological states. Both CO and H₂S are able to preserve blood flow and blood pressure by dilating blood vessels. They also regulate cell growth and death by influencing the expression or activity of proteins that comprise the cell cycle and apoptotic machinery, respectively. In addition, CO and H₂S repress mitochondrial respiration by blocking cytochrome c oxidase activity. Both gases also evoke antioxidant effects by inducing the expression of antioxidant genes and, in the case of H₂S, by directly reacting with free radicals. Moreover, both CO and H₂S possess potent anti-inflammatory properties. However, the molecular mechanism by which these autacoids achieve these effects can differ between the two gases. CO is a relatively stable gas that reacts exclusively with reduced transition metals in metalloenzymes. The interaction of CO with metal centers in heme proteins causes conformational changes in protein structure, which impacts their enzymatic activity in a positive or negative manner. For example, the binding of CO to the heme moiety of soluble guanylate cyclase activates the enzyme leading to a rise in intracellular cGMP levels and vasodilation [10]. In contrast, the binding of CO to cytochrome c oxidase inhibits enzymatic activity and this underlies the anti-inflammatory actions of the gas [11]. Like CO, H₂S also binds to specific metal groups in enzymes. However, unlike CO, H₂S is chemically reactive and directly interacts with free radicals to form hydrogen sulfide. In addition, sulfide reacts with disulfide or sulphydryl groups to generate persulfides. Importantly, H₂S can modify protein function via the electrophoretic addition of H₂S to specific target cysteine residues. In this respect, the ability of H₂S to dilate blood vessels does not involve the activation of soluble guanylate cyclase but rather the opening of ATP-sensitive potassium channels following the sulphydration of a single cysteine residue [12]. In addition, the sulphydration of nuclear factor kappa-light chain enhancer of activated B cells (NF-κB) by H₂S contributes to its anti-apoptotic actions [13]. The sulphydration of proteins by H₂S represents a new and potentially widespread signaling mechanism by which this molecule regulates cell function.

Several strategies aimed at exploiting the therapeutic potential of CO and H₂S are currently under investigation. Inhalation of CO has proven highly effective in animal models and initial clinical studies indicate that acute, episodic inhalation of low concentrations of CO is well tolerated, safe, and of potential benefit to patients with chronic obstructive pulmonary disease [14]. However, further studies are needed to confirm the safety and efficacy of CO inhalation in treating human lung disease. While administration of CO by inhalation is well-suited for the treatment of respiratory disorders, inhalation of CO at doses required to achieve therapeutically effective concentrations of the gas in peripheral tissues may be limited by the high affinity of
hemoglobin for CO in the circulation and the development of systemic hypoxia. The use of prodrugs, such as methylene chloride, provides an alternative vehicle for the systemic administration of CO. Oral ingestion of methylene chloride results in the release of CO secondary to its metabolism by cytochrome P450 isozymes. However, there are serious concerns with toxicity related to the use of this compound. A more promising approach in delivering CO involves the use of CO-releasing molecules (CORMs) that liberate CO under physiologic conditions. Numerous CORMs have been synthesized with various solubility and release kinetics and their biological activity corroborated in diverse experimental settings [2]. These compounds allow for a more controlled release of CO and may elevate local levels of CO without significantly increasing carboxyhemoglobin levels. In addition, the design of tissue-selective CORMs may permit disease-specific targeting of CO.

The development of sulfide-based therapeutics is in its infancy but it also relies on the use of H$_2$S gas, H$_2$S-releasing compounds, and prodrugs. Inhalation of H$_2$S has been used successfully in animal studies but requires testing in the clinic [15]. However, concerns related to the toxicity and reactivity of H$_2$S gas tempers enthusiasm for such an approach. Instead, the development of liquid stable forms of sulfides along with H$_2$S-donor drugs is under active exploration. The attachment of a sulfide-releasing moiety to existing drugs in order to increase the potency and/or reduce the side-effects of the parent compound has proven efficacious in preclinical animal models of inflammation and is under evaluation for a large number of off-patent drugs [16]. The employment of prodrugs that induce the production of sulfide by endogenous metabolic pathways provides another feasible strategy in administering H$_2$S. In fact, the biologically active component of garlic, S-allylcysteine, elicits cardiovascular protective effects via its ability to generate sulfide, suggesting a possible dietary approach in delivering H$_2$S [17].

In conclusion, emerging data on the biological effects of CO and H$_2$S strongly support the development of gaseous autocoid-based therapeutics. The use of inhaled gas, donor molecules, and prodrugs provide viable options for delivering CO or H$_2$S. Future pharmacokinetic, pharmacodynamic, and toxicological studies are needed to establish safe and optimal delivery platforms for these gases. While the advancement of pharmaceutical applications based on CO and H$_2$S will provide novel therapeutic opportunities in treating disease, the unique chemical properties of these gases present challenges in harnessing their therapeutic potential.

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References