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Review

Emerging role of carbon monoxide in regulation of cellular pathways and in the maintenance of gastric mucosal integrity

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ABSTRACT

Heme oxygenase (HO) catalyzes the degradation of toxic free heme to the equimolar amounts of biliverdin, Fe^{2+} and concurrently releases of carbon monoxide (CO). CO is nowadays increasingly recognized as an important signaling molecule throughout the body that is involved in many physiological processes and shows multidirectional biological activity. Recent evidence indicates that CO exhibits the anti-inflammatory, anti-proliferative, anti-apoptotic, anti-aggregatory and vasodilatory properties. The cellular mechanisms underlying the activity of CO involve stimulation of cGMP-dependent signaling pathway and large conductance calcium activated K^+ channels, the activation of mitogen-activated protein kinases and the nuclear factor k-light chain-enhancer of activated B cells transcription factor pathway. Stimulation of endogenous CO production by HO inducers or the inhalation of CO or the delivery of this gaseous molecule by novel pharmaceutical agents have been found in experimental animal models to be promising in the future therapy of various diseases. CO appears to act as a significant component of the complex mechanism of gastrointestinal (GI) mucosal defense. This gaseous molecule plays an important role in diabetic gastroparesis, prevention of the upper GI mucosal damage, post-operative ileus and the healing of ulcerative colitis. This review focuses on the better understanding mechanisms through which CO contributes to the mechanism of protection, resistance to injury and ulcer healing. It is becoming apparent that the pleiotropic effect of this molecule may increase clinical applicability of CO donors and their implementation in many pharmacological research areas, pharmaceutical industry and health-care system.

Contents

1. Endogenous carbon monoxide (CO) production by heme oxygenase (HO)

As demonstrated for the first time in the early 1950 by Torgny Sjöstrand small amounts of CO are continuously produced in

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mammalian tissues [1]. In the late 1960, Tenhunen et al. have discovered microsomal HO enzyme implicating its importance in the heme-dependent CO production [2]. The rate of endogenous CO production in human body is about 16,4 μmol/h which corresponds to more than 500 μmol CO per day [3–5]. About 86% of the endogenously produced CO arises from heme degradation, however, CO may also derive from heme-independent sources such as lipid peroxidation, autooxidation, photooxidation and cytochrome P450-dependent xenobiotics metabolism [6–8].

Three distant, mammalian isoforms of HO have been described, but only HO-1 and HO-2, encoded by different genes, have been shown to be biologically active [9]. HO-3, sharing approximately 90% sequence identity with HO-2, has exclusively been discovered in rat brain [10,11]. Both, HO enzymes catalyze the α-specific oxidative cleavage of the heme ring to yield equimolar amounts of biliverdin, Fe^{2+} and CO. This reaction requires molecular oxygen, NADPH and NADPH-cytochrome P450 reductase for providing reducing equivalents [12].

The family of HO enzymes is an essential component of the smooth endoplasmic reticulum in spleen, liver and kidney being involved in turnover of Hb released from senescent erythrocytes, regulation of hemeprotein level and the cellular protection against toxic effect of intracellular free heme [13,14].

The HO-1 (32 kDa) isoform, a stress protein also known as heat shock protein-32 (HSP-32), is expressed at undetectable or very low levels in a majority of body tissues, except for spleen where HO-1 is constitutively and highly expressed. However, HO-1 expression may be induced by a wide range of stressful stimuli including oxidative stress, ultraviolet A radiation, bacterial lipopolysaccharide (LPS), heavy metals, pro-inflammatory cytokines, nitric oxide (NO) and its substrate- heme [6,15,16]. The induction of HO-1 is considered to be an adaptive mechanism for maintaining cellular homeostasis. Recent studies have identified nuclear translocation of HO-1 following proteolytic cleavage [17]. Even though nuclear localization of HO-1 has been attributed to reduction of enzyme activity, HO-1 is also involved in the mechanism activation of transcription factors in response to oxidative stress [18]. Human HO-1 deficiency has been associated with the growth retardation, hemolysis, nephritis and early death [19,20].

In contrast to HO-1 enzyme known as an inducible isoform, the HO-2 (36 kDa) is constitutive isoform of enzyme with the highest expression being detected in the brain and testes [14]. The heme catalytic domains, being a sequence of 24 amino acid residues, have been identified in both HO-1 and HO-2 enzymes [21]. However, the HO-2 has possessed of two heme regulatory motifs, which are absent in HO-1 structure. This may suggest additional biological functions of HO-2 despite its role in heme degradation process [10,22,23]. For instance, a significant role of HO-2 against neuronal damage has been demonstrated in HO-2 deficient mice and *in vivo* models of ischemic injury [24].

2. Toxicity of exogenous CO

Since years, CO which is a low-molecular-weight diatomic molecule is also conventionally recognized as poisonous gas produced by partial combustion of carbon-based fuels, including gas, oil, charcoal and wood [25]. Due to its invisibility and odourlessness, CO intoxication can evoke fatal health consequences hence being recognized as a "silent killer". The first study pioneered by Claude Bernard revealed that CO reversibly binds to hemoglobin (Hb) forming carboxyhemoglobin (COHb) [26]. Formation of COHb affects two major functions of Hb: 1) decreases the O_2 carrying capacity of blood and 2) impairs the release of O_2 from Hb to the recipient tissues resulting in a hypoxia-induced toxicity [27,28]. Physiological COHb level in the blood ranges from 1% to 3% of total Hb in non-smokers [29]. Smoking was reported to increase COHb levels by an average of 5%–10% in one or two pack of cigarettes per day in smokers, respectively [29,30]. COHb level up to 10% remains asymptomatic, whereas toxic signs of CO poisoning appear when COHb level reaches 15% –20% [31]. Symptoms of CO poisoning are subtle and can be easily misdiagnosed resembling, in initial phase, flu-like symptoms such as headache, dizziness, nausea and seizures, hypotension and coma in phase of severe toxicity [32,33].

Non-hypoxic mechanism of action of CO through binding to heme in proteins other than Hb has been also proposed [34]. The binding of CO with other metalloproteins such as myoglobin, NO synthase, soluble guanylyl cyclase (sGC), heme oxygenase (HO), NADPH oxidase, prostaglandin H synthase, peroxidase, cytochrome P450, cytochrome c oxidase cannot be discounted considering lethality of CO [35–40].

3. Cellular targets of CO

The cellular mechanism underlying beneficial effects of CO is due to competitive binding of heme altering activity of hemoproteins. Physiological action of CO is thought to involve synthesis of cyclic guanosine monophosphate (cGMP) *via* activation of soluble guanylyl cyclase (sGC) [41,42]. The binding of CO to the heme domains of sGC results in about 4-fold increase of this enzyme activity [43]. On the other hand, it has been speculated that sGC activation by CO occurs in CO-saturated conditions in amount of gas that exceeded its physiological concentrations [44]. Other heme-containing proteins may also serve as targets for CO, e.g. the interaction of CO with cytochrome P-450, cytochrome c oxidase or iNOS results in the inhibition of enzymatic activity of these proteins [45–47]. Interaction with hemoproteins such us cyclooxygenase (COX)-1 and COX-2 might be another potential mechanism of action of CO [48]. Moreover, heme degradation process starts with the formation of the ferric heme-HO complex. This complex possesses spectral similarities to ferric myoglobin and Hb, therefore HO seems to be another notable target of CO [37,49,50]. Interestingly, it has been reported that, despite of heme catalytic domains, HO-2 contains heme regulatory domains with conserved Cys-Pro motif region. These domains provide additional heme binding sites which are not present in HO-1 structure [10].

It has been shown that CO may regulate many physiological processes at a molecular level, however the exact mechanisms still remain to be explored. CO is a potent vasorelaxant due to activation of calcium (Ca^{2+})-dependent potassium (K^+) channels [51]. The CO-mediated vasorelaxation through K_{ca} stimulation has been attributed to direct binding to extracellular histidines or channel-associated heme moiety [52,53].

CO can activate antiapoptotic genes in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-dependent manner [54]. This gaseous molecule inhibits mitochondrial cytochrome c oxidase to stimulate the reactive oxygen species (ROS) generation. ROS-induced Act phosphorylation subsequently induces the nuclear translocation of NF-κB, which regulates the transcription and gene expression [55]. Moreover, CO has been shown to exert anti-inflammatory, anti-apoptotic, and anti-proliferative effects through the activation of p38 mitogen-activated protein kinase (p38MAPK) signaling pathway [56–58]. Heat shock protein 70 and caveolin-1 have been recognized as downstream targets for CO-dependent MAPK p38- mediated responses [59,60]. It has been recently demonstrated that CO facilitates NF-E2-related factor 2 (Nrf2) dissociation from Keap1 and therefore enhances the translocation and nuclear accumulation of Nrf2 [61]. Nrf2 binds to antioxidant response element (ARE) sequence in gene promoter and increases Nrf2-regulated transcription of cytoprotective genes.