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Mini Review

Hydrogen sulfide as an effective and specific novel therapy for acute carbon monoxide poisoning

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ABSTRACT

Hydrogen sulfide (H_2S) has been recognized as a toxic gas and environment pollutant. So, it is seldom regarded as a therapeutic gas. H_2S has been recognized recently as a novel gaseous messenger and serves as an important neuromodulator in the central nervous system. Many researches have been focused on the protective role of H_2S in treatment of several diseases. Like nitric oxide (NO) and carbon monoxide (CO), which are considered as two gaseous transmitters, H_2S has been regarded as the third one. Recent studies provided evidence that H_2S exerted antioxidant and anti-apoptotic effects, which protected neurons, cardiomyocytes, pancreatic β-cells and vascular smooth muscle cells against oxidative stress by scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS). It has been known that multiple factors, including oxidative stress, free radicals and neuronal nitric oxide syntheses as well as abnormal inflammatory responses are involved in the mechanism underlying the brain injury after acute CO poisoning. Studies have shown that free radical scavengers can display neuroprotective properties. Therefore, we hypothesize that H_2S might be an interesting potential strategy for curing acute CO poisoning.

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1. Introduction

Hydrogen sulfide (H_2S) has been best known for decades as a pungent toxic gas in the contaminated environmental atmosphere [1]. It is seldom regarded as an important candidate in medicine, especially as a therapeutic gas. Recently, evidence has accumulated that H_2S is an endogenously produced gaseous messenger and serves as an important endogenous vasodilator and neuromodulator [2–6]. It is a colorless, odor of rotten eggs, water-soluble and highly flammable diatomic gas, which can be oxidized by a variety of agents to form sulfur dioxide and sulfuric acid.

However, interestingly, recent studies have shown that H_2S exerts potent neuroprotective [7–10] and anti-inflammatory effects [11]. In the central nervous system, it is reported that H_2S protects neurons against oxidative stress [3], attenuates lipopolysaccharides (LPS) induced neuroinflammation in microglia [12], exhibiting anti-inflammatory [12–14] and anti-apoptotic activities [15], which protected the brain against ischemia–reperfusion injury [16]. Physiological concentrations of H_2S in plasma have been reported between 45 and 300 μM [17]. At physiological concentrations, it has been shown that H_2S inhibits smooth muscle cell proliferation via the mitogen-activated protein kinase pathway and protects the following tissues/cells against oxidative stress: neurons, cardiomyocyte, pancreatic β-cells and vascular smooth muscle cells [10]. Physiologically, H_2S facilitates the induction of hippocampal long-term potentiation, a synaptic model of learning and memory, by virtue of regulating NDMA receptor-mediated response [18,19]. H_2S also modulates the release of corticotrophin-releasing hormone from the hypothalamus [20]. Pathophysiologically, it has been reported that H_2S synthesis is disturbed in the brain of patients with Alzheimer's disease (AD) [21], Down's syndrome [22] and stroke [23]. Thus H_2S may play important roles in regulating central nervous system (CNS) functions. These findings support a hypothesis that H_2S might act as a novel agent which may have a therapeutic potential against neuron damage induced by oxidative stress, inflammation and other factors.

Many efforts have been conducted to restore the blood flow to the ischemic tissues after stroke or a heart attack. However, it is still difficult to relieve this pathological cascade of oxidative damage after reperfusion injury [24], which is companied by inflammation and apoptosis.

2. Acute carbon monoxide poisoning

CO poisoning is the leading cause of poisoning relevant to gas inhalation as a by-product of incomplete combustion of carbon-based fuels and substances. It is the most common lethal poison worldwide, and neurologic sequelae are the most frequent form of morbidity [25–27]. The pathophysiologic mechanisms of CO

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toxicity can be divided into hypoxic and cellular theories [25,28]. The affinity of CO for heme protein is approximately 250 times that of oxygen, and CO binds rapidly to hemoglobin, leading to the formation of carboxyhemoglobin (COHb). The formation of COHb reduces the oxygen-carrying capacity of blood, leading to tissue hypoxia [25,29]. CO could inhibit the mitochondrial electron transport enzyme system and activate polymorphonuclear leukocytes, which undergo diapedesis and cause brain lipid peroxidation yielding the delayed effects of CO poisoning [26,27,29]. In addition, oxidative stress, neuronal apoptosis and necrosis occur over hours to days following CO poisoning; inhibiting these pathologic processes can reduce brain damage and improve functional recovery and survival [30–34].

Autopsy has revealed that CO poisoning injures several brain regions including the cerebral cortex, globus pallidus, caudate putamen, hippocampus and striatum [35]. Furthermore, CO poisoning commonly results in acute and delayed neuropsychological sequelae (DNS) including delirium, amnesia, urine and fecal incontinence, gait disturbance, Parkinson-like syndromes, depression, anxiety and mutism [36–39], which frequently happens 1–3 weeks (sometimes longer) after CO poisoning. However, DNS, which is always called cognitive sequelae, may not be easy to identify clearly at clinical situation [40,41]. The specific mechanism underlying the brain damage, including DNS after CO poisoning, still remains elusive. Recent studies reveal some mechanism though which CO mediated toxicity. One hypothesis is that CO-induced tissue hypoxia may be followed by reoxygenation injury to the CNS. Hyperoxygenation facilitates the production of oxygen species, which in turn can oxidize nucleic acids and essential proteins, resulting in typical reperfusion injury. In addition, CO exposure has been shown to cause lipid peroxygenated, that is to say, degradation of unsaturated fatty acids leading to reversible demyelination of CNS lipids. CO exposure also creates substantial oxidative stress on cells companied by the production of oxygen radicals resulting from the conversion of xanthine dehydrogenase to xanthine oxidase. In additional, previous studies have indicated that significantly increase in ROS production may play a vital role in the pathophysiology of CO intoxication [35,42,43]. The brain is highly vulnerable to oxidative stress. Once the defense against these ROS is insufficient, these ROS may inevitably cause oxidation of unsaturated fatty acids resulting in lipid peroxidation [44,45]. Previous studies shown that CO increases the generation of ROS, including superoxide and hydrogen peroxide via its interaction with mitochondrial oxidases [46], which initiate immediate signal transduction and activate oxidant stress response factors [47,48]. Increase in the ROS generation followed by brain insults, including cerebral ischemia/hypoxia, brain trauma and CO poisoning, may break the balance of the defense system, deteriorating the process of the neural injury further [49,50].

Numerous strategies have been applied in the treatment of CO poisoning, including application of free radical scavengers, monoamine oxidase inhibitors, aggressive supportive care and N-methyl-D-aspartate blockers as well as hyperbaric oxygen (HBO) therapy. Indeed, HBO treatment has been shown to be an effective therapy [51–53]. The main mechanism underlying the beneficial effects of HBO on acute CO poisoning is by accelerating the dissociation of CO from hemoglobin. However, the efficacy and indications of HBO treatment remain controversial [54,55]. The adverse effects in HBO therapy should be paid more attention to. The negative perspective was further supported by an animal study which showed HBO therapy aggravated liver ischemia/reperfusion injury in rats [56]. Meanwhile, increased mortality in CO poisoning patients after HBO therapy had also been noted in previous studies [57–59].

Despite many studied have been widely performed on the neuroprotective agents in the past decades, few agents are found to meet the criteria of an optimal neuroprotectant. Various researchers have engaged in identifying novel, nontoxic, effective and convenient compounds to protect against tissue injuries caused by acute CO poisoning. However, no study has been conducted to investigate the effects of H_2S in the treatment of CO poisoning.

3. Hypothesis and theoretical fundamental to the hypothesis

Our hypothesis is that H_2S may be a promising, effective and specific treatment of acute CO poisoning. This hypothesis is based on the following facts: H_2S has been shown to protect the heart, kidney, liver, lung and brain in ischemia/reperfusion or hypoxic pulmonary hypertension models [60–64]. H_2S can increase the viability of rat cardiac cells in hypoxia-induced cell injuries [65]. Preinhalation of moderate H_2S also improved the survival rate of mice exposed to hypoxia [66] Previous study showed that the endogenous H_2S synthase and cystathionine-synthase (CBS) were present in the medullary respiratory center and exogenous H_2S could affect respiratory activities in a diphasic pattern manifested as an initial inhibition followed by excitation in medullary slices of neonatal rats [67].

It is shown above that H_2S is protective in many biological systems as a cytoprotective agent. H_2S has a wide range of physiological roles in mammalian tissue. In the nervous system, it has been shown to function as a neuromodulator [18] and modulate NMDA receptors (NMDAR) by inducing the production of cyclic-adenosine monophosphate (cAMP) [19], and also acts as an inhibitor of peroxynitrite ($ONOO^-$) [68]. Numerous roles for H_2S have been identified: vasorelaxant [69] and antiapoptotic properties by opening of KATP channels, proangiogenic factor through the phosphorylation of Akt [70], modulator of leukocyte-mediated inflammation [71], upregulator of antioxidant signaling [72] and involved in cytoprotection through the preservation of mitochondrial function [73]. We have reason to believe that H_2S might act as a novel agent which may have a therapeutic potential against neuron damage.

H_2S is so mild that it neither disturbs metabolic oxidation–reduction reactions nor disrupts ROS involved in cell signaling. Furtherore, it can penetrate biomembranes and diffuse into the cytosol, mitochondria and nucleus. As a potential treatment, H_2S has distinct advantages over pharmaceutical drugs: it easily diffuses across the blood–brain barrier to reach target tissues, may act via multiple pathways. Last but not least, the tissue compatibility of H_2S is stronger than many other antioxidants because it is an endogenous substance.

It has been known that the mechanism underlying the brain injury after acute CO poisoning is interlaced with multiple factors, including oxidative stress, free radicals, apoptosis and neuronal nitric oxide syntheses as well as abnormal inflammatory responses, and H_2S can modulate K-ATP channels and Ca^{2+} handling [70,74]. In animal models of critical illness, H_2S donors protect from lethal hypoxia, reperfusion injury [75–77] and exert anti-inflammatory effects [71]. Then we hypothesize that H_2S can be potentially effective for acute CO poisoning. That is to say, H_2S may be a promising novel neuroprotectants. We believe that in vitro and in vivo work for H_2S on neuroprotection against acute CO poisoning should commence as soon as possible.

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