REVIEWS

Effects of Hydrogen Sulfide on Erectile Function and Its Possible Mechanism(s) of Action

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ABSTRACT

Introduction. The current pharmacotherapy for erectile dysfunction (ED) relies significantly on the use of phosphodiesterase type 5 (PDE5) inhibitors, but quite a proportion of ED patients are resistant to this therapy, necessitating a search for an alternative treatment. We reviewed available published data to analyze current evidence of hydrogen sulfide (H_2S) as a novel pharmacotherapeutic agent with supportive role in sexual function.
Aim. To discuss the role of H_2S in erectile function, its possible mechanism of action, and how this knowledge may be exploited for therapeutic use.
Methods. Pubmed and Medline search was conducted to identify original articles and reviews.
Main Outcome Measures. Data from peer-reviewed publications.
Results. Animal studies using different species, including in vitro study done in humans, show evidence of H_2S's pro-erectile effects. The mechanism behind is still unclear, but evidence in literature points out the involvement of K^+_{ATP} channel, modulation of protein with anti-erectile effects, as well as involvement of the nitrergic pathway through a complex cross-talk. A new drug called H_2S-donating sildenafil (ACS6), which incorporated an H_2S-donating moiety in sildenafil, has been developed. While more studies are still needed, this heralded a new pharmacotherapeutical approach, which is multipronged in nature.
Conclusions. Given the mounting evidence of H_2S's role in erectile function and how it appears to achieve its pro-erectile effects through different mechanisms, H_2S represents a potentially important treatment alternative or adjunct to PDE5 inhibitors. **Liaw RL, Srilatha B, and Adaikan PG. Effects of hydrogen sulfide on erectile function and its possible mechanism(s) of action. J Sex Med 2011;8:1853–1864.**

Key Words. Hydrogen Sulfide; Nitric Oxide; Gasotransmitter; Corpus Cavernosum; Erectile Function

Introduction

In light of recent discoveries, the scientific community's perspective of hydrogen sulfide (H_2S) has undergone a paradigm shift. This toxic pollutant with rotten egg smell is now considered an important biological mediator. H_2S is currently placed as a member of the "gasotransmitter" family together with other members, viz., carbon monoxide (CO) and nitric oxide (NO), the term conceived to distinguish their action from the classical signaling molecules [1]. There is a growing number of evidence that H_2S can exert a multitude of biological effects, e.g., in inflammation, antinociception, myocardial ischemia–reperfusion, cardiovascular pathology, shock/sepsis, pulmonary hypertension, and diabetes.

H_2S is a weak acid with a pKa of 6.76 at 37°C, dissociating in aqueous solution as follows: $H_2S \leftrightarrow HS^- + H^+ \leftrightarrow S^{2-} + 2H^+$. At physiological pH of 7.4, about 18.5% of the total sulfide has been shown to exist as H_2S and 81.5% as HS^- [2]; however, it is unknown as to which of the H_2S moiety (H_2S, HS^-, or S^{2-}) is the "active" component responsible for the net biological effects observed in different systems [3]. H_2S is endogenously

produced from L-cysteine by the activity of two enzymes, cystathionine β-synthase (CBS)—existing predominantly in the brain and central nervous system—and cystathionine γ-lyase (CSE)—expressed mainly in the liver, and vascular and non-vascular smooth muscles [4]. Systemically, H_2S can be oxidized to form sulfate or sulfite in mitochondria; it can be scavenged by methemoglobin or glutathione, and it can also be methylated [5]. A lot of studies have employed the use of CSE inhibitors, viz., DL-propargylglycine (PAG) and β-cyano-L-alanine (BCA), to delineate H_2S effects. They are the only pharmacological agents known today to inhibit H_2S production by CSE; however, it is important to note that they are of modest potency and selectivity, and have limited membrane permeability [6]. Therefore, the results from such studies have been less useful in investigating the physiological role of H_2S compared with NO synthase (NOS) inhibitors such as L-N^G-monomethyl arginine in delineating the physiology of the NO pathway.

Erectile Physiology

Erectile physiology is an intricate interplay of vascular, neurologic, and endocrine factors. Disturbances to any of these system can give rise to erectile dysfunction (ED), making it a multifactorial disorder that is rather difficult to treat. As it is known thus far, relaxation of the corpus cavernosum (CC) smooth muscle brings about penile erection through an increase in arterial flow and restriction of venous outflow; detumescence is associated with the α-adrenoceptor activity, whereas tumescence is attributed to both cholinergic and nitrergic involvement, with the nitrergic (NO/cyclic guanosine monophosphate [cGMP]) pathway being the primary mediator [7].

As an important prerequisite for erectile process, NO is endogenously produced from L-arginine by the NOS isoforms: endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS), and inducible nitric oxide synthase (iNOS) [8]. The released NO activates soluble guanylyl cyclase to result in an increased conversion of the guanosine triphosphate to second messenger cGMP (which, through its interaction with cGMP-dependent protein kinases, cyclic nucleotide-gated ion channels, or cyclic nucleotide phosphodiesterases, governs many aspects of cellular function in the body). In the cavernosum, cGMP stimulates the protein kinase G, which in turn initiates phosphorylation of membrane-bound proteins at K^+ channels. This will lead to K^+ ion outflow into the extracellular space resulting in hyperpolarization, closure of L-type Ca^{2+} channels, and decrease in intracellular Ca^{2+} ion concentration. Together with these changes, there is decreased activation of myosin light chain (MLC) kinase, decreased phosphorylation of MLC chains, and, subsequently, reduced actin–myosin interaction to result in cavernosal relaxation and physiological erection [9] (Figure 1).

Pro-Erectile Effects of H_2S

Considering the substantial endogenous production of H_2S by mammalian tissues and the growing evidence that H_2S can act as a regulatory mediator similar to NO, it can be expected that H_2S may exert important biophysiological effects in erectile function. In fact, onion—with its complex sulfur compound biochemistry—was considered to be a popular, natural remedy for impotence [12]. In a pilot study by Srilatha et al., it was demonstrated that administration of sodium hydrosulfide hydrate ($NaHS.xH_2O$, a stable H_2S donor) increased penile length, perfusion, and intracavernosal pressure (ICP) in vivo in a nonhuman primate model [13]; this serves as the first direct evidence for the pro-erectile effect of H_2S in CC. Such facilitatory effects on erectile function have also been observed in other animal models. In particular, administration of PAG decreased ICP in rats [13]. Organ bath study showed that NaHS can dose-dependently relax pre-contracted rabbit and human CC [14,15]. As expected, L-cysteine (H_2S precursor and CBS/CSE substrate) has similar effects to NaHS in increasing ICP, and this effect is blocked by PAG. Adenylyl cyclase (AC) inhibitor MDL 12,330A was shown to block the H_2S-induced relaxation of pre-contracted rabbit cavernosum; however, this inhibition was *incomplete* [14], suggesting that relaxation mediated by H_2S is only partially dependent on cAMP pathway, highlighting the presence of other mechanisms contributing to its relaxant effect, possibly via K^+_{ATP} channel. Inhibition of H_2S production with PAG or aminooxyacetic acid (a CBS inhibitor) is also able to significantly increase electrical field stimulation-induced contraction (associated with detumescence) at different frequencies in both rabbit and human CC [14,15]. Therefore, endogenous H_2S's role is possibly twofold: (i) relaxation of CC smooth muscle; and (ii) inhibition of basal tone in penis. This finding is significant considering that both impaired relaxation and increased contractility can contribute to ED. However, it is still