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Role of Hydrogen Sulfide in the Physiology of Penile Erection

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Abstract

Hydrogen sulfide (H_2S), which is a well known toxic gas, has recently been recognized as a biological messenger, which plays an important role in physiological and pathophysiological conditions. Relatively high levels of H_2S have been discovered in mammalian tissues. It is mainly synthesized by two enzymes including cystathionine β-synthase and cystathionine γ-lysase, which utilize L-cysteine as substrate to produce H_2S. H_2S has been demonstrated to exhibit potent vasodilator activity both in vitro and in vivo by relaxing vascular smooth muscle. Recently, H_2S has been discovered in penile tissue with smooth muscle relaxant effects. Furthermore, other effects of H_2S may play a role in the physiology of erection. Understanding of H_2S in the physiology of erection might provide alternative erectile dysfunction (ED) strategies for those patients with poor or no response to type 5 phosphodiesterase inhibitors (PDE5i). This review intends to present the H_2S pathway in penile tissue and the potential role of H_2S in the physiology of erections.

Keywords

Hydrogen Sulfide; Erection; Corpus Cavernosum; Smooth Muscle; Erectile Dysfunction

Introduction

Erections are a neuro-vascular event. Under sexual stimulation, vasodilation and relaxation of trabecular smooth muscle allows blood flow into the cavernosal sinusoids and increase the intracavernosal pressure (ICP). Erection is maintained by the compression of subtunical venules against tunica albuginea (Christ and Lue, 2004, El-Sakka and Lue, 2004, Lue, 2000, Gratzke, et al., 2010). Relaxation of the smooth muscle of the corpus cavernosum is the crucial physiological event in penile erections. Nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway had been acknowledged as a classic pathway in mediating relaxation of corpus cavernosum smooth muscle (Burnett, 2004). Cavernos nerve activation induces the release of NO from the nerve terminals in the corpus cavernosum. Additionally, NO is released from the endothelium in response to shear stress. NO is synthesized by neural nitric oxide synthase (nNOS) in the corpus cavernosum nerve terminals and by endothelial oxide synthase (eNOS) in endothelium, which utilizes L-arginine and oxygen as substrate to produce NO (Albersen, et al., 2010). Subsequently, NO activates soluble guanylate cyclase (GC) and increases cGMP levels in smooth muscle cells.

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As a second messenger, cGMP initiates a chain of reactions, which results in a decrease in intracellular calcium and a subsequent relaxation of the smooth muscle cells (Zhang, et al., 2011).

cGMP is hydrolyzed by type 5 phosphodiesterase (PDE5). The application of type 5 phosphodiesterase inhibitor (PDE5i) for treatment of erectile dysfunction (ED) is based on role of PDE5 on regulating cGMP level in corpus cavernosum smooth muscle cells. Oral administration of PDE5i has revolutionized the treatment of ED. It has been considered to be the first-line oral treatment for ED patients (Carson and Lue, 2005). Although PDE5i have been proved to be effective in treating ED, there is still a percentage of patients with poor or no response to PDE5i. Lower response rates were observed in diabetic patients (59% for type-1 diabetes, 64% for type-2 diabetes) and in patients who had undergone prostatectomy for prostate cancer (43%) (Boulton, et al., 2001, Briganti, et al., 2005). It is therefore necessary to explore novel strategies that might overcome the shortfalls of PDE5i.

Recently, H_2S, which is mainly produced endogenously from L-cysteine (L-Cys) by the activity of two enzymes: cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) (Tang, et al., 2006), has been demonstrated as a potential neurotransmitter in the central and in some peripheral systems (Boehning and Snyder, 2003, Gadalla and Snyder, 2010). Both H_2S-producing enzymes are pyridoxal phosphate-dependent and are expressed in a range of tissues. CBS seems to be the main H_2S-producing enzyme in the central nervous system while CSE is the main H_2S-producing enzyme in the cardiovascular system (Moore, et al., 2003, Wang, 2002). H_2S exerts a negative feedback effect on the activity of these enzymes to regulate the synthesis of H_2S (Wang, 2002). Additional endogenous sources of H_2S include production from L-methionine via the transulfuration pathway as well as erythrocyte production (Searcy and Lee, 1998, Wagner, 2009).

Many studies have demonstrated the vasorelaxant effect of H_2S in animals and humans (Zhao, et al., 2001, Bianca, et al., 2009), indicating the potential role of H_2S on the relaxation of vascular smooth muscle. Furthermore, hypertension has been reported in CES gene knockout mice, suggesting the important role of H_2S on physiologically regulating the cardiovascular system (Yang, et al., 2008). Erectile tissue contains abundant smooth muscle and endothelium. ED shares the same risk factors with cardiovascular disease such as diabetes, hyperlipidemia and obesity (Shin, et al., 2011). How about the role of H_2S in the physiology of erections? In this review, we intend to present the synthesis of H_2S and H_2S-synthesizing enzymes in erectile tissue, and discuss the physiology of the smooth muscle relaxant effect of H_2S.

Synthesis of H_2S in penile tissue

Hydrogen sulfide has been demonstrated to be neurotransmitter in the central nervous system and vascular system (Geng, et al., 2004). Recently, growing evidence suggests the existence of L-Cys/H_2S in penile tissue. Direct evidence to prove the existence of L-Cys/H_2S system in penile tissue was firstly provided by Srilatha in 2007 (Srilatha, et al., 2007). H_2S was detected in rabbit corpus cavernosum homogenized and incubated with L-Cys (Bianca, et al., 2009). The biosynthesis of H_2S was increased by 3-fold over basal value after incubation of tissue homogenates with L-Cys. Aminoxyacetic acid (AOAA, CBS inhibitor) or the combination of AOAA and propargylglycine (PAG, CSE inhibitor) significantly inhibited the increase in H_2S production.

CBS and CSE are expressed in many tissues. Both CBS and CSE were reported to be expressed in the brain and produce H_2S from cysteine (Abe and Kimura, 1996, Diwakar and Ravindranath, 2007, Vitvitsky, et al., 2006). CBS and CSE were also reported to be present in human corpus cavernosum using qRT-PCR and western blot by Bianca's group (Bianca,

et al., 2009). They also described the location of these 2 enzymes. Immunohistochemical staining demonstrated that CBS and CSE were localized in the muscular trabeculae and smooth-muscle components of the penile artery (Fig. 1). It has been published that rat's main cavernous nerve branches to the dorsal nerve and intrcavernous nerve, and the damage to the main cavernous nerve results in structural changes in dorsal nerve (Albersen, et al., 2011). CSE but not CBS was also expressed in dorsal nerves of rat's penis (Fig. 1), indicating that CSE might play a role in the corpus cavernosum by triggering the H_2S pathway both in smooth muscle cells and neural cells.

No direct evidence has showed the existence of H_2S synthesis associated enzymes in the endothelium of the corpus cavernosum until recently. Since the effect of H_2S on vascular smooth muscle was slightly enhanced in the presence of endothelium, it was thought that H_2S might stimulate the endothelium to release endothelium-derived relaxant factors (EDRFs) or endothelium-derived hyperpolarization factors (EDHFs), which interact with smooth muscles (Hosoki, et al., 1997, Zhao, et al., 2001). It was recently reported that CSE was found in endothelial cells of mice, bovine and human (Yang, et al., 2008). Shibuya et al. (Shibuya, et al., 2009, Shibuya, et al., 2009) reported that 3-mercaptopyruvate sulfurtransferase (3MST) and cysteine aminotransferase (CAT), which were demonstrated to be H_2S-producing enzymes in the brain, were localized in vascular endothelium in the thoracic aorta. Additionally, lysate of vascular endothelial cells could produce H_2S from cysteine and α-ketoglutarate (Shibuya, et al., 2009). H_2S synthesis associated enzymes have yet to be found in endothelial cells of the corpus cavernosum.

Effects of H_2S on penile tissue

It has been reported that H_2S acts on smooth muscles, significantly relaxing vascular and intestinal preparations in vitro (Teague, et al., 2002, Kimura, 2011). H_2S also has a relaxant effect on smooth muscle in corpus cavernosum both in vitro and in vivo. In 2006, Srilatha et al (Srilatha, et al., 2006) reported that intracavernous administration of PAG significantly impaired the normal ICP response to cavernous nerve electrostimulation, indirectly suggesting the possible role of H_2S system on relaxing smooth muscle in penile tissue. This was confirmed by in vitro organ bath study. Inhibitors of H_2S-forming enzymes including AOAA, beta-cyanoalanine (beta-CA, inhibitor for CSE) and PAG markedly increased the noradrenergic contractile neurotransmission of corpus cavernosum strips to field stimulation (Srilatha, et al., 2007).

The H_2S donor, sodium hydrogen sulfide (NaHS), consistently relaxed rabbit (Srilatha, et al., 2007) and human (Bianca, et al., 2009) corpus cavernousm strips in a concentration-dependent manner. Intracavernous injection of sodium hydrogen sulfide to primates resulted in significant increases in penile length and cavernosal pressure (Srilatha, et al., 2006).

In contrast to the well known stimulatory effect of NO and carbon monoxide (CO) on GC to increase cGMP level, the effect of H_2S on cGMP remains unknown. In 2002, Zhao et al. (Zhao and Wang, 2002) demonstrated that H_2S-induced vasorelaxation was partially attenuated by blockade of NO synthase, indirectly suggesting the role of NO/cGMP pathway in H_2S induced vasorelaxation. Recently, one study provided evidence to prove the possible role of H_2S as an endogenous inhibitor of PDE. Pretreatment with tadalafil, a PDE5i, increased the survival rate of mice with cardiac ischemia/reperfusion injury (Salloum, et al., 2009). Inhibition of CSE activity impaired the protective effect of tadalafil on myocardial infarct size. Furthermore, tadalafil could not offer a similar cardiac protective effect in CSE knockout mice. Although whether H_2S increased the activity of GC directly was not examined, the possible role of H_2S on mediating NO/cGMP pathway has been speculated. Tadalafil probably stimulates CSE to produce H_2S and inhibits PDE5 activity to increase

cGMP level (Fig. 2). Furthermore, Salloum's group (Salloum, et al., 2009) demonstrated that administering NaHS to cultured rat aortic smooth muscle cells or overpression of CSE in these cells increased cGMP concentration. Also, they indicated that silencing of CSE expression led to reduced intracellular cGMP levels. This study provided direct evidence to indicate the effect of H_2S on inhibiting breakdown of cGMP.

It was speculated that the possible mechanism involved in the effect of H_2S on relaxation of corpus cavernosal smooth muscle was likely by inhibiting the breakdown of cGMP. However, Srilatha et al. demonstrated that classic cyclic adenosine monophosphate pathway is partly involved in H_2S effect on relaxing smooth muscle of the corpus cavernosum (Srilatha, et al., 2007). MDL 12,330A (adenylate cyclase inhibitor) and 1-H-[1,2,4]-oxadiazolo-[4,3-a]-quinoxalin-1-one (a soluble guanylase inhibitor) inhibited the NaHS relaxation by 22.5% and 4.7%, suggesting thereby that the H_2S-mediated relaxation is only partially dependent on the classical pathways of penile erection operating though cyclic adenosine monophosphate (cAMP) or cGMP systems. This is further confirmed by the lack of effect of N-nitro-Larginine (NO synthase inhibitor) on the H_2S mediated relaxation of the corpus cavernosum.

Based on the observation that H_2S significantly relaxes the thoracic aorta even after the removal of endothelial cells (Hosoki, et al., 1997, Zhao and Wang, 2002), H_2S must have a direct effect on the thoracic aorta's smooth muscle. The most recognized molecular target of H_2S in smooth muscle cells is the ATP sensitive K channel (K_{ATP} channel) (Zhao, et al., 2001). H_2S activates K_{ATP} channels which lead to subsequent membrane hyperpolarization. The closure of voltage-dependent calcium channels by membrane hyperpolarization results in smooth muscle relaxation. It has been reported that H_2S induced vasorelaxation was partially attenuated by blockade of Ca^{2+} dependent K channel (K_{Ca} channel) blockers, suggesting the key role of K_{Ca} channel in H_2S induced smooth muscle relaxation (Zhao and Wang, 2002). K_{ATP} and K_{Ca} channel activation by H_2S might be the main mechanism involved in H_2S relaxing smooth muscle of the corpus cavernosum. (Fig. 2)

The ability of H_2S to relax smooth muscle is lightly enhanced in the presence of endothelial cells, suggesting that endothelial cells may release EDRFs or/and EDHFs in response to H_2S (Zhao, et al., 2001). The exact components of EDRFs or EDHFs remain unknown. (Fig.2)

It has been demonstrated that H2S, as a transient receptor potential A1 (TRPA1) ion channels agonist, increased micturition frequency and reduced voiding volume in vivo (Streng, et al., 2008), and produced relaxation of phenylephrine contracted urethral preparations in vitro (Weinhold, et al., 2010). It is conceivable that another mechanism whereby H_2S may be involved in relaxing penile smooth muscle is via its potential effects on activating TRPA1.

Other effects of H_2S

(1) Cell proliferation regulation

H_2S was found to increase the growth of cultured human umbilical vein endothelial cells (HUVECs) (Papapetropoulos, et al., 2009). H_2S has also been demonstrated to enhance the capillary-like structure formation and motility of endothelial cells cultured on reduced-growth factor Metrigel. Yang et al. (Yang, et al., 2010) reported that the speed of wound healing was reduced in CSE knockout mice. This data indicates that H_2S has a proliferative effect on endothelial cells.

However, as opposed to the proliferative effect on endothelial cells, H_2S is probably an anti-proliferative factor for smooth muscle cells. It was reported by Yang's group that the

proliferation rate of smooth muscle cells derived from CSE gene knockout mice was significantly faster compared with those derived from wild type mice (Yang, et al., 2010). This was confirmed when SMCs derived from the media of the aorta from CSE knockout mice also exhibited enhanced proliferation in comparison with those from wild-type mice. Extracellular signal-regulated kinase (ERK1/2) (Papapetroulos, et al., 2009, Yang, et al., 2004, Yang, et al., 2010) and K_{ATP} channel (Papapetropoulos, et al., 2009) are believed to be involved in H_2S regulating SMCs and ECs proliferation.

The corpora cavernosa are composed of sinusoids that are lined with a single layer of endothelial cells and are surrounded by multiple layers of smooth muscle cells. The corpus cavernosa is in fact a vascular organ (Lin, et al., 2011). The effect of H_2S on regulating growth of smooth muscle cells and endothelial cells may play a role on mediating the physiology of normal erection.

(2) Antioxidant effect of H_2S

Elevated oxidative stress is reported to be associated with risk factors for cardiovascular diseases such as diabetes, hypertension and hyperlipidemia (Rains, et al., 2011, Yang et al., 2010), which are also considered to be risk factors for erectile dysfunction. Oxidative stress occurs as a consequence of an imbalance between reactants, such as reactive oxygen and nitrogen species, and antioxidants. Increases in reactive species cause damage to lipoproteins, lipids, DNA and proteins (Strobel, et al., 2011). Recently, some studies suggest that there is an antioxidant effect of H_2S. Yan et al. demonstrated that the cytoxicity induced by homocysteine in cultured SMCs was reduced in the presence of low levels of NaHS (30 or 50μmol/l). Additionally, the cellular levels of H_2O_2, $OnOO^-$ and O_2^- were significantly reduced (Yan, et al., 2006), indicating the antioxidant effect of H_2S. This is further confirmed by another study showing that H_2S delayed the accumulation of lipid peroxidation products in HUVECs, including conjugated dienes, lipid hydroperoxides (LOOH), and thiobarbituric acid reactive substances during heminmediated oxidation (Jeney, et al., 2009). It has been demonstrated that the antioxidative effect of H_2S might have important implications in the vascular remodeling process and the development of atherosclerosis (Meng, et al., 2007). Recently, this has received further support from a study demonstrating that H_2S (25–50μmol/l) reduced the LOOH content of oxidized lipid extracts derived from human aorta or its primary branches which contain atherosclerotic lesions. Pretreatment of the cultured HUVECs with H_2S (50 μmol/l) also directly protected these cells against hydrogen peroxide and oxidized LDL-mediated endothelial cytotoxicity (Jeney, et al., 2009). It has been reported that extracellular H_2S protected cells from oxidative stress by enhancing the production of glutathione, which is a major endogenous antioxidant (Griffith, 1982). Moreover, H_2S produced by 3MST and CAT might suppress oxidative stress in mitochondria (Kimura, et al., 2004).

H_2S: a possible perspective for ED treatment strategy

The efficacy of PDE5i is based on the integrity of nerve and endothelium in corpus cavernosum, which produces sufficient NO. In some conditions such as the post-prostatectomy state and diabetes, the integrity of nerve and endothelium in corpus cavernosum are severely compromised, leading to the lack of NO to trigger the NO/cGMP pathway. That's why the efficacy of PDE5i is lower in ED patients due to diabetes (Goldstein, et al., 1998, Rendell, et al., 1999) or post-prostatectomy (Kendirci and Hellstrom, 2004). Unlike NO, which is produced by both endothelium and nerves, H_2S is mainly produced by smooth muscle in corpus cavernosum. The mechanisms involved in H_2S mediated relaxation of smooth muscle are complex and include K_{ATP} and K_{Ca} channels activation, synergetic effect with NO/cGMP pathway, and inducing endothelium to produce

EDRFs or/and EDHFs. Hence, H_2S provide urologists a new therapeutic approach for ED patients with poor or no response to PDE5i.

One of the possible treatment strategies for ED is to provide exogenous H_2S. Shukla et al. (Shukla, et al, 2009) studied the effect of H_2S-donating sildenafil (ACS6) on smooth muscle relaxation. ACS6 and sildenafil elicited dose-dependent relaxation of isolated rabbit corpus cavernosum strips. Even though ACS6 was equipotent with sidenafil alone, ACS6 was more effective at reducing formation of superoxide induced by TGF-β, indicating the antioxidant effect of H_2S in the corpus cavernosum. It is reasonable that ACS6 and sidenafil had equipotent effect on relaxing rabbit corpus cavernosum strips since the strips contained intact endothelium and nerve. However, corpus cavernosum strips from diabetic animals would be a better model to explore the potential use of H_2S in ED with poor response to PDE5i.

Another possible approach to use H_2S to treat ED is to activate endogenous H_2S production. L-Cysteine/H_2S system could be the possible targets to develop new therapeutic strategies for ED treatment. It has been demonstrated that H_2S-producing associated enzymes are located in smooth muscle and nerve of human corpus cavernosum (Bianca, et al., 2009). Recently, H_2S-producing associated enzymes had been found in endothelial cells (Shibuya, et al., 2009). Any treatment designed to activate L-Cys/H_2S system in the corpus cavernosum would be an alternative treatment strategy for ED with poor or no response to PDE5i.

Conclusion

H_2S is implicated as the third neurotransmitter with a relaxant effect in cavernosal smooth muscle, suggesting the potential role of H_2S in the physiology of erection. H_2S-synthesizing associated enzymes have been identified in penile tissue, confirming the L-cysteine/H_2S system in the physiology of erection. Unlike NO, main relaxant effect of H_2S on smooth muscle is direct through activation of K_{ATP} and K_{Ca} channels. This provides an alternative approach for ED treatment, especially for those patients with poor or no response to PDE5i.

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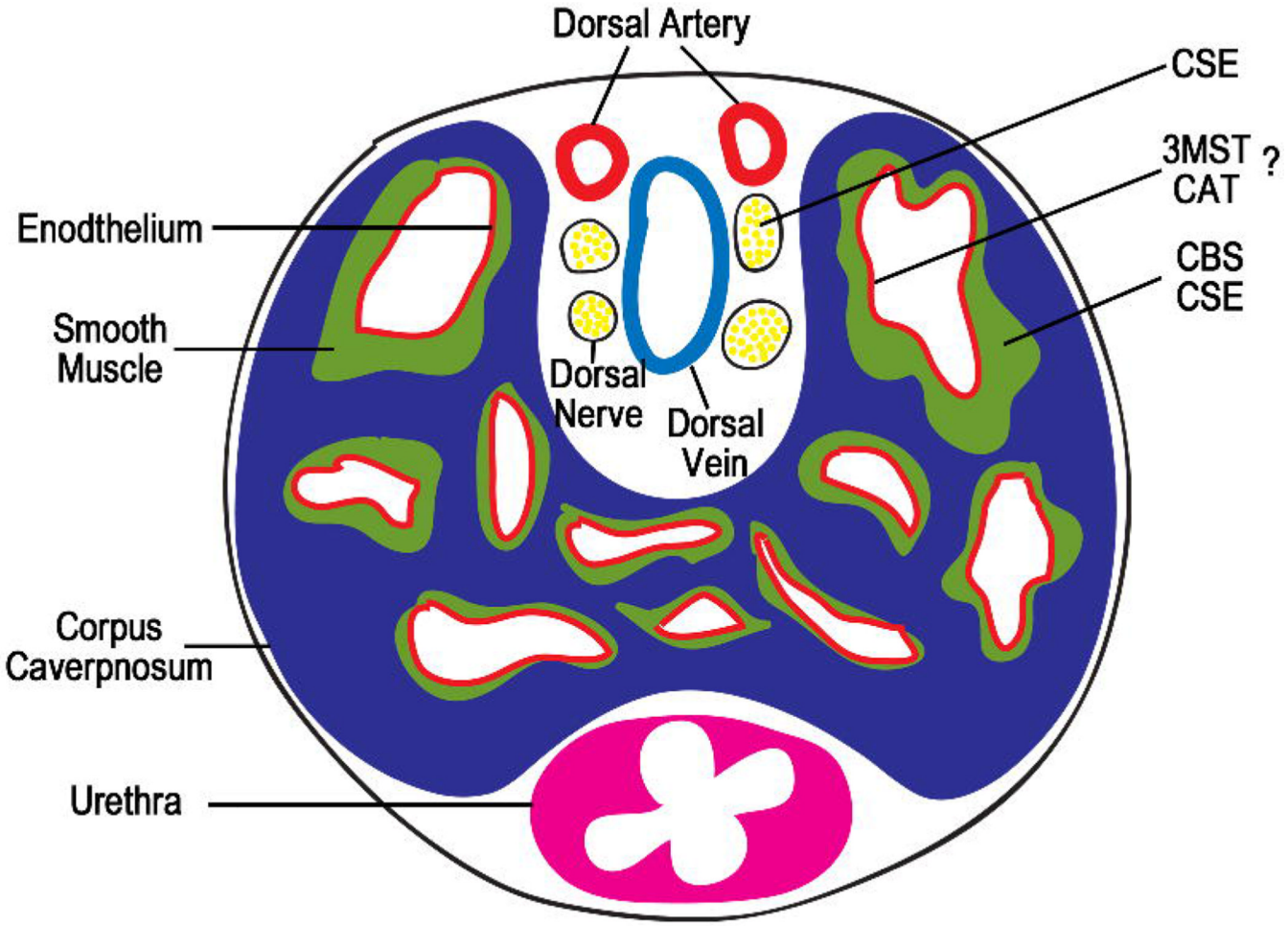

Fig.1. Distribution of H_2S-producing associated enzymes in penile tissue

H_2S-producing associated enzymes were demonstrated to localize in smooth muscle cells (CBS, CSE) and nerve terminal (CSE) within the corpus caversnosum. H_2S-synthesizing associated enzymes including CBS, 3MTS and CAT were found in vascular endothelial cells. Even without direct evidence, endothelial cells in corpus cavernosum might contain these enzymes.

Abbreviations: CBS= cystathionine β-synthase, CSE= cystathionine γ-lyase, 3MTS=3-mercaptopyruvate sulfurtransferase, CAT= cysteine aminotransferase.

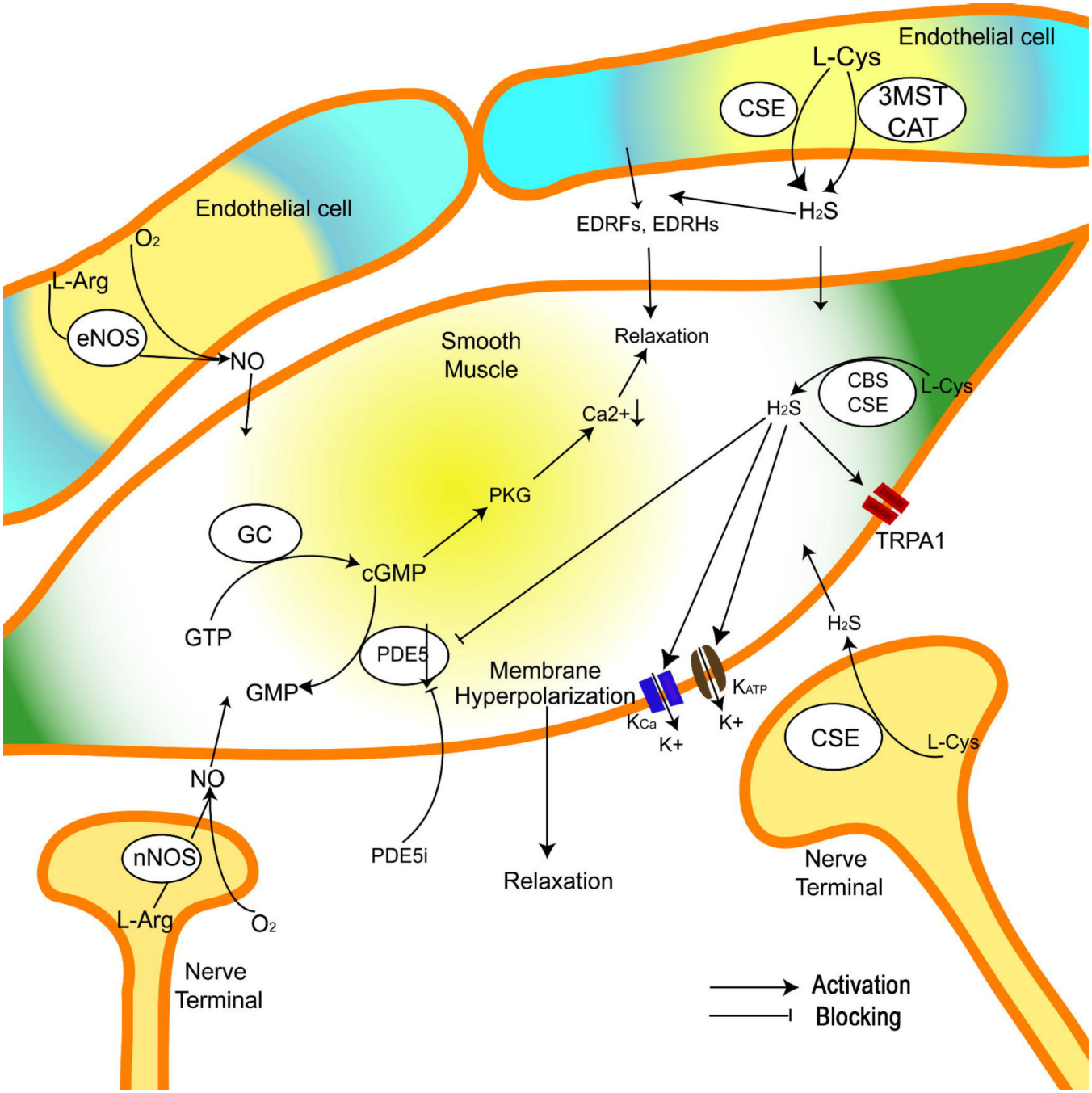

Fig. 2. Smooth muscle relaxant effect of H_2S in corpus cavernosum

Three possible mechanisms are involved in H_2S relaxing smooth muscle cells in corpus cavernosum: 1. Activating of K_{ATP} channel and K_{Ca} channel and inducing membrane hyperpolarization. 2. Inhibiting the activity of PDE5 and breakdown of cGMP. 3. Enhancing endothelial cells to release EDRFs or/and EDHFs. 4. Activation of TRPA1 ion channels. Abbreviations: PDE5= type 5 phosphodiesterase, cGMP=3',5'-cyclic guanosine monophosphate, EDRFs= endothelium-derived relaxant factors, EDHFs= endothelium-derived hyperpolarization factors, TRPA1= transient receptor potential A1.