Journal of
Pharmacology & Clinical Research
ISSN: 2473-5574

Juniper Publishers
key to the Researchers

Review Article
Volume 5 Issue 3 - April 2018
DOI: 10.19080/JPCR.2018.05.555661

J of Pharmacol & Clin Res

Hydrogen Sulfide (H_2S) - Poison Gas to Signaling Molecule in Regulation of Human Biology

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Submission: March 22, 2018; **Published:** April 10, 2018

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Abstract

Hydrogen sulfide is a blossomed exploration of whiff. It is a well known poisonous gas but now serve as a gaseous transmitter which may act as an important signaling mediator in different cellular and physiological processes. It is recently discovered, that H2S is generated enzymatically from L-cysteine in various mammalian and human tissues to carry out number of signaling pathways in human biology. It has been revealed that ATP-sensitive K+ (KATP) channel is widely accepted cellular target associated with H_2S which is responsible for vasorelaxation, cardioprotection, neuroprotection and also in diabetes mellitus. Evidence is accumulating to demonstrate that H_2S exerts significant effects in different diseases by different mechanisms of action; also this review summarizes a detailed description of current signaling mechanism responsible for various effects in human biology.

Keywords: Hydrogen sulfide (H_2S); Cystathionine-β synthase (CBS); Cystathionine-γ lyase (CSE); 3-mercaptopyruvate sulfurtransferase (3-MST); KATP channel

Abbreviations: H_2S: Hydrogen Sulfide; CBS: Cystathionine-β-synthase; CSE: Cystathionine-Y-Lyase; CAT: Cysteine Aminotransferase; MST: 3-Mercaptopyruvate Sulfurtransferase; NO: Nitric Oxide; CO: Carbon Monoxide; PKA: Protein Kinase A; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; NaHS: Sodium Hydrosulfide; MAPK: Mitogen-Activated Protein Kinase; AOA: Aminooxyacetate; ICAM-1: Intercellular Adhesion Molecule; TNF-α: Tumor Necrosis Factor-α; TRPV-1: Transient Receptor Potential Vanilloid-1; ERK: Extracellular Signal Related Kinase; EGFR: Endothelial Growth Factor Receptor; LTP: Long Term Potentiation; ROS: Reactive Oxygen Species; RNS: Reactive Nitrite Species.

Introduction

Hydrogen sulfide is a small gaseous and the diffusible compound with the formula H_2S that constitute a family of labile gas-transmitters together with Nitric oxide (NO) and Carbon monoxide (CO) [1,2]. Although all three gas-transmitters has the same toxicity status, H_2S yet has not been awarded the degree of initial skepticism which is associated with other two NO and CO [3]. It is a colorless, flammable gas with the characteristic foul smell of rotten eggs. Often it results from the bacterial decomposition of organic matter in the absence of oxygen. It also occurs in volcanic gases, natural gas, and some well waters. Despite being as environmental pollutant and bio hazardous compound it is widely integrated in various human physiological processes and diseases [4,5]. The main mechanism behind H2S toxicity is mitochondrial damage or oxidative damage through blockade of cytochrome-c oxidase [6,7]. Recent studies suggested that H_2S acts as an important mediator in various signaling pathways of human biology. Endogenously it is produced in various parts of the body like blood vessels [8], heart [9], GIT and central nervous system [10]. The present article reviews the prominent role of H_2S in human biology with special focus on current literature and clinically relevant studies.

Synthesis of Hydrogen Sulfide in Mammalian and Human Tissues

L-Cysteine (sulfur containing amino acid) is the major substrate for producing H_2S in mammalian tissues via two pyridoxal-5'phosphate (PLP) dependant enzymes: cystathionine-β synthase (CBS) and cystathionine-γ lyase (CSE) as well as a PLP independent enzyme 3-mercaptopyruvate sulfurtransferase (3-MST) [11-14] as depicted in Figure 1. Both CBS and CSE exist in cytosol whereas the 3-MST present mainly

in mitochondria and expressed in vascular endothelium. H_2S formation through biosynthetic pathway is dependent on tissue location [15]. Enzymatically, H_2S is produced in different areas of the human body at a particular concentration [16] as shown in Figure 2. A recent investigation shows that CBS is predominantly found in the brain and nervous tissues whereas CSE is in the vascular system and other organs including GI tract, lungs and kidneys. 3-MST is also present in kidney, liver, lung and heart [17,18] CBS and CSE both can produce H_2S by catalyzing different sulfur containing substrates, L-cysteine that can be derived from alimentary canal and can be liberated from endogenous proteins [19] whereas sulfur transfer reactions from 3-mercaptopyruvate can only be catalyzed by 3-MST [20]. These sulfur transfer reaction yields hydropersulfide not H_2S directly, further a redox reaction between RSSH and a biological thiol (GSH) is required for releasing H_2S. Recently it has been investigated by Kumara et al. [21] that for production of H_2S from 3-mercaptopyruvate and 3-MST depend on biological dithiol-thioredoxin or dihydrolipoic acid. In tissue homogenates it has been observed that 1-10 pmoles per second per mg protein range of sulfide is produced that can cause low micromolar extracellular concentrations of sulfide [22-25].

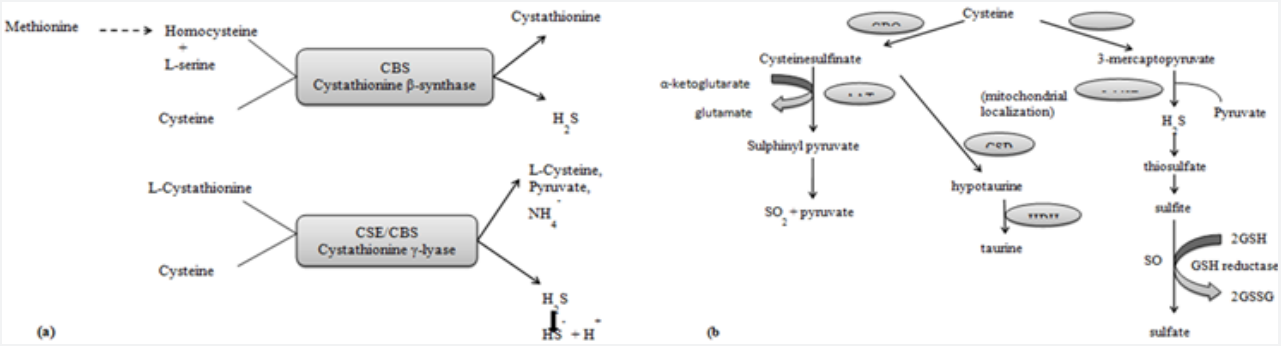

Figure 1: (a) Enzymatic synthesis of H_2S and (b) metabolism of sulfur containing amino acids: Major enzymes of Homo-cysteine dependent trans-sulfuration pathway are CBS, CSE and 3-MST which are responsible for catalyzing L-cysteine into H_2S in mammalian tissues. Homocysteine and L-serine form cystathionine from CBS and can convert cystathionine to form H_2S by CSE. Whereas cysteine dioxygenase (CDO) and aspartate aminotransferase (AAT) catabolises cysteine and forms sulfur dioxide (SO_2).

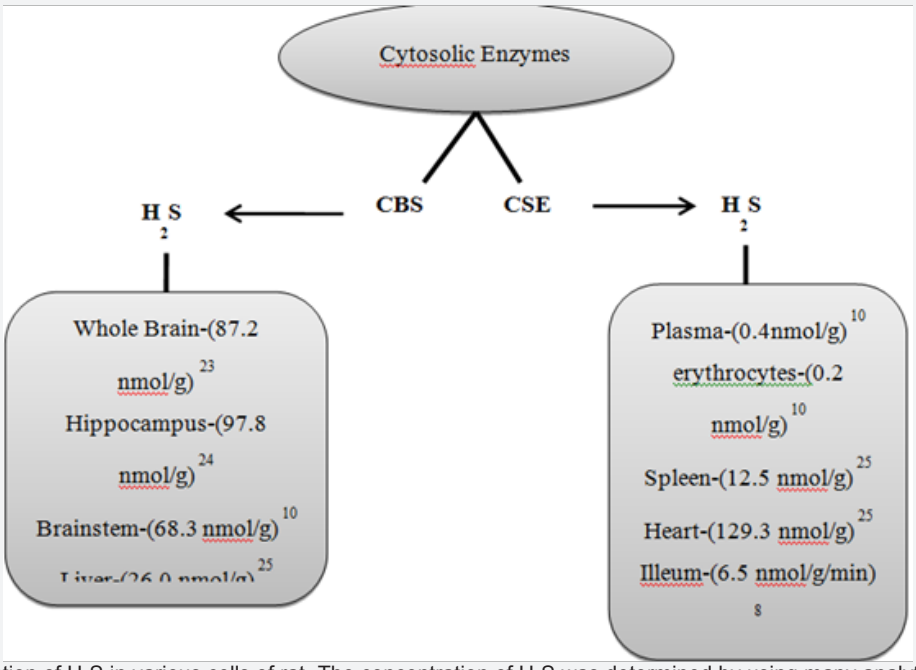

Figure 2: Concentration of H_2S in various cells of rat- The concentration of H_2S was determined by using many analytical methods incited studies.

Potential Effects of H_2S in Human Biology

H_2S together with NO and CO, comes under a family of labile transmitters termed as gas-transmitters. Being a potential endogenous gas-transmitter, H_2S is a highly lipophilic molecule that is rapidly diffusible through the cell membranes without using any specific transporters [26] and it is 5 fold more soluble in lipophilic solvent than aqueous solvent [2,27]. H_2S is weakly acidic in nature (pKa = 6.76 at 37°C) in aqueous solution [28].

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H_2S dissociate into two dissociation states: HS- (pKa = 7.04) and S2- (pKa = 11.96). Approximately 18.5% of total sulfide are present in undissociated form and 81.5% exists as HS- [28]. Various studies have suggested that H_2S exerts many potential effects on a large number of biological targets and is involved in several physiological and pathological processes (Figures 3 & 4).

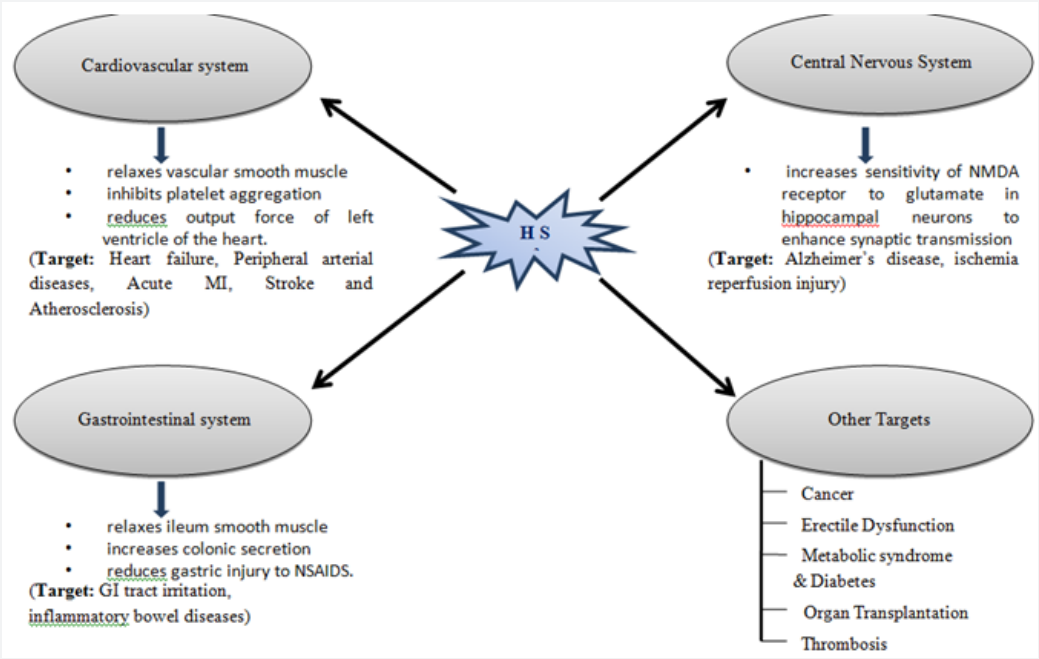

Figure 3: Potential targets for Hydrogen sulfide (H_2S). Various experimental investigations suggest that H_2S plays a prominent role in normal physiology and pathophysiology. Therefore, targets for H_2S therapy includes heart failure, peripheral arterial diseases, acute MI, stroke, atherosclerosis, GI irritation, Alzheimer's disease, cancer, thrombosis, organ transplantation, diabetes and erectile dysfunction.

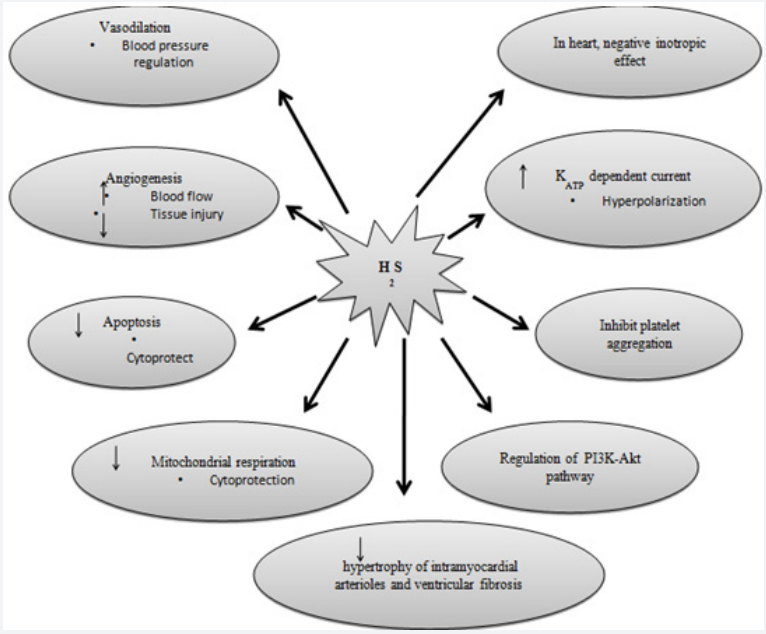

Figure 4: This figure illustrates the major cardiovascular actions of H_2S.

H_2S and Cardiovascular Effects

For various important physiological processes H_2S needs to interact with a wide range of ion channels. There are varieties of experimental models, including a canine model of cardiopulmonary bypass with hypothermic cardiac arrest that describes the cardioprotective effects of H_2S. Cardioprotective action is through modulation of ATP-sensitive potassium (KATP) current [29] and voltage-gated L-type calcium current [30]. It

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has been seen that H_2S plays a prominent role in myocardial pre and post conditioning responses [31]. H_2S exerts a negative inotropic and chronotropic effects both in-vivo and in-vitro in the heart [32] and protect the heart against injury following coronary artery ligation [33] and ischemia [34]. Recent review suggested that in vasculature, H_2S in combination with NO generates nitrosothiol with inotropic properties [129,130].

Mechanistic Pathways that are Implicated in the Cardioprotective Effect of H_2S are

a) Involvement of ATP sensitive K^+ channel and Voltage gated L-type calcium current [29,30]

b) Regulation of mitochondrial respiration [7]

c) Regulation of cytoprotective genes such as Nrf-2 [35]

d) Activation of cardiac extracellular-signal-regulated kinase (ERK) and/or phosphotidyl-inositol 3-kinase (PI3K-Akt) pathway [36].

Along with these cardioprotective effects H_2S also interacts with those ion channels that are involved in the membrane action potential and may be effective in cardiac arrhythmias [37]. In addition to these effects against collagen, ADP and aggregating agents H_2S can inhibit human platelet aggregation *in-vitro* [38]. Furthermore, several studies on vascular tissue have been concluded that H_2S is a potent vasodilator and perhaps an EDHF (endothelium derived hyperpolarizing factor) [8,35]. Experimentation in isolated rat aortic and portal vein and using a perfused rat mesenteric showed that H_2S dilates only blood vessels [8,39-41] not coronary [39] and vascular beds. The Vasodilatory effect of H_2S is independent of guanylyl cyclase/cGMP pathway [42]. However H_2S induces vasorelaxation through involvement of cGMP-dependent protein kinase-I. Recently, it was focused on the role of H_2S in chronic changes of vasculature. It has been reported that chronic treatment with NaHS can reduce hypertrophy of intramyocardial arterioles and ventricular fibrosis in hypertensive rats [43]. In addition, H_2S also inhibits L-type calcium currents in rat cardiomyocytes and the study suggested that if cardiomyocytes were treated with (dithiothreitol) DTT, an H_2S donor could change in cardiac function [44]. Wei H et al. [132] reported that H_2S could inhibit hyperpolarization of activated inward current and delayed rectifier potassium channels in human cardiomyocytes. These effects could have a significant role in prolongation of the action potential and vasodilatory function of H_2S [45].

H_2S and Nervous System

Biosynthesis of H_2S and its Regulation in CNS

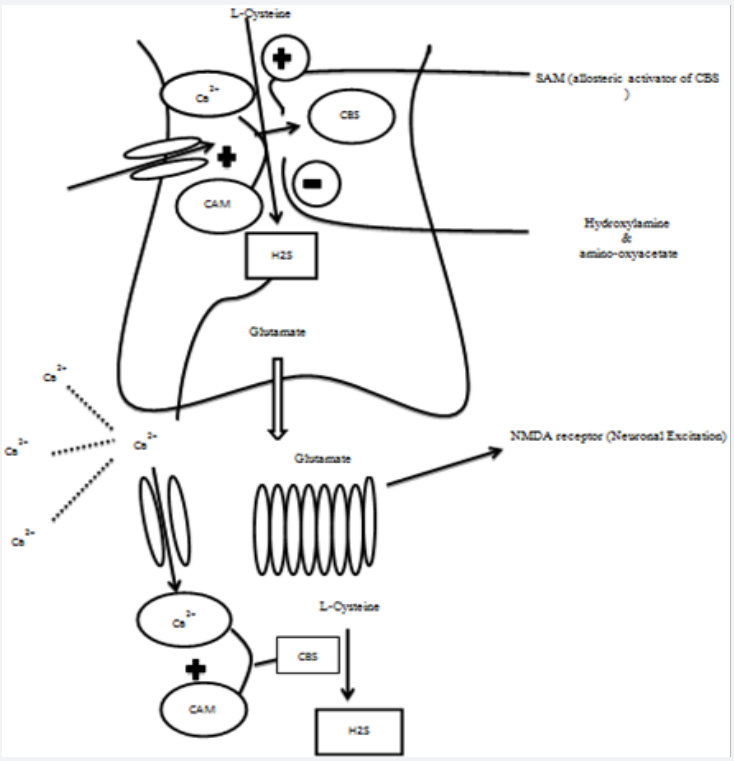

Figure 5: Production and Regulation of H_2S in central nervous system: when electrical stimulation or neuronal excitation occurs, electrical signals descend to axon terminals and Ca^{2+} enters into the nerve terminal then interact with calmodulin which activates the CBS and the formation of H_2S. An influx of Ca^{2+}, perhaps triggered by the activation of NMDA receptors by glutamate or via separate channels, binds to calmodulin (CaM), thereby activating CBS. CBS seems to be the main H_2S-forming enzyme in the CNS. SAM is an allosteric activator of CBS whereas hydroxylamine and amino-oxyacetate are inhibitors of CBS.

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In the CNS, H_2S is enzymatically produced by three major enzymes- CBS, CSE [11] and 3-MST [46] and there it is usually stored in astrocytes as bound sulfane sulfur and releases free H_2S in response to neuronal excitation [47]. The concentration of CBS is highly present in the hippocampus and the cerebellum [48] whereas it is highly localized to microglial cells [49] and astrocytes [50]. Generally, mRNA of CBS is found in the brain especially hippocampus [48]. Lee et al. [51] investigated that H_2S is enzymatically produced in astrocytes 7.9 fold greater than in cultured microglial cell and suggest that astrocytes is the largest brain cell for producing H_2S [51]. CSE is also the second major enzyme for producing H_2S and in CNS; it is highly expressed in the spinal cord [52] and cerebellar granule neurons [53]. In the brain, endogenous H_2S is formed from L-cysteine by pyridoxal 5'-phosphate dependent enzyme CBS. CBS activity is enhanced by S-adenosyl-L-methionine (SAM) and pyridoxal 5'-phosphate and mediated by Ca^{2+} and a calmodulin pathway [54, 55] as shown in Figure 5. Longer-term regulation of CBS activity most probably is dependent on SAM whereas hydroxylamine and amino-oxyacetate reverses the activity of CBS. In AD brains, the level of SAM is lower than the brains of normal individuals [56]. It has also been reported that production of H_2S is stimulated in response to neuronal excitation as well as electrical stimulation. Furne et al. [57] has investigated the brains of eight mice and estimated free concentration of H_2S around 14 ± 3.0 nM [57]. It has been suggested that 50-160μM of H_2S in the brain is found for physiological function [58,59].

Effect of H_2S in Regulation of Intracellular Signaling Pathways in CNS

Brain function is regulated by phosphorylation of intracellular proteins and Ca^{2+} release. These both processes are regulated by activation of protein kinase-A (PKA). Maintenance of long term potentiation (LTP) requires activation of PKA that may phosphorylate NMDA receptors and can enhance permeability of Ca^{2+} [60,61]. Kimura et al. [17] found that NaHS, an H_2S donor enhances cAMP production in cerebral cortex and cerebellum neuron culture which activates protein kinase-A [62]. Another one is tyrosine kinase which is present on the surface of cell receptor; where H_2S activates receptor tyrosine kinase and protect neurons against oxidative stress [63]. H_2S also activates endothelial growth factor receptor (EGFR) and EGFR activation can modulate signaling of NMDA receptors and LTP [48]. Whiteman et al. [64] suggests that H_2S may work as an antioxidant because it potentially inhibits intracellular nitration of proteins and oxidation of proteins in human neuroblastoma cells with inhibition of peroxynitrite induced cytotoxicity and presumably increases GSH production [64] and additionally this can enhance glutamate uptake [65]. Kimura and Kimura [66] reported that increased GSH level can increase neuroprotection using immature cortical neurons culture and HT22 cells that depends on extracellular cysteine [66]. Taking together, these effects of H_2S can regulate intracellular signaling in CNS i.e. oriented towards neuroprotection and other CNS diseases.

Role of H_2S in Neuronal Diseases with their Mechanism

Various recent studies suggested that H_2S has played a prominent role as an antioxidant, antiapoptotic in neurons and glial cells [66,67]. Additionally, H_2S may also have anti-inflammatory activity because it induces alteration in Ca^{2+} in astrocytes and microglial cells [68,69]. H_2S seem to have multiple roles as it can enhance NMDA receptor mediated responses and facilitate long term potentiation in hippocampus but it can block excitatory postsynaptic potentials (EPSPs) (inhibit synaptic transmission). Literature findings also suggested that H_2S enhances NO-induced relaxation of smooth muscles [70] and decreases corticotrophin secretion from hypothalamus [71]. Therefore Kimura et al. [17] demonstrated the function of H_2S as a neuromodulator in the brain. It was reported that H_2S is abundantly found in cerebrospinal fluid of patients with Down syndrome because of chromosome 21 which encodes CBS [72]. Neurodegenerative diseases of the CNS such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and Amylotropic lateral sclerosis (ALS) are strongly associated with oxidative stress causing neuronal cell death [73]. Endogenous H_2S can activate protective signaling pathways that are processed through antioxidant enzymes such as SOD, GSH and heme-oxygenase-1 (HO-1) and further their expression is regulated by transcriptional factors like NFe2, NrF2 and PGC-1α [74,75]. H_2S may protect neuronal damage from oxidative stress via increasing levels of GSH or redistributing GSH into mitochondrial localization [76]. It was also investigated that in AD, NaSH attenuated lipposaccharide-induced cognitive defects [77] and inhibited Aβ induced cellular injury or death in rats [78]. H_2S may also reduce amyloid-β plaques in AD [79], can prevent neurodegeneration in mouse models of PD [80] and can enhance analgesia via μ-opioid receptor interaction [81]. In ischemia/reperfusion, mitochondria are the major part of cell which is affected and enhances the production of ROS with depolarizing the mitochondrial membrane. H_2S scavenges the free radicals and decreases the generation of ROS [82,83]. During ischemia, mitochondrial cytochrome oxidase activity was enhanced that can generate ROS. H_2S decrease the level of ROS and imparting cytoprotection, also inactivates the activity of mitochondrial cytochrome oxidase and stimulate SOD to lower the level of ROS [84].

Mechanistic role of H_2S in CNS –

(a) It increases cAMP levels in neuronal and glial cell lines and primary neuron cultures

(b) It hyperpolarizes CA1 and dorsal raphe neurons by activating KATP channels [85, 62]

(c) Increasing the sensitivity of NMDA receptors following a rise in intracellular cAMP facilitates hippocampal LTP and increase H_2S production and NaHS (H_2S donor) with direct electrical stimulation and glutamate application. H_2S promotes glutamate mediated neurotransmission via NMDA receptors (Figure 6a).

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(d) It scavenges ROS and RNS (free radicals) directly or indirectly via enhancing GSH production and enhances mitochondrial protection (Figure 6b).

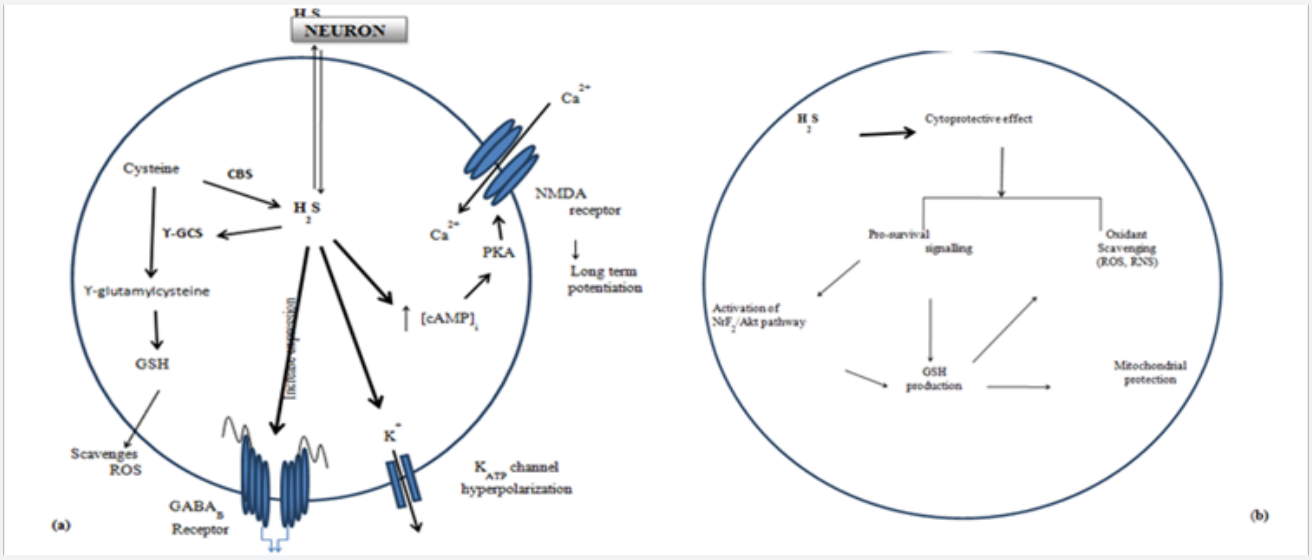

Figure 6: (a) This figure briefly explains the physiological role of H_2S in neurons including- cAMP and NMDA receptors on $[Ca^{2+}]i$ and the role of GABAB receptor in the maintenance of excitation/inhibition balance. **(b)** It represents the cytoprotective effect of H_2S in neurons including scavenging of free radical and mitochondrial protection.

H_2S and inflammation

The contribution of H_2S in inflammation is becoming clearer. A hallmark of inflammation is that H_2S has capability to relax vascular smooth muscles [51,86]. There are various animal models like carageenan induced monoarthritis [87] and synovitis [88] in rats, ischemia-reperfusion injury [89] and tobacco-smoke induced lung inflammation [90,91] in mice that describes the role of H_2S in inflammation. Some key effects of H_2S that influences inflammation and injury are illustrated in Figure 7. H_2S donors or Sulfide salt donors are capable to decrease infiltration of neutrophils and lymphocytes [88,92] which is practically proved by the concussion of H_2S in suppression of leukocyte adhesion to the vascular endothelium, inhibit migration of leukocytes into sub endothelial space and the subsequent extravasation of leukocytes [92]. H_2S can also inhibit the ability to suppress activation of nuclear transcription factor (NF-κB and P38 MAPK) [93,94,95] with reduction of many proinflammatory cytokines, chemokines and enzyme expression like [iNOS] [88,96-98]. Another anti-inflammatory effect of H_2S is through inhibition of enzyme phosphodiesterase and thus elevating cGMP and cAMP levels [99]. In acute and chronic rat models of paw edema, it has been reported that H_2S enhances the edema reducing effects from NSAIDS releasing H_2S and therefore can reduce plasma exudation [100,101]. Recently it has been reported by Whitteman et al. [98] that H_2S is also present in patients with rheumatoid arthritis and osteoarthritis [102]. In different animal disease models like ischemia/reperfusion injury [103], ventilator-induced lung injury [104] or oleic acid induced acute lung injury [105]. H_2S and their donors exert its protective effects; the mechanism behind the effects is able of H_2S to attenuate activation of transmigrated neutrophil cells and the release of pro-inflammatory cytokines. Faller S et al. [104] investigated that inhalation of hydrogen sulfide substantially reduced lipossacharide induced acute lung injury due to its anti-inflammatory effect [106].

H_2S and GI tract:

Due to its anti-inflammatory action H_2S is gaining important therapeutic value in the GI tract. It is synthesized from two important enzymes CSE and CBS in many parts of GI tract like stomach ileum, jejunum, and colon. CSE is predominantly found throughout the whole GI tract because of its association with vascular whereas CBS is restricted to some parts like muscular mucosa, lamina and propria [107]. Recently various studies suggested that H_2S exerts several actions including relaxation of smooth muscles of the intestine [108], stomach [109] and colon [110] via different mechanisms with anti-inflammatory [96] and anti-nociceptive effects [52].

Mechanistic Action of H_2S in Different Parts of GI Tract

a) In stomach- H_2S activates myosin light chain phosphatase and relaxes smooth muscles.

b) In ileum- H_2S relaxation is independent of NO, KATP and Ca^{2+} channels.

c) In colon- The effect of H_2S is not involved major known K^+ channel, activation of MLCP or rho-kinase.

d) In intestine- H_2S stimulates chloride secretion via excitation of secreto motor neurons and through targeting on vanilloid receptors (TRPV1) which is found in afferent nerves of guinea pig and human colon [111].

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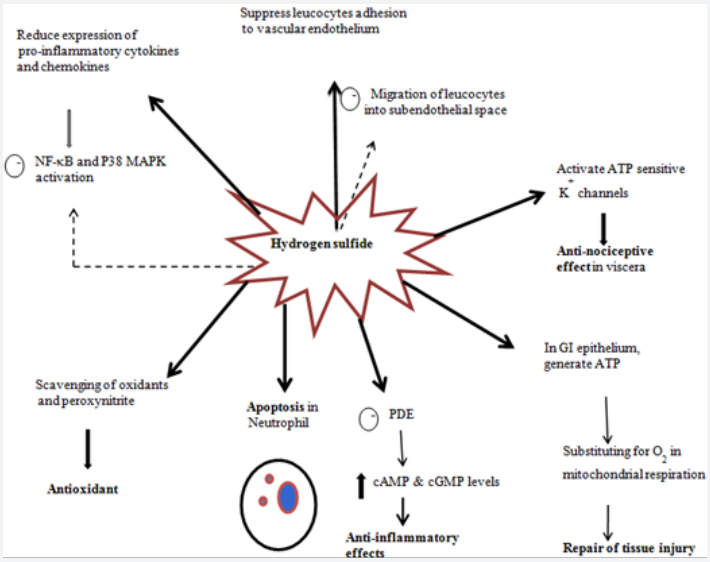

Figure 7: This figure describes the way of H_2S showing anti-inflammatory, anti-nociceptive and antioxidant effects.

Various early studies investigated that concentration of H_2S is relatively high in the lumen of the gut because human GIT is a home of various bacterial species that are capable of producing H_2S, but most is bound to fecal material. Therefore it cannot diffuse through the epithelium, only a small amount (i.e. Micromolar concentrations) is free to diffuse across the epithelium that is absorbed and primarily metabolized via mitochondrial sulfide quinine reductase (SQR) to thiosulfate and produces ATP. Thus H_2S is an important energy source for colonocytes and protects gastric mucosa from injury [112].

Moreover, it is known that H_2S has dual nature, both anti-inflammatory and inflammatory effects in the GI tract. Anti-inflammatory activity and ulcer healing activity by H_2S both are independent of major known K^+ channel and NO synthase [112] and in an experimental model of colitis H_2S protects and promotes resolution against colitis [113]. Whereas H_2S can modulate cell cycle progression via expression their genes and can cause colorectal cancer through inflammatory and DNA repair processes [114]. In caerulein induced pancreatitis model, H_2S acts like inflammatory signaling molecule [115-117]. H_2S enhances intracellular adhesion molecule-1 (ICAM-1) expression and through NF-κB stimulates neutrophil adhesion [118]. However, it is also investigating that H_2S protects the pancreas from oxidative damage [119-130].

H_2S and Respiratory System

It has been proposed that H_2S produce its effect on lung and showed action on pulmonary blood flow and pulmonary vascular resistance [131]. It was also observed that H_2S production decreases during chronic hypoxia and pulmonary hypertension in rats [132,133]. Exogenous H_2S or sulfide salt donors attenuate pulmonary arterial pressure and tissue GSSG whereas H_2S enhances the total antioxidant capacity [133]. It also relaxes pre contracted bronchial smooth muscles of mouse [134]. It was also reported that H_2S attenuates oleic acid induced lung injury [135] and ovalbumin induced lung asthma and generates anti-inflammatory action whereas exogenous H_2S enhances inflammation and attenuates iNOS activation.

Mechanistic Action of H_2S on Respiratory System

a) It relaxes bronchial smooth muscles i.e., independent of KATP channel, cyclooxygenase-1 & 2 and guanylyl cyclase [134].

b) It reduces tissue GSSG [132].

H_2S and Diabetes Mellitus

Diabetes mellitus and its complications depend on the enhanced generation of ROS. Many substances such as hormones, neurotransmitters and nutrients can control pancreatic-β cells to release insulin. Furthermore, experimental studies have been reported that H_2S may inhibit the release of insulin via opening of KATP channel. However, it was also explained that this mechanism is independent of the opening of KATP. H_2S has dual effects on cell survival/death of pancreatic-β cells. Yang et al [123] investigated that H_2S and over expressive CSE activates mitogen activated protein kinase (P-38 MAPK) and induce apoptosis in rat insulinoma INS-1E cells ,whereas, H_2S may also protect intact mouse islets and MIN 6 cells against high glucose, fatty acids or cytokines induced cytotoxicity .

Mechanistic Actions of H_2S to Protect Pancreatic-β Cells and in Diabetes are:

a) H_2S donor, NaHS or L-cysteine scavenges ROS via increasing content of glutathione.

b) In MIN-6 cells, H_2S stimulates Akt phosphorylation (important for β-cell survival).

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H_2S and Reproductive System/Erectile Dysfunction (ED)

It has been investigated that CBS and CSE were found in the Leydig, Sertoli and germ cells of rat testis [125] as well as in intrauterine tissues and human placenta [126]. Although H_2S relaxes vas deferens smooth muscle and showed vasodilatory properties in the corpus cavernosum [127]. Therefore, H_2S is an effective therapy for ED. The study explores the mechanism that H_2S enhances the NO production via expression of constitutive nitric oxide synthase (NOS) isoforms i.e. endothelial NOS (eNOS) and neuronal NOS (nNOS) in rat corpus cavernosum and states that exogenously applied NaHS enhances eNOS but not nNOS. This can cure inherited erectile impairment which happens due to attenuation of endothelial NO formation in cavernosum [128]. However, per se effect of H_2S in reproduction is still under investigation.

Conclusion

During the past decade, several researches have been focused on H_2S. This review has centered the role of H_2S in human biology. Indeed, efforts are going on to investigate the therapeutic potential of H_2S in human diseases. It was discovered that H_2S is continuously produced enzymatically in mammals and regulates the vast array of physiological processes. Now recently it is considered as a new gaseous signaling molecule that effect on all organ systems and in various pathological states. Accumulating evidence suggests that H_2S have been implicated in neurotransmission via various pathways. It acts as a physiologic vasodilator and plays a prominent role in cardioprotection, pro and anti-inflammatory processes and several metabolic disorders such as diabetes, obesity, gout. Nevertheless, our understanding of mechanistic action is still fragmentary. Since it has a diverse biological profile to treat a number of diseases, H_2S has come under a promising research to develop H_2S-releasing prodrugs. It might be possible that H_2S prodrugs can enhance H_2S bioavailability and be efficacious in physiological processes.

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How to cite this article: Shivani C, Lubhan S, Vipul K, Chandrakala. Hydrogen Sulfide (H_2S) - Poison Gas to Signaling Molecule in Regulation of Human Biology. J of Pharmacol & Clin Res. 2018; 5(3): 555661. DOI: 10.19080/JPCR.2018.05.555661

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How to cite this article: Shivani C, Lubhan S, Vipul K, Chandrakala. Hydrogen Sulfide (H_2S) - Poison Gas to Signaling Molecule in Regulation of Human Biology. J of Pharmacol & Clin Res. 2018; 5(3): 555661. DOI: 10.19080/JPCR.2018.05.555661

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How to cite this article: Shivani C, Lubhan S, Vipul K, Chandrakala. Hydrogen Sulfide (H_2S) - Poison Gas to Signaling Molecule in Regulation of Human Biology. J of Pharmacol & Clin Res. 2018; 5(3): 555661. DOI: 10.19080/JPCR.2018.05.555661

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