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Review Article

Review and Prospective: Hydrogen Sulfide Rescues Mercury- Induced Toxicity

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ABSTRACT

We previously reported that Hydrogen Sulfide (H_2S) may attenuate Methyl mercury (meHg) -induced neurotoxicity via mitochondrial preservation, the encouraging results prompt further investigation on this topic. This paper is intended to review published data on issues of Hg toxicity, mainly chronic neurotoxicity, existing treatments and remedy values of H_2S. For issues of Hg toxicity, the main Hg intoxicant syndrome of Minamata Disease, sources of exposure, pharmacokinetics and toxic mechanisms were reviewed. For the existing treatments, the merits and defaults of chelating agents and other approaches by enhancing antioxidant defense mechanisms were discussed. The remedy values of H_2S were emphasized, besides the well known that H_2S as gaseous and cyto-protective mediator, H_2S reacting with metal ions including Hg, H_2S superior to other sulfides for protecting organelles because of its freely penetrating cellular membranes, development of H_2S donors, plant organosulfurs as potential H_2S donors, and several experimental evidences of H_2S antagonizing Hg toxicity were also mentioned, which provide reasonable ground for selecting suitable H_2S donors to combat Hg toxicity. Prospective: promoting endogenous H_2S production or supplying exogenous H_2S to some extent may have benefits for Hg intoxication. Activating the enzymes which producing H_2S and administrating the reaction substrates for H_2S production, or modulating intestinal microbiota may increase the endogenous production of H_2S, and developing more stable and slow-releasing H_2S donors from chemically synthesized compounds and nature plant organ sulfurs should be done for supplying the exogenous H_2S goal.

Keywords: Heavy Metal; Pollution; Hydrogen Sulfide Donor; Organosulfurs; Polysulfides; Mitochondria

ABBREVIATIONS

ATSDR: Agency For Toxic Substances and Disease Registry; AIF: Apoptosis-Inducing Factors; ADT-OH: ([5-(4-Hydroxyphenyl)-3H-1,2-Dithiole-3-Thione]; AP-1: Activator Protein-1; BAL; Dimercaprol : British Anti-Lewisite; Bismethylmercury Sulfide ((MeHg)2S); BKCa: Ca^{2+}-Sensitive K^+ Channel (); Cystathionine β-Synthase (CBS); Cystathionine γ-Lyase (CSE); Central Nervous System (CNS); Catalase (CAT); Cytochrome C (Cyt-C); D-Amino Acid Oxidase (DAO); Diallyl Sulfide (DAS); Diallyl Disulfide (DADS); Diallyl Trisulfide (DATS); 2,3-Dimercaptosuccinic Acid (DMSA); 2,3-Dimercaptopropanesulfonate (DMPS, Unithiol); Food And Drug Adminstration (FDA); Glutathione (GSH); Glutathione Peroxidase (GPX); Glutathione Peroxidases (GPxs) ; Glutathione Reductase (GR); Glutamic Acid (Glu); Hydrogen Polysulfide (H_2S_n); Hypochlorous Acid (HOCl); Mercuric Chloride ($HgCl_2$); Mitochondrial Permeability Transition (MPT); 3-Mercaptopyruvate Sulfurtransferase (3MST); 3-Mercaptopyruvate (3MP); 3-Mercaptopyruvate Sulfurtransferase (3MST); Mercury (Hg); N-Acetyl-5-Methoxytryptamine (Melatonin); N-Methyl-D-Aspartate Receptors (NMDARs); Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); Nitric Oxide (NO); Nuclear Factor κB (NF-κB); Organosulfur Compounds (OSC); Peroxynitrite ($ONOO^-$); Phosphatase And Tensin Homolog (PTEN); Protein Kinase A (PKA); Reactive Oxygen Species (ROS); Superoxide Dismutase (SOD); Seleno Groups (-SeH) ; Sulforaphane (SFN) ; Superoxide (O^{2-}); Sodium Thiosulfate ($Na_2S_2O_3$); Seleno (-SeH); Thiol (-SH); Thiol Groups (-SH); Thioredoxin Reductase (TrxR).

INTRODUCTION

Elemental and compound Mercury (Hg) exist everywhere in our environment, and human exposure to Hg is unavoidable. The human body lacks effective mechanisms to excrete, thus Hg accumulates in the body, especially in nerve tissues [1]. Although the mechanism of Hg toxicity is still unclear, most studies agree that Hg firmly binds to thiol (-SH) and seleno (-SeH) containing macromolecules, the binding controls the movement of Hg and disrupts the biological function of various important molecules, chiefly, unbalancing the redox state, leading to free radicals overproduction, mitochondrial damage, apoptosis, finally, neurodegeneration and many other diseases [2].

Despite a massive search for strategies to counteract Hg toxicity, no ideal approach to completely abolish Hg toxicity has been identified. Chelating agents are the major antidotes which can assist the elimination of Hg in acute intoxication; however, these drugs are of limited use because of their chronic effects largely unestablished [1]. Approaches by enhancing antioxidant defense mechanisms were also developed, which include thiol- and seleno- group donors, antioxidative vitamins and others, however, as complementary therapeutic approaches, lots of them limit their application by toxicities or unclear effects. There is a long way to go before solving the problem of Hg toxicity.

Hydrogen Sulfide (H_2S) is a pungent, toxic gas, and also a reducing agent. It can react with some metal ions including Hg to form insoluble metal sulfides, and is able to freely penetrate the membranes of cells for its highly lipophilic character. In recent decades, H_2S is discovered to be synthesized in mammalian and human tissues, and has attracted considerable interests in a relatively short period of time as an endogenous gaseous mediator and potential therapeutic tool [3]. Firstly demonstrated that exogenous H_2S protected cortical neurons from glutamate-induced oxidative stress. Since then, numerous studies have shown protective effects of H_2S to not only brain but various tissues under different stressors, therapeutic roles of H_2S are dynamically explored.

The above-mentioned facts remind us that H_2S may be beneficial for dealing with Hg toxicity. This area has not received enough attention. Recently, we explored whether H_2S donor (NaHS) could attenuate methyl mercury (MeHg)-induced neurotoxicity in rats. The results showed that NaHS significantly reduced MeHg-induced oxidative stress, mitochondrial damage and cellular apoptosis. And also, NaHS increased DNA and RNA content, and the activities of acetyl cholinesterase and Na^+/ K^+-ATPase, these parameters were compromised by MeHg exposure. Our results demonstrate that H_2S positively protect brain against MeHg-induced toxicity, and the mechanisms appear to involve the inhibition of oxidative stress and the protection of mitochondria.

As a kind of toxic gas, H_2S gas is inconvenient for conventional research and therapeutic purpose. Some compounds, including NaHS and Sodium Thiosulfate ($Na_2S_2O_3$) [4], which can release H_2S under physiological conditions, known as H_2S donors, and some plant organosulfurs compounds are regarded as potential H_2S donors, furthermore several slow-releasing donors have shown some clinical values. It should be noted that H_2S -releasing capabilities of the donors are quite different, the functions of H_2S donors vary to a

certain degree [5], the selection of suitable H_2S donors is important for the further investigation on the present topic.

The previous encouraging results prompt further investigation on this topic. This paper is intended to review published data on issues of Hg toxicity, mainly chronic neurotoxicity, current available approaches for reducing Hg toxicity, and remedy values of H_2S. The data of H_2S were emphasized, from physicochemical property, physiologic source, biological activities, development of H_2S donors, to experimental evidences of H_2S antagonizing Hg toxicity, which provide reasonable ground for suitable donors to combat Hg toxicity. Finally, we give the prospective for increasing the H_2S level to some extent by promoting endogenous H_2S production or supplying exogenous H_2S to combat Hg toxicity. The review and prospective may provide some helps for scholars who are interested in the campaign for dealing with Hg toxicity.

TOXICITY OF HG

Mercury (Hg) was named after the planet Mercury. It exists in three basic states: elemental Hg or Hg vapor, inorganic Hg, and organic Hg. Elemental Hg was known to the ancient Chinese and Hindus and has been found in Egyptian tombs of 1500 BC. Hg also widely used in many areas, in industry for the production of batteries, in plastic production as a catalyst, in paper production as a slimicide, in instruments as a working fluid, and so on. Medically, it was once used to treat syphilis in the European pandemic of the late 15th century [6], and Cinnabar (mainly contains Hg sulfide, HgS) has been used for 2000 years in traditional Chinese medicines. Nowadays, Hg is used as a germicidal and bactericidal agent in the making of amalgam dental fillings [6] and as a preservative in vaccine.

Since 1940s, toxicity of Hg was known, first, deadly Hunter-Russell syndrome and then Minamata disease were reported, public health disaster also occurred in Japan, Iraq, Canada and other areas. Now, In America, Hg is listed as the third-most frequently found heavy metal behind lead and arsenic, and the most toxic substance in the United States [7]. The biological behavior, pharmacokinetics and clinical significance of the various forms of Hg vary with different states [8]. Generally, the target organ for inhaled Hg vapor is primarily the brain, inorganic Hg chiefly damage the gut lining and kidney, while organic Hg especially MeHg is widely distributed throughout the body, causes neurological deficits and other damages [9].

Hunter-Russell Syndrome and Minamata disease

In 1940s, Hunter and Russell described MeHg intoxication in four workers from a factory that produced Hg-contained fungicidal agents. An autopsy of one worker revealed marked neuronal destruction and cerebral atrophy with cortical loss. Owing to their description, MeHg poisoning subsequently became known as Hunter-Russell syndrome [6].

In Japan, from the 1920s to the 1960s, a chemical factory was using Hg as a catalyst, led to MeHg chloride in the factory' s effluent was released into Minamata bay on the southwest coast of Kyushu. In May 1956, physicians at nearby Kumamoto University Hospital were confronted with a new central nervous system disease, latterly named "Minamata Disease", when four factory workers presented with brain damage, and soon more people developed similar symptoms [10]. In October 1959, MeHg was proved to be the causative agent. It was because fish in Minamata Bay was contaminated and accumulated MeHg, humans consumed the fish get disease. In the 1960s and 1970s, chronic brain damage, mental retardation, developmental disturbances, liver disease, hypertension, and poor metabolism were noted in the children of mothers exposed to Hg contaminated fish. Children exposed in utero also exhibited chorea, ataxia, tremors, and seizures [11,12].

MeHg led public health problem also occurred in Niigata of Japan and Canada for MeHg contaminated fish consumption [10,13]. In Iraq, over 6000 people were hospitalized following consumption of bread made from MeHg-treated grain, and infants exposed in utero demonstrated developmental anomalies similar to those at Minamata [14,15].

Sources of Exposure

Environmental source: Elemental Hg or as an inorganic sulfide compound are found primarily in the earth's crust at approximately 0.5 parts per million. It has been estimated that annual worldwide emissions of Hg into the atmosphere at 2,200 metric tons [16]. One-third of these emissions originates from natural sources (volcanic eruptions and decay of Hg-containing sediment), while two-thirds from man-made sources. Twenty-five percent of total worldwide emissions come from fossil fuel combustion [17,7]. The ATSDR considers anyone who lives in close proximity to a former Hg mining site, recycling facility, municipal or medical incinerator, or coal-fired electric generating plant to be at risk for Hg toxicity [6].

Food source: Elemental and organic Hg settle in water, where they are converted by microorganisms into organic Hg, in which Hg is bonded to a Me, ethyl, phenyl, or similar group, organic Hg is ingested by smaller creatures, which are consumed by larger fish. Fish at the top of the food chain may concentrate considerable Hg in their tissues [8]. Food and Drug Administration (FDA), presented data warning of the consequences for fetuses of women who follow the current FDA's fish consumption advisory and eat 12 ounces of "safe" fish per week [18]. The Environmental Working Group estimates that more than 25 percent of children in utero in the United States would be exposed to levels of Hg above the EPA safe reference dose (0.1 g MeHg/ kg body weight/ day) for at least 30 days during gestation and would have an increased risk for neurological damage [19, 20].

Dental amalgam source: Human metallic Hg exposure comes from Hg vapor out gassing from amalgam fillings, at a rate of 2 to 28 micrograms per facet surface per day, of which about 80% is absorbed, according to the World Health Organization [8,21]. It is estimated approximately 100 tons of Hg placed in people's mouths, dental amalgam has been characterized as one of most important human Hg exposure source [22,23].

Consumer products and other medical products sources: Some consumer products and medical products have Hg ingredient, such as skin-lightening creams or antiseptic facial products, vaccines used Hg as preservative, Hg-containing diuretics or laxatives, and teething powders, those who use these products containing Hg are also considered at significant risk, especially pregnant or nursing women and their developing fetuses and breast-fed babies [8].

Pharmacokinetics of Hg exposure

The toxicological roles of organic and inorganic Hg remain a matter of debate. While some authors state that the different forms of Hg have the same toxic entity and that toxicity depends mainly on differential bioavailability, others state that each Hg form has different physicochemical properties and toxicity profiles. Nevertheless, both forms can induce a wide range of toxic effects [8,9], and the

pharmacokinetics of Hg exposure must be distinguished when discussing their toxicity [8].

Elemental Hg: Mercury vapor is transported to the brain, either dissolved in serum or adherent to red cell membranes. Metallic Hg passes easily through the blood brain barrier and through the placenta, where it lodges in the fetal brain [8]. In addition to the brain, metallic Hg is also deposited in many other organs, i.e., thyroid, breast, adrenals, liver, kidneys and others, and may be associated with dysfunction of those organs [8,24].

Metallic Hg is largely excreted as mercuric Hg. The excretory half lives of metallic and mercuric Hg vary widely, depending on the organ of deposition and redox state, with values ranging from a few days to several months, with some pools (e.g., CNS) having a half life exceeding several years [25].

Inorganic Hg

Mercurous Mercury: Mercurous Mercury is the chemical compound with the formula Hg_2Cl_2, also known as calomel; it is a component of reference electrodes in electrochemistry [137]. It is poorly soluble in water and poorly absorbed by the intestine, although some portion is thought to undergo oxidation to more readily absorbable forms, and some absorption evidently occurs, as calomel is occasionally associated with pink disease, or acrodynia [8].

Mercuric Mercury: Mercuric Chloride ($HgCl_2$) was used as a preservative and for development of photographic film and is a component of some skin-lightening creams. Only about 2% of ingested $HgCl_2$ is absorbed initially [26], although it is believed that its corrosive effect on the intestine may increase permeability [27]. Available data on skin penetration of $HgCl_2$ are insufficient to make quantitative comparison with ingestion or with metallic Hg.

Cinnabar: Cinnabar is the naturally occurring mineral with Hg in combination with sulfur, the major source for metallic Hg production. It is red in color so called red Hg sulfide, Zhu Sha in Chinese. Cinnabar is insoluble and stable, and cinnabar powder has been used as an important ingredient in traditional Chinese medicines and in Indian Ayurvedic medicines [28,136]. Approximately 40 traditional Chinese medicines contain some cinnabar according to Pharmacopeia of China, and it is the major source of Hg found in traditional medicines. Cinnabar is insoluble and poorly absorbed from the gastrointestinal tract. Absorbed Hg from cinnabar is mainly accumulated in kidney, resembling the disposition pattern of inorganic Hg, following long-term use of cinnabar, renal dysfunction may occur. The doses of cinnabar required to produce neurotoxicity are thousands times higher than MeHg [29-31]

Organic Hg: Most available data on organic Hg compounds refer to MeHg, which is a major source of human Hg exposure from food. Intestinal absorption of MeHg from fish is fairly efficient, as is absorption through the skin. On entry to the blood stream, MeHg adheres to sulfhydryl groups, particularly to those in cysteine. MeHg is deposited throughout the body, with equilibrium between blood and body occurring approximately four days after exposure [32]. Concentration of MeHg occurs in the brain, liver, kidneys, placenta, and fetus, especially in the fetal brain, as well as in peripheral nerves and bone marrow. Although MeHg has low lipid solubility, the ingested MeHg easily permeates the blood–brain barrier [33], since the complex of MeHg and cysteine may act as a "molecular mimic" for the amino acid methionine and gain entry into the central nervous system via the same mechanism methionine uses to cross the blood-brain barrier [34,35]. Deposited MeHg slowly undergoes demethylation to inorganic Hg. The excretory half life of MeHg in man is about 70 days, with approximately 90% being excreted in stool. Some degree of entero-hepatic circulation apparently occurs [8,36]. Perhaps 20% of MeHg is excreted in breast milk, with the actual amount varying with severity of exposure [8].

Mechanisms of Hg Toxicity

Mercury can cause biochemical damage to tissues and genes through diverse mechanisms, such as thiol and -Selenol Binding, Oxidative stress, depletion of glutathione, interrupting intracellular calcium homeostasis, interrupting excitatory amino acid pathways [37,38].

Mercury-Thiol and- Selenol Binding: Most studies agree that Hg has a high affinity for Thiol groups (-SH) and seleno groups (-SeH) that are present in amino acids, proteins and enzymes, such as Glutathione (GSH, a -SH containing molecule) and Glutathione Peroxidase (GPX, a -SeH containing protein). Since the stability constants (energy necessary to form and break bonds) for Hg and thiol complexes are so high, Hg will bind to any free thiol available and the thiol in the highest concentration will be the most frequently-bound. Selenols (–SeH) have a lower pKa than thiols (5.3 versus 8.5) and under physiological conditions are fully ionized to selenolates (–Se) and thus are more reactive and can easily interact with Hg. Selenoenzymes such as Glutathione Peroxidases (GPxs) and Thioredoxin Reductase (TrxR) are good targets for Hg [39]. The binding can alter protein conformation, or creating protein adducts through modification of side chains leading to changes in protein shape and activity [40].

Oxidative stress: Changes in the activity of several enzymes involved in antioxidant action, such as GPxs, TrxR, Glutathione Reductase (GR), Superoxide Dismutase (SOD), and Catalase (CAT) are indicative of Hg induced oxidative stress. Glutathione depletion, resulting from complexation with mercurials is also a good but unspecific indicator of Hg effects [41]. Hg could induce oxidative damage in the mitochondria directly, which leads to accumulation of ROS. ROS can lead to cell injury through several mechanisms, including direct damage to lipid peroxidation, protein and DNA oxidation [42].

Excitotoxicity: Excitotoxicity usually refers to the injury and death of neurons arising from overactivation of Glutamic acid (Glu) receptors that impairs cellular Ca^{2+} homeostasis, further leading to a generalized acute oxidative stress [42]. Glu, the main excitatory neurotransmitter, plays a crucial role in MeHg neurotoxicity, since the inhibition of Glu metabolism by MeHg leads to the over activation of N-methyl-D-aspartate receptors (NMDARs) which support neuronal survival or mediate neuronal death, depending on the degree of activation [43]. Meanwhile, the ensuing increase in the extracellular Glu levels is also likely associated with ROS overproduction [44]. Such mechanisms may operate in concert to cause the symptoms of MeHg poisoning [45].

Mitochondrial damage and apoptosis: MeHg have been shown to accumulate in mitochondria, MeHg induces oxidative stress and results in mitochondrial damage [46]. Mitochondria are cellular powerhouses responsible for generating energy and heat that are vital for cellular survival. In addition, mitochondria are involved in the apoptosis-signaling pathway. Mitochondria are vulnerable to free radicals, since they contain DNA (mtDNA); but, unlike nuclear DNA,

mtDNA has no histones to protect against the action of free radicals [2]. In addition, MeHg inhibits several mitochondrial enzymes, i.e. subunits of the respiratory chain complexes, ADP/ ATP translocase, Pi carrier, and decreases the mitochondrial transmembrane potential, subsequently reducing ATP production and Ca^{2+} buffering capacity [47].

Such mitochondrial damage usually begins at the onset of the Mitochondrial Permeability Transition (MPT), outer membrane rupture [48], and the release of proapoptotic factors, such as Cyt-C and AIF into the cytosol; this signaling further activates a caspase-independent pathway of apoptosis through DNA fragmentation and chromatin condensation, culminating in cell death [49]. Neurocytes are delicately connected to each other, extensive apoptosis will devastate their normal organizational structure and function, which might be associated with the many toxic symptoms of MeHg [50].

Inhibition of enzymes activities and DNA/RNA/protein synthesis: Covalent binding of Hg with -SH groups inhibits important enzymes, i.e AChE and Na^+/ K^+-ATPase in the neurosystem [51,52]. AChE is involved in various functions, e.g., keeping normal neurotransmission, brain development, learning and memory and neuronal damage [53]. The Na^+/ K^+-ATPase is responsible for translocating sodium and potassium ions across the cell membrane using ATP as the driving force, thus maintaining the normal gradient of these cations in animal cells, which is important for cell physiology. It is also involved in nerve impulse propagation and neurotransmitter release [54]. Inhibition of these enzymes contributes to the Hg-induced impairment of nerve function.

MeHg also Decreases Contents Of Nucleic Acid (DNA/ RNA) and protein, which are molecules central to all life processes. Inhibition of DNA and RNA synthesis by Hg compounds has been reported earlier, This decrease in nucleic acid content may be attributed to free radical damage to DNA and inhibition of RNA synthesis by direct interaction of ROS [1,55,56]. There are various theories which attribute MeHg inhibition of protein synthesis, including from inactivation of RNA polymerase I by binding to Hg, to direct interaction of protein synthetic machinery [57,56].

CURRENT AVAILABLE APPROACHES FOR REDUCING HG TOXICITY

Current available approaches for reducing Hg toxicity are mainly by chelating or enhancing antioxidant defense mechanisms. The former can effectively remove Hg from the body in acute intoxication, however, their effects in chronic Hg intoxication is largely unestablished [58]. The latter include thiol- and seleno-group donors, antioxidative vitamines and others, as complementary therapeutic approaches, their application are limited by toxicities or unclear effects.

Chelating agents

Although the Hg-sulfhydryl bond is stable, it is labile in the presence of other free sulfhydryl groups; therefore, Hg will be redistributed to other competing sulfhydryl containing ligands. This is the basis for chelation of heavy metals with sulfhydryl Chelators [9]. The first chelator British anti-lewisite (BAL; dimercaprol) was developed more than 70 years ago, latter in the late 1950s, two dithiol water-soluble analogs of BAL, 2,3-Dimercaptosuccinic Acid (DMSA) and 2,3-Dimercaptopropanesulfonate (DMPS, Unithiol), were developed, which have a higher therapeutic index than BAL. DMSA acts only as an extracellular chelator, whereas DMPS enters hepatocytes and renal cells. DMSA has been found to be more effective than DMPS at removing Hg from the brain, while DMPS appears to be more effective at removing Hg from the kidney, and DMSA is less toxic than DMPS [60]. Nowadays, these three agents remain the main stay of chelation treatment for Hg and other heavy metal intoxication. In acute Hg intoxication, they offer therapeutic benefit if administered promptly (within minutes to hours). However, the efficacy declines or disappears as the time interval increases. For chronic Hg intoxication, although chelators may accelerate Hg excretion and diminish Hg concentration in some tissues, their potential efficacy in terms of decreased morbidity and mortality is largely unestablished [58].

Thiol- and seleno-group donors

Hg binding damages -SH and –SeH contained molecules, results in serious consequences [51]. In this sense, the exogenous addition of sulphides and selenides would be protective, and some of these compounds were investigated for this purpose.

Glutathione: Glutathione (GSH) is a thiol-containing tripeptide, has multiple roles in the disposition of Hg in the body. It provides a reducing milieu for the maintenance of protein thiols, and is also important in the hepatobiliary transport of Hg [59]. Addition of GSH can increase the availability GSH for its biological function, and promote Hg excretion. It is reported GSH is 50% as effective as DMSA in preventing inorganic Hg accumulation in renal cells [60]. However, the transport of exogenous GSH cross the biological membrane is not very easy [61,62], which limits the protective roles GSH on organelles like mitochondria.

N-acetylcysteine, cysteine and homocysteine: N-Acetylcysteine is a precursor of GSH and is being used and studied in conditions characterized by decreased GSH or oxidative stress. N-acetylcysteine can stimulate GSH synthesis, enhance glutathione S-transferase activity, promote detoxification, and act directly on reactive oxidant radicals [63,64]. The administration of N-acetylcysteine was found to markedly protect the rat kidneys against Hg toxicity, lipid and protein oxidation and the decline in tissue GSH concentration and it increased the renal clearance of $HgCl_2$ [65].

Other thiol-containing molecules – cysteine and homocysteine, cherish similar biological function to N-acetylcysteine as a source of thiol groups; also show some effects antagonizing Hg toxicity [135,66].

However, cysteine and homocysteine S-conjugates of inorganic Hg or organic Hg can serve as transportable substrates of certain amino acid transporters [67]. There are experiments shows that cysteine, homocysteine, and N-acetylcysteine, coadministered with inorganic Hg, greatly influence the magnitude and/ or site of uptake of Hg ions in the kidney [68]. As such, care should be made to consider these thiol-containing amino acids in treating Hg toxicity.

Selenium compounds: Selenium (Se) appears in various forms such as selenite, selenate, selenomethionine, and selenocysteine, it is an essential trace element for living organisms [69]. Selenium is a natural antagonist to Hg, which was first shown experimentally by Parizek and Ostadalova in 1967 [70], later a positive correlation between Hg and Se has been commonly reported. Se has been proposed to sequentially bind to Hg and selenoprotein P in the blood stream, to form a non-toxic complex, and the formation of Hg–Se complex with selenoprotein P causes redistribution of Hg in the organism or reduces the absorption of Hg [71,72].

As an essential trace element, the need for Se in human and animal nutrition is well recognized. However, selenium is not currently used in the treatment of human Hg intoxication, possibly because Se toxicity may be manifested after ingestion only slightly higher than those nutritionally required [40].

Antioxidative vitamins

Vitamin E is a lipid soluble antioxidant, which plays an important role in stabilizing the cell membranes by scavenging free radicals. It has a protective effect against oxidative damage in the liver and other tissues caused by Hg and heavy metal intoxication [73,74].

Vitamin C is a water-soluble antioxidant, and is an indispensable nutrient required to maintain the physiological processes. Small amount of this vitamin is sufficient to prevent and cure scurvy; while, larger amount may be essential to maintain good health during environmental adversities. Experiments have found that vitamin C influences Hg accumulation, and detoxifies Hg toxicities [75-77].

Other vitamins, such as B12 and vitamin K [78,79] are also reported in experiments to combat Hg, but vitamins can provide only supplementary roles for combating Hg, the real clinic efficacy is doubtful.

Plant antioxidants and others

Many plant extracts and plant-derived compounds such as polyphenols, flavonoids and xanthones have been known to have protective roles against heavy metal toxicity [80]. A highly mentioned candidate is quercetin, one of the most abundant flavonoids found in many fruits and vegetables, notably, blueberries, onions, curly kale and broccoli. It is well documented that quercetin is a potent antioxidant that can inactivates radicals and activate indirectly transcription factors that regulate genes encoding for antioxidant enzymes, and lots of experiments have showed efficacy of quercetin for deal with Hg toxicity [81-84].

Melatonin (N-acetyl-5-methoxytryptamine), the main secretory product of the pineal gland, and now is found exist in many kinds of food, is a potent free radical scavenger and antioxidant. Melatonin was reported effectively protect against Hg (ii)-induced oxidative tissue damage in rats, and against Hg induced intoxication in spermatozoa in vitro [85-88].

REMEDY VALUES OF H_2S FOR REDUCING HG TOXICITY

H_2S has historically been considered to be a toxic gas, an environmental and occupational hazard. However, over the last decade, with the discovery of its presence and enzymatic production through precursors of L-cysteine and homocysteine in mammalian tissues, H_2S is emerging as a highly significant endogenous gaseous mediator which may play a substantial regulatory role in a variety of physiological systems [89-91], and therapeutic potential of exogenous H_2S is extensively investigated.

Physicochemical property

H_2S is a sulfur analog of water and, due to its weak intermolecular force, exists in a gaseous form. When exposed to air, it slowly oxidizes to form elemental sulfur. H_2S readily dissolves in water, acts as a weak acid (pK_a = 6.9 in 0.01–0.1 mol/ litre solutions at 18°C) and dissociates to H^+, HS^-, and S^{2-}. Under physiological conditions, approximately 20% exist as H_2S and the remaining 80% as HS^-, with only trace amounts of S^{2-}. The term "Hydrogen Sulfide (H_2S)" has been used to refer to H_2S, HS^-, and S^{2-}, and NaHS is one of the physiological donors of H_2S [92,106].

H_2S superior to other sulfides for protecting organelle**s:** H_2S is a highly lipophilic molecule, and able to freely penetrate the membranes of cells of all types by diffusion and without the requirement for specialized membrane transporters [89], which makes is superior to other sulfides for protecting intracellular organelles [93,94].

H_2S reacts with metal ions: H_2S reacts with metal ions to form metal sulfides, which are often insoluble solids, in reverse, treating metal sulfides with strong acid often liberates H_2S. This conversion is widely exploited. In the purification of metal ores by flotation, mineral powders are often treated with H_2S to enhance the separation [95]. And gases or waters contaminated by H_2S can be cleaned with metal. In this case, elemental Hg and Hg ions are reported to react with H_2S directly to form less toxic inorganic HgS, which is the main ingredient of cinnabar, cinnabar is now used for 2000 years in traditional Chinese medicines [96].

H_2S transformed to hydrogen polysulfides: In the presence of oxygen, H_2S can be transformed to Hydrogen Polysulfides (H_2S_n), which possesses a higher number of sulfur atoms than H_2S.

$$2nH_2S + \frac{1}{2}(2n-1)O_2 \rightarrow H_2S_{2n} + (2n-1)H_2O$$

HS^- also reacts with zero valent sulfur to produce H_2S_n with varying numbers of sulfurs until the number reaches 8, at which point sulfur molecules cyclize and separate from polysulfides:

$$HS^- \leftrightarrow HSS^- \leftrightarrow HSSS^- \leftrightarrow \ldots \leftrightarrow HS_7^- \rightarrow S_8$$

In body, endogenous H_2S_n is produced by 3-Mercaptopyruvate Sulfurtransferase (3MST) from 3-Mercaptopyruvate (3MP) and is generated by the chemical interaction of H_2S with Nitric Oxide (NO) [97], the significance of endogenous H_2S_n has recently been recognized, much more potently than that of the parental molecule H_2S [98-100].

Physiologic source of H_2S

H_2S was first detected in mammalian brains in 1989 [138], and to be synthesized from sulfur-containing amino acids, methionine, cysteine and cystine, catalyzed by different enzymes, Cystathionine β-Synthase (CBS) and Cystathionine γ-Lyase (CSE). It has been widely suggested that the expression of CSE, CBS, MPST showed some degree of tissue specificity, however, the previous assumption on distinct tissue distribution is not clear [89]. Latterly, Norihiro Shibuya, et al reports an additional biosynthetic pathway from D-cysteine involving 3-Mercaptopyruvate Sulfurtransferase (3MST) and D-Amino Acid Oxidase (DAO). D-cysteine-dependent pathway operates predominantly in the cerebellum and the kidney [101]. The enzymatic generation of H_2S may be directly regulated by a number of hormones and other signaling molecules. The activity of CBS is directly inhibited by 2 different gaseous signal molecules, NO and CO, and stimulated by bacterial endotoxins. Also glucocorticoids appear to regulate CBS and CSE activity [102,103].

Besides tissue sources, the intestinal flora produces H_2S, which is a second source of H_2S [104]. And erythrocytes also produce H_2S, where H_2S is produced from organic polysulfides in a glutathione-dependent manner [105].

Biological activities

Modification of synaptic transmission: Astrocytes and microglial cells play important roles in the regulation of brain pH levels, neurotransmitter levels and neuronal excitability. It is reported H_2S evokes Ca^{2+} waves in astrocytes that trigger a Ca^{2+} influx via its channels in the plasma membrane and also reversibly increases Ca^{2+} levels in microglia in a dose dependent manner [139]. In addition H_2S facilitates hippocampal LTP via the activation of N-Methyl-D-Aspartate (NMDA) receptors as well as the phosphorylation of these receptors by Protein Kinase A (PKA) and regulates intracellular Ca^{2+} level in astrocytes and hippocampal slices, which is involved in the formation of memory. Studies also have established that H_2S upregulates the GABA -receptor at both pre- and postsynaptic sites [107,139]. Which have even increased its prospective potential in physiological standpoint [110,139] .

Cytoprotective mediator: H_2S has been proposed as a novel cytoprotective mediator, and there is growing evidences of direct and indirect antioxidant effects of H_2S.

H_2S enhancing the production of GSH: Increased GSH production by H_2S is prominent under conditions of oxidative stress caused by glutamate, when extracellular concentrations of glutamate are increased, the import of cystine in exchange for glutamate by the cystine/ glutamate antiporter is decreased. Since cystine is reduced to cysteine in cells for the synthesis of GSH, a decline in cystine import leads to a depression in the synthesis of GSH [91]. Since H_2S is a reducing substance and cysteine is present in plasma and blood at certain concentrations, H_2S may inhibit the reaction of reducing cystine into cysteine in the extracellular space and increase the transmembrane transport of cysteine into cells for GSH production. Increased cysteine transport contributes to a greater extent to the synthesis of GSH. Increased hepatic GSH synthesis and decreased lipid peroxidation are also observed with Na_2S treatment in a murine hepatic ischaemia/ reperfusion injury model. This finding led to the identification of a cytoprotective effect on various organs, including the heart and kidney. In bacteria as well, inactivation of the bacterial homologs of CBS, CSE, and 3MST decreases the production of H_2S, causing vulnerability of bacteria for antibiotics, suggesting that the cytoprotective effect of H_2S is considered a universal defense mechanism that functions from bacteria to mammals [108-91].

Free radical scavenger: H_2S also scavenges free radicals. 3MST and CAT are mainly localized to the mitochondria, where the respiratory chain produces ROS. Cells expressing 3MST and CAT show significant resistance to oxidative stress [91]. Furthermore, glomeruli isolated from $CBS^{-/+}$ mice showed increased production of endogenous ROS (reactive oxygen species) compared with glomeruli from wild-type animals. H_2S also scavenges peroxynitrite ($ONOO^-$), which is formed from the interaction of $^{\cdot}NO$ with superoxide (O^{2-}), and Hypochlorous Acid (HOCl), and has been shown to protect the glial cell line SH-SY5Y from its toxicity [110]. In animal models of smoke/ burn injury, renal and hepatic ischaemia/ reperfusion, H_2S salt donors reduced the formation of nitrosatively and oxidatively modified cellular proteins, DNA and lipids, suggesting further an 'antioxidant' role for H_2S [89].

Mitochondrial protection and bioenergetic stimulation: Mitochondria are central to oxidative phosphorylation and are also involved in various aspects of apoptosis. Mitochondrial dysfunction contributes to a wide range of human pathologies [91]. Emerging mitochondrial roles of H_2S include antioxidant effects, modulation of mitochondrial cell death pathways and the regulation of cellular bioenergetics. Multiple studies have demonstrated that H_2S donors can maintain mitochondrial integrity, reduce the release of mitochondrial death signals and attenuate mitochondrially-regulated cell death responses of various types [111].

H_2S was once viewed as a toxic gas, primarily attributed to a shutdown of mitochondrial electron transport and cellular ATP generation. However, recent studies showed that H_2S serves as a mitochondrial electron donor at lower concentrations, endogenous H_2S supports basal, physiological cellular bioenergetic functions. Meanwhile, CSE and CBS, the enzymes producing H_2S, also can serves as endogenous stimulators of cellular bioenergetics supply of ATP during hypoxia [112]. Recent data also show that H_2S, in lower concentrations, serves as an inorganic source of energy in mammalian cells; via these pathways, H_2S acts as an alternative supporter of mitochondrial electron transport and ATP generation [111,113].

Apoptosis modulation: Under different conditions, H_2S may exhibits opposing pro- or anti-apoptotic effects. Overexpression of CSE in human smooth muscle cells results in significant inhibition of cell growth and in increased apoptosis, which are proposed to be due to an increased endogenous production of H_2S [72]. Anti-apoptotic effects have also been reported for H_2S. Human neuroblastoma SH-SY5Y cells were protected by H_2S from 6- hydroxydopamine-induced injury, and PC12 cells were protected by H_2S against methyl phenylpyridinium-induced cytotoxicity and cell death, and H_2S protected cells from oxidative glutamate toxicity by stimulating production of glutathione [97]. The anti-apoptotic action of NF-κB is mediated by H_2S-dependent persulfidation and is markedly diminished in CSE knockout mice [114]. However, the proapoptotic effects of H_2S and antiproliferative have also been reported to be a significant influence on various disorders such as vascular graft occlusion, atherosclerosis, and neointimal hyperplasia [139]. Further studies are needed to elucidate the opposing pro- and anti-apoptotic effects of H_2S [140,141].

Other mechanism: H_2S functions as vasorelaxant, which is ascribed primarily to activation of K_{ATP} channels. The effect of H_2S on relaxation of blood vessels is sensitive to the presence of K_{ATP} channel inhibitors and believed to involve direct channel activation by H_2S [8]. H_2S has also been implicated as a modulator of other channels including the Ca^{2+}-sensitive K^+ channel (BKCa), L-type and T-type Ca^{2+} channels, chloride channels, members of the TRP (transient receptor potential) family of channels and Na^+ channels. Of these, regulation of the BKCa is particularly interesting, since H_2S also functions as an oxygen sensor [139].

Hydrogen polysulfide activities: Hydrogen polysulfide (H_2S_n), recently emerged as a potential signaling molecule, some of the previously reported effects of H_2S are now attributed to the more potent H_2S_n [115]. They regulate Keap1 to release Nrf2, which, in turn, upregulates antioxidant genes such as HO-1 and GCL and modifies the activity of Phosphatase and Tensin Homolog (PTEN), a lipid phosphatase, the physiological roles of polysulfides should be robust [99].

H_2S donors

Although, inhalation of H_2S has found to have acutely protective effect under some circumstances, i.e., lung injuries induced by ventilators [116], neuropathic pain and brain edema [117], however, as a kind of toxic gas, H_2S gas is inconvenient for conventional

research and therapeutic purpose. As a result, H_2S donors are applied to replace H_2S gas. The vast studies have utilized commercially available inorganic sulfide salts such as Na_2S and NaSH. However, they are not particularly relevant tools to examine the physiology of H_2S in vitro or in vivo [89], since excessive H_2S may be instantaneously released, leading to exacerbate pathogenesis of neurological diseases [118]. Thus, various organic molecules that are capable to release H_2S over extended periods of time have been developed [119].

NSAIDs with ADT-OH derivatives: The majority of these donors have modified existing pharmacological compounds of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with ADT-OH [5-(4-hydroxyphenyl)-3H-1,2-dithiole- 3-thione]. ADT-OH as well as its derivatives is enzymatically metabolized to release H_2S by the mitochondria [120]. Unlike from NaHS, H_2S generated from ADT-OH and its derivatives slowly increased intracellular over 48 h [118]. These novel compounds have shown substantial promise in alleviating and limiting gastrointestinal side effects and toxicity of NSAIDS and in the treatment of inflammatory bowel disease, oedema, endotoxic shock and acute inflammation. However, since NSAIDs and ADT-OH are themselves biologically active, it is possible that some of the observed biological effects associated were due to themselves rather than released H_2S [89].

GYY4137: Recently, H_2S donors which do not consist of structurally modified drug molecules such as GYY4137 have been synthesized and characterized [89]. GYY4137 is a very slow-releasing H_2S donor compound which releases two molecules of H_2S, and has been shown to exert prominent vasodilatory activity via K_{ATP}-channel-dependent mechanisms, as well as exert anti-inflammatory activity via inhibition of nuclear factor κB (NF-κB)/ activator protein-1 (AP-1)- dependent pro-inflammatory signalling [89].

D-Cysteine: D-Cysteine can be used as a raw material for H_2S synthesis to increase the production of H_2S. Compared to traditional pathway from l-cysteine, 3MST/ DAO pathway using d-Cysteine to produce H_2S much more efficiently. Moreover, d-Cysteine is also less toxic than l-cysteine, and it promises novel therapeutic and clinical applications [110]. And there are reports that administration of d-cysteine protects primary cultures of cerebellar neurons from stress of hydrogen peroxide and attenuates ischaemia-reperfusion injury in the kidney, results showed more effective than l-cysteine [101].

Plant organosulfurs as potential H_2S donors

In recent years, natural plant Organosulfur Compounds (OSC) come to be regarded as potential H_2S donors. The Allium family and Cruciferous vegetables are known for their rich contents of bioactive organosulfur compounds. The main garlic OSC is allicin, known as diallyl thiosulfinate, that is synthetized from alliin after release of alliinase when garlic is crushed. In aqueous solutions, Allicin is rapidly metabolized in into Diallyl Sulfide (DAS), Diallyl Disulfide (DADS), Diallyl Trisulfide (DATS) and ajoene [121,122]. Cruciferous vegetables are rich in glucosinolates, which undergo hydrolysis by thioglucosidase (myrosinase) to isothiocyanates including sulforaphane in the broccoli [123]. Benavides et al., were the first to show that garlic-derived OSCs release H_2S which is responsible for the vasoactivity of garlic in human blood cells [124]. From then, DATS is found to be a fast H_2S donor in opposition to DADS [125]. Cruciferous sulforaphane was also found to release H_2S in human prostate cancer cells [126]. From a chemical point of view, OSCs with more than two tethering sulfur atoms are able to release H_2S through thiol-disulfide exchange with GSH [127]. These researches open up a new avenue for developing H_2S donors from nature source.

Evidences of H_2S antagonizing Hg toxicity

H_2S-producing enzymes: Eiko Yoshida et al. report that cystathionine β-synthase (CBS), which catalyzes the production of hydrogen sulfide, contributes to cellular protection against MeHg. overexpression of CBS reduced MeHg cytotoxicity, whereas transfection with CBS small interfering RNA enhanced MeHg toxicity in human neuroblastoma SH-SY5Y cells [128]. Bismethylmercury sulfide ((MeHg)2S), was identified as a metabolite of MeHg in SH-SY5Y cells exposed to MeHg and in the livers of rats treated with MeHg [129], which was formed by interactions between MeHg and endogenous free persulfide species, as well as protein-bound cysteine persulfide, these persulfides are also metabolites of H_2S [129]. (MeHg) 2S had little chemical protein modification capability and little cytotoxicity compared with MeHg in vitro and in vivo [130,128].

Plant organosulfurs compounds: Organosulfurs are the main active ingredients in garlic, garlic extract have shown effectively prevents mercury induced neruotoxicity in vitro [131], liver and kidney damage induced by mercury chloride in the rats [132], and methyl mercury-induced cytotoxicity in peripheral blood leukocytes [133].

Sulforaphane (SFN) is the main OSC of Cruciferous vegetables, Feng et al [42] explored the preventive effects of sulforaphane (SFN) on MeHg-induced neurotoxicity in rat cerebral cortex, results indicated that pretreatment with SFN might prevent the MeHg-induced neurotoxicity by reinforcing the activation of the Nrf2-ARE pathway and then down regulating the interaction between oxidative damage and excitotoxicity pathways. These facts provide OSCs as a fascinating molecular library for screening donors dealing with Hg toxicity.

NaHS, physiological donors of H_2S: In our previous report, NaHS positively protect brain against MeHg-induced toxicity, reduced MeHg-induced oxidative stress, mitochondrial damage and cellular apoptosis. And also, NaHS increased DNA/ RNA content, and the important activities of acetylcholinesterase and Na^+/ K^+-ATPase, which were compromised by MeHg exposure. The mechanisms appear to involve the inhibition of oxidative stress and the protection of mitochondria [134].

CONCLUSION AND PROSPECTIVE

This paper reviews published data on issues of Hg toxicity, mainly chronic neurotoxicity, existing treatments and remedy values of H_2S. The remedy values of H_2S were emphasized, besides the well known H_2S as cytoprotective mediator, H_2S reacting with heavy metal ions including Hg, H_2S superior to other sulfides for protecting organelles because of freely penetrating cellular membranes, development of H_2S donors and plant organosulfurs as potential H_2S donors were also mentioned, and especially, evidences of H_2S antagonizing Hg toxicity, including reported roles of H2S-producing enzymes and plant organosulfurs compounds, together with our previous report were reviewed, these data provide reasonable grounds for suitable H_2S donors to combat Hg toxicity.

We prospect that increasing the H_2S level to some extent may have benefits for Hg intoxication. This may be achieved by promoting endogenous H_2S production or supplying exogenous H_2S [142]. For promoting endogenous H_2S production purpose, activating the enzymes which producing H_2S and providing the materials for H_2S production are good choices. In addition, Intestinal bacteria is one of the important sources of the H_2S production, and the intestinal

tract is the major organ for Hg absorption and excretion, modulating intestinal micro ecology may increase the production of H_2S, reduce the absorption and increase the excretion of Hg and reduce the toxicity. For supplying the exogenous H_2S goal, the known H_2S donors provide us some good choices, meanwhile, we should actively look for more stable and slow-releasing donors from chemically synthesized compounds and nature plant organosulfurs, the latter are usually regarded to have better safety.

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