Hydrogen Sulfide

Subjects: Others

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Hydrogen sulfide is a colorless gas with a characteristic smell like rotten eggs. It is flammable and corrosive at very high concentrations. It has been always considered a toxic molecule, but more recently, it has been proved it is a metabolite and signaling molecule in biological tissues that regulates many physiological processes.

Keywords: signaling molecule, persulfidation, PTM, SSH,

1. Introduction

Hydrogen sulfide (H_2S) has always been considered toxic, but a huge number of articles published more recently showed the beneficial biochemical properties of its endogenous production throughout all *regna*.

2. Physiological Role

During the past century, H_2S was thought to only be a toxic molecule, and it was not until 1990 that Kimura and coworkers revealed its role in essential functions in human physiology, opening a new emerging field in life science [1]. The first physiological assay published in 1996 demonstrated that H_2S acts as an endogenous neuromodulator [2]. The participation of H_2S in many physiological and pathological processes in animals has been described over the last two decades, including its role in the regulation of cell proliferation, apoptosis, inflammatory processes, hypoxia, neuromodulation, and cardioprotection [3][4][5]. Therefore, H_2S is now accepted as playing roles as a gasotransmitter (gaseous signaling compound) that is as important as nitric oxide (NO) and carbon monoxide (CO) in mammals, and as a signaling molecule that is as important as hydrogen peroxide (H_2O_2) in plants [2][6][7].

Although the first descriptions of the effects of H_2S in plants were from the 1960s [8], interest in the role of H_2S in plant systems arose later. It was not until the past decade that the effects of H_2S were described in seed germination [9], the number and length of adventitious roots [10] and the regulation of genes involved in photosynthesis [11]. Thereafter, the protective effects of exogenous H_2S against different stresses were documented, such as protection against oxidative and metal stresses [9][12][13][14][15][16][17], drought and heat tolerance [16][18], and osmotic and saline stresses [19]. Thus, publications on these dose-dependent effects of H_2S have emerged, postulating H_2S to be an important signaling molecule that has analogous functions in plant systems to those previously described in mammals. H_2S was also shown to be a regulator of other important physiological processes in plants, such as stomatal closure/aperture [20][21][22][23]; thus, its importance in drought stress relief is due to the ability of H_2S to induce stomatal closure in *Arabidopsis thaliana* [23][24].

More recently, there has been increasing interest in the effect of H_2S on autophagy regulation in the scientific community. In mammals, the protective effect of H_2S against some of the diseases mentioned above has been linked with the regulation of autophagy [25][26]. Autophagy is a cellular catabolic pathway that is evolutionarily conserved from yeast to mammals, and it involves the digestion of cell contents to recycle nutrients or to degrade damaged or toxic components. The AMP-dependent kinase (AMPK) and mammalian target of rapamycin (mTOR) pathways play important roles in the control of autophagy. To this end, activation of AMPK or inhibition of mTOR has been shown to activate autophagy [27]. Exposure to H_2S has been shown to cause a significant increase in AMPK phosphorylation, which increases its activity and inhibits the activation of downstream targets, such as mTOR [28]. In plants, H_2S was shown to inhibit autophagy by preventing ATG8 (autophagy-related ubiquitin-like protein) accumulation [29]. H_2S is able to inhibit starvation-induced autophagy in Arabidopsis roots, and this repression is independent of redox conditions [30].

The first mechanism proposed for H_2S was based on its chemical properties, since this nucleophilic molecule is able to react with reactive oxygen/nitrogen species and reduce the cellular oxidative state [31][32]. In addition, H_2S is able to regulate several antioxidant enzymes, such as ascorbate peroxidase (APX) [33][34][35], catalase (CAT) [36][37], superoxide dismutase (SOD) [36][38], and glutathione reductase (GR) [35], and non-enzymatic compounds, such as the glutathione anti-oxidant pool [39][40].

The antioxidant role of H_2S has been the focus of numerous studies in mammalian systems as a critical mediator of multiple pathophysiological processes [41]. In plants, the number of studies on the effects of H_2S in the model plant Arabidopsis has increased in recent years; in addition, the effects of H_2S in agricultural crops are relevant as an exogenous treatment to cope with economic loss due to environmental stress. The effects of exogenous (pre-)treatment with water-soluble donors of H_2S have been the focus of numerous studies in several agricultural species. Fotopoulos et al. have reviewed these studies regarding the effects of H_2S on plant growth, its ability to improve resistance against abiotic and biotic stress, and its positive postharvest effects [42]. Thus, a better understanding of the mechanism of action of H_2S is important to fight against crop loss. This knowledge would help in agricultural sustainability and in producing the food required by the increasing world population [43].

3. H_2S Mechanism of Action

The underlying mechanisms of H_2S action are poorly understood. There is an important effect of H2S binding to heme moieties in target proteins such as cytochrome c oxidase, hemoglobin and myoglobin, among others [44]. It has, however, become widely accepted that a huge number of the processes controlled by H_2S are caused by a posttranslational modification of cysteine residues called persulfidation [45][46][47]. Protein persulfidation is an oxidative posttranslational modification of cysteine residues caused by H_2S, in which a thiol group (–SH) is transformed to a persulfide group (–SSH). Sulfane sulfur species, persulfides and polysulfides are more nucleophilic than H_2S and therefore more effective at persulfidation [48]. Due to the intrinsic instability of persulfides and their higher reactivity than thiols, protein persulfides largely remain understudied. Nevertheless, over the last decade, study of this protein modification has become more relevant for researchers because it can affect protein function, localization inside cells, stability, and resistance to oxidative stress [7][33][49][50][51]. The broad physiological importance of persulfidation has only recently started to emerge; a proteomic analysis revealed that approximately 10–25% of liver proteins contain this modification [51], and at least 5–10% of the entire proteome may undergo persulfidation in plants [52].

In mammals, the mechanism of action of H_2S has been deeply studied since 2009, when Mustafa et al. described this new posttranslational modification [51]. By contrast, in the plant system, persulfidation has been described more recently [33], but a greater number of proteins have been shown to undergo this modification [52]. A total of 3147 proteins were found to be persulfidated in Arabidopsis leaves under physiological conditions, suggesting that this number may be higher under certain stress conditions [52]. These proteins are mainly involved in important biological pathways, such as the tricarboxylic acid cycle, glycolysis, Calvin cycle, photorespiration and autophagy. Further physiological studies of these proteins must be performed to decipher the role of persulfidation in these biological pathways. Nevertheless, initial studies in plants demonstrated that persulfidation regulates the enzymatic activity of chloroplastic glutamine synthetase (GS2), cytosolic ascorbate peroxidase (APX1), and cytosolic glyceraldehyde 3-phosphate dehydrogenase (GapC1) [33]. Persulfidation regulates the cytosolic/nuclear localization of GapC1, allowing it to likely act as a transcription factor [49]. The actin cytoskeleton and root hair growth are regulated through persulfidation of ACTIN2 [53]. Furthermore, ethylene biosynthesis is regulated by persulfidation of 1-aminocyclopropane-1-carboxylic acid oxidase (ACO1) in tomato [54]. Recently, a peroxisomal proteome study in Arabidopsis revealed that the interplay of different PTMs such as *s*-nitrosation, nitration, persulfidation, and acetylation regulates redox signaling to protect proteins against oxidative damage [55]. From an evolutionary point of view, it is reasonable to assume that ancestral purple and green sulfur bacteria lived in an H_2S-rich atmosphere; and therefore bacteria developed H_2S-mediated signaling processes to resist oxidative stress. Similarly as peroxide (H_2O_2) produces ROS, persulfide (H_2S_2) produces RSS (reactive sulfide species), but with the difference that persulfides can be produced with several sulfur molecules (S_x) and stored [56].

4. H_2S in Human and Plant Therapies

It is well known that sulfurous water baths were used by ancient civilizations and were known to have healing effects against particular diseases. H_2S has been recognized as having anti-inflammatory, anti-bacterial, vasodilator, and anti-fungal properties owing to its sulfur content [41][57][58]. Several extracts from the genus Allium, mainly onion and garlic, and their derivatives have been used since ancient times in China as medicines to treat numerous diseases, including cancer [59], cardiovascular disease [60] and other diseases. It is known that these extracts are a source of sulfur-containing flavor compounds such as diallyl sulfide, allicin and cycloalliin, among others, and which release H_2S in cells upon interaction with reductants [61][62].

Currently, these beneficial effects are still under study to develop new strategies and therapies to treat certain diseases in mammals and to address agricultural challenges. In mammals, therapies that include H_2S are used for their anti-inflammatory effects, cytoprotective properties and antiapoptotic features [63]. The aim of these therapies is to be able to use this signaling molecule in heart failure, neurodegenerative diseases and stroke, and ischemia, among others. There

has recently been an increasing number of publications indicating that deficiency or excess sulfur amino acids (SAAs), namely, methionine and cysteine, in the diet affect the normal growth of animals and that it is important that SAAs are ingested at the appropriate dose [64][65], since they affect signaling in cells through H_2S [66]. These amino acids are metabolized through the transsulfuration pathway, which is the one of the main sources of H_2S in cells; H_2S has been shown to increase the lifespan of *C. elegans* [67] and even humans [68].

Nevertheless, clinical research on H_2S is not easy to perform due to its toxicity, and H_2S therapy is still in a preliminary preclinical stage. A bottleneck for developing gasotransmitter-based therapeutics is the lack of a safe administration drug. There are some candidate compounds for CO and NO prodrugs [69][70][71] and more interestingly, some H_2S-releasing drugs are currently in clinical trials [72][73]. In a recent study, intraperitoneal injections of JK-1 (a H_2S donor) were administered to mice after transverse aortic constriction and were shown to have substantial beneficial effects on renal and vascular function [74]. Another exciting approach was a high increase in the dietary intake of taurine, which boosted CSE-mediated H_2S production to exert significant protective effects in atherogenesis, hypertension and heart failure [75]. However, most therapies use an increase in the dietary intake of sulfur amino acids or directly use slow-releasing H_2S donors to avoid the toxicity of high H_2S concentrations [76]. These therapies in mouse models can be used as models to study H_2S donors in humans. A recent study revealed that persulfidation decreases with aging and that dietary/pharmacological interventions could be used to increase persulfidation and extend lifespan [77]. Moreover, a few recently published articles described the interplay between H_2S, CO and NO within the gastrointestinal tract, especially in ulcer healing and prevention of non-steroidal anti-inflammatory *drugs* (NSAIDs)—induced gastropathy [78][79]. In addition, a novel H_2S donor not only increases H_2S levels, but also increases circulating NO bioavailability in heart failure patients, highlighting the crosstalk between these gasotransmitters in therapeutic trials [80].

In plants, new therapies or strategies using H_2S are being used to deal with economic losses due to fruit and vegetable ripening or crop stress resistance. It has been shown that H_2S fumigation slows fruit ripening and senescence in fruits and vegetables by inducing antioxidant activities, such as ascorbate peroxidase, catalase, peroxidase, glutathione reductase, and superoxide dismutase [81][82][83]. Treatments with exogenous H_2S have also been used to control the color degradation of certain horticultural vegetables and fruits by suppressing the degradation of anthocyanins [81] and downregulating some chlorophyll degradation genes [84]. Interactions between H_2S and other signaling molecules, such as NO and ethylene, have also been a focus of recent investigations on the senescence of flowers or ripening of fruits. Hydrogen sulfide alleviates postharvest ripening and senescence of fruits by antagonizing the effect of ethylene [85][86]. In addition, a cooperative effect of H_2S and NO has been observed on delaying the softening and decay of fruits [87], and the crosstalk between these two gasotransmitters is associated with the inhibition of ethylene biosynthesis [88].

There is a long list of publications on the beneficial effects of H_2S treatments in crops, such as enhancing resistance to metal, heat, cold, salt and drought stresses, which have been recently summarized [89]. It has been demonstrated that sulfur fertilization of crops reduces sensitivity to pathogens, in a process mediated by hydrogen sulfide [90]. H_2S-induced pathogen resistance is conferred through increased expression of salicylic acid-dependent pathogen-related (PR) genes [91] and increased transcription levels of microRNA393 (*MIR393)* genes [16]. Another important beneficial effect of H_2S treatment of crops is its influence on the modulation of photosynthesis [11] and autophagy regulation [30]. Apparently, H_2S is able to regulate energy production in mitochondria, protecting against aging and increasing the lifespan of plants in a similar way as in animals [92]. All of these advantageous outcomes lead to increased yields and biomass and enhanced germination of agricultural crops after H_2S administration [93][94].

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