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Working Title: Hydrogen Sulfide - Biochemical and Biological Considerations

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Abstract

In the past years biomedical research has recognized hydrogen sulfide (H_2S) not only as an environmental pollutant but also, along with nitric oxide and carbon monoxide, as an important biological gasotransmiter with paramount roles in health and disease. Current research is focused on several aspects of H_2S biology such as the biochemical pathways that generate the compound, functions in human pathology or drug synthesis that block or stimulate its biosynthesis. The present editorial addresses the knowledge we have to date on H_2S production and its biological roles in the general human environment with a special focus on the oral cavity.

Keywords: Hydrogen sulfide; Superoxide dismutase; 3-mercaptopyruvate sulfurtransferase; Cystathionine b-synthase; Cystathionine g-lyase

H_2S - Generalities

In the past years biomedical research has recognized hydrogen sulfide (H_2S) not only as an environmental pollutant but also, along with nitric oxide and carbon monoxide, as an important biological gasotransmiter with paramount roles in health and disease. Current research focuses on several aspects of H_2S biology such as the biochemical pathways that generate the compound, its functions in human pathology or drug synthesis that block or stimulate its biosynthesis. The present editorial addresses the knowledge we have to date on H_2S production and its biological roles in the general human environment with a special focus on the oral cavity.

H2S - Production

In mammalian organisms, including the human body, enzymatic H_2S synthesis is generally connected to three endogenous enzymes: 3-mercaptopyruvate sulfurtransferase (3MST), cystathionine b-synthase (CBS) and cystathionine g-lyase (CSE) all three taking part in the cysteine synthesis pathway [1] (Figure 1). It is important to note that each of the three enzymes are responsible for H_2S homeostasis and regulates H_2S levels found in the bloodstream. Each of the enumerated enzymes is found at specific sites in the organism. Thus 3MST has a mitochondrial location and is usually found in the brain and blood vessels. The enzymes participates in a series of chemical reactions that starts with cysteine metabolism transformed to 3-mercaptopyruvate by cysteine aminotransferase. Further 3-mercaptopyruvate is reacted to pyruvate and finally to H_2S by 3MST. CBS is found mostly in hepatic, cerebral tissues and the nervous system and produces H_2S as an end product of a reaction involving cystathionine generation starting from cysteine and serine. CSE resides in blood vessels and hepatic cells and produces H_2S trough a reaction that starts with cysteine and generates pyruvate and ammonia. H_2S catabolism involves several oxidative steps that converts the gas to persulfide, thiosulfate and sulfate with an oxidation rate this is organ specific. H_2S oxidation was shown to occur in virtually all cell types and tissues of the human body including colon, kidney, liver, brain or lung cells [2].

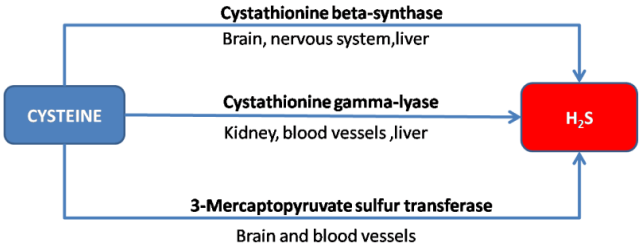

Figure 1: Hydrogen sulfide production - Cysteine biosynthesis pathway is the main pathway responsible for H_2S production in mammalian organisms usually with the help of three enzymes.

H_2s - Biological Roles

H_2S is a gaseous mediator and with multiple roles depending on the tissue or organ. Thus H_2S is involved in blood vessels dilatation, inflammation, cardiac reaction to ischemic injuries. In the human body increased concentrations of H_2S are associated with respiratory affections such as chronic bronchitis, emphysema, pneumonia or diseases related to the cardiovascular system such as hypertension [3]. Other volatile sulfur compounds related to H_2S (i.e. dimethyl sulfide) were shown to be significantly elevated in patients with cerebrovascular pathology, for example subarachnoid or intracerebral hemorrhages as well as increased cholesterol level, asthma or hepatic affections such as cirrhosis [4](Table 1).

BIOLOGICAL EVENT	H_2S - EFFECT
Angiogenesis	Increases blood flow Decreases the risk of tissue injury
Mitochondrial respiration	Decreases the function Cytoprotection
Vasodilatation	Regulates blood pressure
Leukocyte adhesion	Anti-inflammatory effect
Apoptosis	Decreases apoptosis - cytoprotective effect
Antioxidant	Up-regulation of antioxidant molecules

Table 1: Hydrogen sulfide - systemic effects. Adapted after [3].

In the oral environment among other volatile sulfur compounds, H_2S is an important compound in the development of physiological and pathological halitosis [5]. Together with periodontal disorders and dental caries, halitosis or oral malodor represents one of the main causes for which patients visit dental practices. Halitosis is the general term used to describe offensive smells detected in human breath. H_2S production is mainly caused by metabolic products of oral bacteria that degrade substrates such as cysteine, arginine or tryptophan. Aside its esthetics roles (i.e. involvement in oral malodor) several studies have also focused on the H_2S toxicity for the oral environment (Tables 2 and 3).

TISSUE/CELLS		ORIGIN	BIOLOGICAL EVENT
ORAL EPITHELIA	Normal keratinocytes	Ca9-22 cell line	Apoptosis - mitochondrial pathway activated; DNA damage
	Keratinocyte stem cells	Human skin cell line	Apoptosis - mitochondrial pathway activated; DNA damage; p53 and Bax activity increased
	Keratinocyte stem cells	Human oral mucosa	Apoptosis - mitochondrial pathway activated; DNA damage; activation of genes from p53 pathway connected with DNA repair, cell cycle arrest
	Keratinocyte cells	Animal oral mucosa	Increases the permeability of the epithelium
ORAL DERMIS	Fibroblasts	Human oral mucosa	Apoptosis - mitochondrial pathway activated; DNA damage;
	Collagen Fibers	Extracelular matrix	Increases collagen degradation/ decreases collagen synthesis.
DENTAL PULP	Dental pulp stem cells	Human dental pulp	Apoptosis - mitochondrial pathway activated; DNA damage;
BONE	Osteoblasts	Mouse calvaria	Apoptosis - mitochondrial and death ligand pathway activated; DNA damage Bone resorption

Table 2: Biological effects of high physiological concentrations of H2S on different oral cell types (50ng/ml H2S) [7].

TISSUE/CELLS		ORIGIN	BIOLOGICAL EVENT
DENTAL PULP	Dental pulp cells	Human pulp	Differentiation to hepatic like cells
	Dental pulp cells	Human pulp	Differentiation of pancreatic like cells
BONE	Osteoclasts	Mouse	Osteoclast activation followed by bone resorption

Table 3: Biological effects of low physiological concentrations of H2S on different oral cell types (1ng/ml H2S) [7].

Thus reports show that H_2S is directly linked to the initiation and development of periodontal diseases: the compound inhibits the proliferation process of oral keratinocyte cells [6], decreases protein synthesis in oral fibroblasts, and inhibits collagen synthesis or basal membrane synthesis [7]. There seem to be a direct relation between the type of the biological effect induced by H_2S and the H_2S levels. Low physiological concentrations of H_2S have been shown to induce dental pulp cells differentiation towards hepatic or pancreatic cells; mouse osteoclasts cells have been shown to switch from a passive state to an active one that induces bone resorption [8]. On the other hand high physiological concentrations of H_2S are demonstrated to induce programmed cell death through different molecular pathways in a number of cell types. These concentrations induced apoptosis through inhibition of superoxide dismutase (SOD) in human gingival fibroblasts. This enzyme is paramount in eliminating reactive oxygen species and leads to damage to DNA structure. The same process was observed in normal keratinocytes [9] and keratinocytes stem cells. DNA damage is shown to activate several molecular pathways such as p53 pathway that can decide cellular fate through activation of DNA repair molecules, cell cycle arrest or apoptosis. Volatile sulfur compounds and especially H_2S were shown to induce the apoptotic process in several cell types belonging to oral structures. Generally apoptosis follows well established pathways such as: intrinsic mitochondrial pathway where the inner mitochondrial membrane is depolarized followed by cytochrome C release into cytosol, assembly of the apoptosome that leads to activation of initiator caspase 9 ultimately followed by executioner caspase 3 activation [10]. This pathway was activated in most studied cell types: oral fibroblasts oral keratinocytes, oral keratinocyte stem cells, general keratinocyte stem cells. The extrinsic pathway, or the ligand-activated pathway was shown to be responsible for apoptosis induction only in cells isolated from the alveolar bone, osteoblast cells. At the same time after H_2S-exposure human oral keratinocyte stem cells expressed key p53-related molecules associated with cell death, DNA repair and cell cycle control.

Future Considerations

To date there is no general consensus regarding H_2S biochemistry and its functions in cell biology (i.e. its pro- or anti-inflammatory effects). In this respect the field can be further expanded together with the development of tools that could correctly identify and quantify H_2S synthesis and catabolism in organs and tissues [2]. Another important issue would be the elucidation of endo- or exogenous signals that initiate H_2S production together with a better understanding of the chemical pathways responsible for its removal. Overall a more clear understanding of the biochemistry of H_2S in relation to its biological roles is greatly needed.

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