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EDITORIAL

Hydrogen Sulfide: not just a malodorous gas?

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Hydrogen sulfide or H_2S (greek: *υδρόθειον*) is a colorless gas with a characteristic unpleasant smell. It emerges from volcanoes (Figure 1) and several natural springs. It is also produced through the anaerobic breakdown of organic material by sulfate-reducing bacteria. For many years, our knowledge concerning its effects on human beings was limited to its toxicity. Hydrogen sulfide is a highly toxic gas, disturbing the function of several organs and mainly the nervous system. Inhaled H_2S is absorbed through the alveolar epithelium. The safe levels for H_2S concentration in the air are defined as 10-20 ppm (parts per million: it means concentration of 1 unit of a certain substance in a total of a million units). It is well known that when humans are exposed to relatively high H_2S levels -occurring mainly in industrial environments, such as tanneries, mining, paper mills and petroleum refineries- several symptoms may appear, ranging from irritation of the eyes and mucus membranes (in lower toxic concentrations) to pulmonary injuring and even loss of consciousness and cardiopulmonary arrest, in higher concentrations. Hydrogen sulfide is considered lethal in concentrations

FIGURE 1. Hydrogen sulfide emerging from the crater of a volcano in Nisyros, Greece (personal archive).

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of about 1000 ppm.[1]

Until recently, we practically ignored any intervention of H_2S in mammals' physiology. An old publication of 1942 claimed that incubation of rat liver homogenates with sulfur-containing amino acids resulted in the production of hydrogen sulfide, probably through a liver transsulfuration pathway.[2] However, no mention was given to this observation at the time. Only 50 years later, it was proved that hydrogen sulfide is produced in mammalian cells and has a physiologic role as a signaling molecule[1]. So, it is now recognized as another gasotransmitter. Under this term, are included gaseous chemical compounds that are normally produced in the human tissues and act as transmitters in the nervous system and other organs. Such a role was already known for nitric monoxide (NO) -also produced by an amino acid, arginine- and carbon monoxide (CO) -generated from haem. Gasotransmitters, unlike other neurotransmitters, cannot be stored in vesicles. Several sulphur-containing substances act as H_2S pools, liberating it when needed.[3]

It is currently accepted that H_2S is synthesized in several tissues through the action of three different enzymes that metabolize l-cysteine. They are cystathionine-β-synthase, cystathionine-γ-lyase and 3-mercaptopyruvate sulfurtransferase (which probably acts in collaboration with a fourth enzyme, cysteine aminotransferase).[1] The first of these enzymes predominates in the brain and its activity can be modulated by CO and NO, indicating a collaboration of all three gasotransmitters, at least in the brain. Cystathionine γ-lyase is the most inducible of all H_2S-synthesizing enzymes, its expression being affected by several substances, such as tumor necrosis factor-α (TNF-α) and lipopolysaccharides (produced in inflammatory states), glucose, glucocorticoids and also by dietary restriction.[3]

The precise biological role of hydrogen sulfide is not yet clarified. An important action seems to be exerted on the mitochondria. It may offer electrons to the mitochondrial electron transport chain and also protect its structures through an antioxidant effect.[4] It is also suggested that it may enhance the activity of some mitochondrial DNA repair enzymes, thus facilitating the repair of its injuries[1]. Experimental data have shown that in low (normal) concentrations, hydrogen sulfide stimulates ATP synthase and increases energy production,[5] while in higher concentrations it has the opposite effect, because of inhibition of cytochrome c oxidase. This inhibitory effect is further aggravated when pH shifts to acidosis.[6] A same effect has also been shown for cyanide, but the difference is that in the case of H_2S it is reversible. A hypothesis, that has to be proved, is that such an action may be protective for the cell by temporarily decreasing its oxygen demands under conditions of hypoxia.

H_2S is currently considered to interfere in several normal procedures, including intrinsic regulation of vascular tone and blood pressure, the function of erection, angiogenesis, neurotransmission, sense of pain, cell reaction to stress, apoptosis, leucocyte function and inflammation.[1] Of major importance is the fact that it increases levels of glutathione, one of the main defense mechanisms of the cell against oxidative stress, that is the harmful effect of free oxygen radicals produced in several abnormal conditions, as in inflammation or reperfusion injury.[1]

H_2S has multiple protective effects on the cardiovascular system. It has a similar role to NO, causing vasorelaxation through sulfhydration of ATP-dependent potassium channels.[3] It also seems to inhibit several mechanisms involved in atherogenesis, such as atherogenic modification of LDL, monocytes adhesion to the endothelial cells, foam cell formation and macrophage-derived inflammation, smooth muscle cell proliferation, neointimal hyperplasia, vascular calcification, and thrombogenesis. Experimental data suggest that it may also decrease plasma levels of homocysteine, another substance involved in atherogenesis.[7]

Several studies have shown that atherosclerosis is associated with vascular cystathionine γ-lyase deficiency, resulting in decreased production of H_2S, although it is not yet clear whether this deficiency shares a considerable pathogenetic role in it.[7] Experimental data in mice with genetic deletion of cystathionine γ-lyase fed an atherogenic diet, have shown accelerated atherosclerosis as compared to wild-type mice.[8] So, there is a possibility that pharmaceutical induction of this enzyme might prove beneficial in the prevention and treatment of atherosclerosis. Furthermore, experimental administration of sodium hydrosulfide (NaHS) -which acts as a H_2S donor- was found to protect rat aorta from toxic factors contributing to the development of atherosclerosis.[9] In another study with mice fed with an atherogenic diet, those with deficient cystathionine γ-lyase developed early fatty streak lesions in the aortic root, elevated plasma levels of total cholesterol, low-density lipoprotein cholesterol and homocysteine as well as enhanced aortic intimal proliferation. Treatment of these mice with NaHS prevented the development of accelerated atherosclerosis.[8]

Another possible action of H_2S on atherogenesis is related to the oxidized low- density lipoprotein (ox-LDL), a form of LDL in which both the protein and the lipids undergo oxidative changes and form complex products. Ox-LDL has been considered to play a role in atherosclerosis since the observation that in vitro incubation of macrophages with oxidized LDL -and not with native LDL- led to cholesterol ester accumulation. It sems that this damaged molecule of LDL is avidly scavenged and degraded by macrophages.[10] In an in vitro study, it was shown that overexpression of cystathionine γ-lyase reduced the generation of ox-LDL-stimulated TNF-α in macrophages, while knockdown of this enzyme enhanced it. A subsequent study showed that both the levels of mRNA and protein expression of this enzyme and hydrogen sulfide production were decreased in ox-LDL-treated macrophages.

Exogenous administration of NaHS decreased the production of TNF-α and other proinflammatory molecules. Their conclusion was that ox-LDL may downregulate the H_2S pathway, which plays an anti-inflammatory role in ox-LDL-stimulated macrophages.[11]

A study in apolipoprotein-E knockout mice -which are prone to atherogenesis- found decreased plasma H_2S level and aortic H_2S production as well as increased levels of intracellular adhesion molecule-1 (ICAM-1) in plasma and aorta. When such mice were treated with NaHS, plasma H_2S levels were increased, while the size of atherosclerotic plaque and plasma and aortic ICAM-1 levels were decreased. Thus, H_2S showed an antiatherogenic effect and administration of NAHS seemed to prevent aortic atheromatosis.[12]

Hydrogen sulfide has multiple roles in the central nervous system, either in normal function or disease. The endogenous level of H_2S in the brain is significantly higher than in other tissues. It is synthesized in astrocytes and released in response to neuronal excitation. It influences active synapses and this may mean a role in associative learning. There are also some indications that dysregulation of its metabolism may contribute to neurodegeneration. A deficient H_2S signaling has been found in Alzheimer's disease and Parkinson's disease.[3]

It is also considered of special importance in secondary neuronal injury. After an event of acute neuronal insult (e.g. stroke, traumatic brain injury or spinal cord injury) several secondary neuronal injuries may follow, exacerbating the initial damage. Such injuries include microcirculation failure, glutamate-mediated excitotoxicity, oxidative stress, inflammatory responses, neuronal apoptosis and calcium overload. Hydrogen sulfide activates smooth muscle cell plasma membrane ATP-sensitive potassium channels resulting in vasodilatation of cerebral vessels. It also induces glutamate uptake by astrocytes from the extracellular space, thus protecting the neurons from glutamate-mediated excitotoxicity. Further protection of neurons is mediated through its anti-oxidant, anti-inflammatory and anti-apoptotic actions. The administration of H_2S donors was found to have neuroprotective effects in mice. On the other hand, a possibly undesired effect of H_2S may be enhancement of calcium overload.[8]

Clinical observations have shown changes of H_2S in several abnormal conditions. In some of them (e.g., reperfusion injury, asthma, diabetic vascular complications, acute and chronic cardiac diseases, aging) there is a local or systemic H_2S deficiency, due to either inhibition of its synthesis or increased consumption.[1] In these cases, administration of H_2S donors might be of some use. Such an administration has already been tested in animals with encouraging results in several disease models. Some of these donors are already investigated in clinical trials.[13]

On the contrary, in other abnormal conditions, such as malignancies, critically ill patients or patients with Down syndrome, there is an upregulation of hydrogen sulfide enzymes and so its levels are increased. In these cases, the possible utility of enzyme inhibitors is under consideration.[1]

In an experimental procedure, hydrogen sulfide administration produced a hibernation-like state in rodents. The results were hypothermia and reduction in metabolic rate and oxygen demand. Such a state could be protective against hypoxia, as in ischemia-reperfusion injury.[14] Combined with an antiinflammatory action, it can be beneficial in cases of acute lung injury, as it was shown with the intravenous administration of NaSH in an experimental model in anesthetized rats.[15] Potential therapeutic applications of hydrogen sulfide-induced hibernation are currently investigated.

However, the effects of hydrogen sulfide may not be always beneficial. A probably harmful biological role of H_2S was detected in cystathionine γ-lyase deficient mice. When these mice were infected by Mycobacterium tuberculosis they had, as compared to the wild-type mice, a longer survival, reduced pathology and lower bacterial burdens in the lung, spleen, and liver. In vitro experiments confirmed that excessive H_2S production -as happens in the normal mice- reduces hypoxia inducible factor 1 alpha (HIF-1$^{\alpha}$) levels, thereby suppressing glycolysis and production of interleukins 1β, 6 and 12, and increases bacterial burden.[16]

There is certainly much uncertainty concerning the possible biological role of hydrogen sulfide and our abilities to prevent or treat human diseases by an intervention to its metabolism. However, it seems to be a new and promising field which may prove more interesting in the future.

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