TRIMETHYLSULFONIUM: A PROMISING NEW BIOMARKER FOR HYDROGEN SULFIDE?

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ABSTRACT

Hydrogen sulfide is a toxic gas but is naturally produced in human tissues and is referred to as the "third gaseous signaling molecule". Little is known about the metabolic pathways of hydrogen sulfide and its endogenous natural production in humans. Thiosulfate is the currently used biomarker for hydrogen sulfide but its utility has been shown to be limited to exposure to high levels of inhaled hydrogen sulfide rather than probing low levels of environmental exposure or as a biomarker for the endogenously produced third gaseous signaling molecule. We recently identified a new metabolite in human urine, trimethylsulfonium. In the present review, we discuss the little information known about trimethylsulfonium production in humans, its potential to serve as a biomarker for hydrogen sulfide, and its utility as a biomarker under various settings.

Hydrogen sulfide as a naturally produced signaling molecule

Hydrogen sulfide is notoriously known as a toxic gas. However, it is known to be produced endogenously in human tissues from the amino acid cysteine by various enzymatic activities (1). The importance of endogenously produced hydrogen sulfide has been increasingly recognized and it has been established as the third gaseous signal transmitting molecule along with nitric oxide and carbon monoxide, which plays important roles in the central nervous system, cardiovascular function, and aging (2). Tissue hydrogen sulfide is produced at a high rate of 30-600 µmol h^{-1} Kg^{-1} (3), which can cause the buildup of lethal levels, and therefore hydrogen sulfide is rapidly oxidized to thiosulfate (5), which keeps tissue hydrogen sulfide levels in the low nanomolar range (e.g. 17±2.6 nM in rat tissues, 14±3.0 nM in rat brain) (4). The regulation of hydrogen sulfide and its metabolic pathways remain however largely unknown. Given the multiple health effects that can be mediated by hydrogen sulfide and the difficulty of directly studying this compound in human samples due to its high volatility, there is a need for new biomarkers that are stable, easily analyzed, and indicative of the hydrogen sulfide body pools.

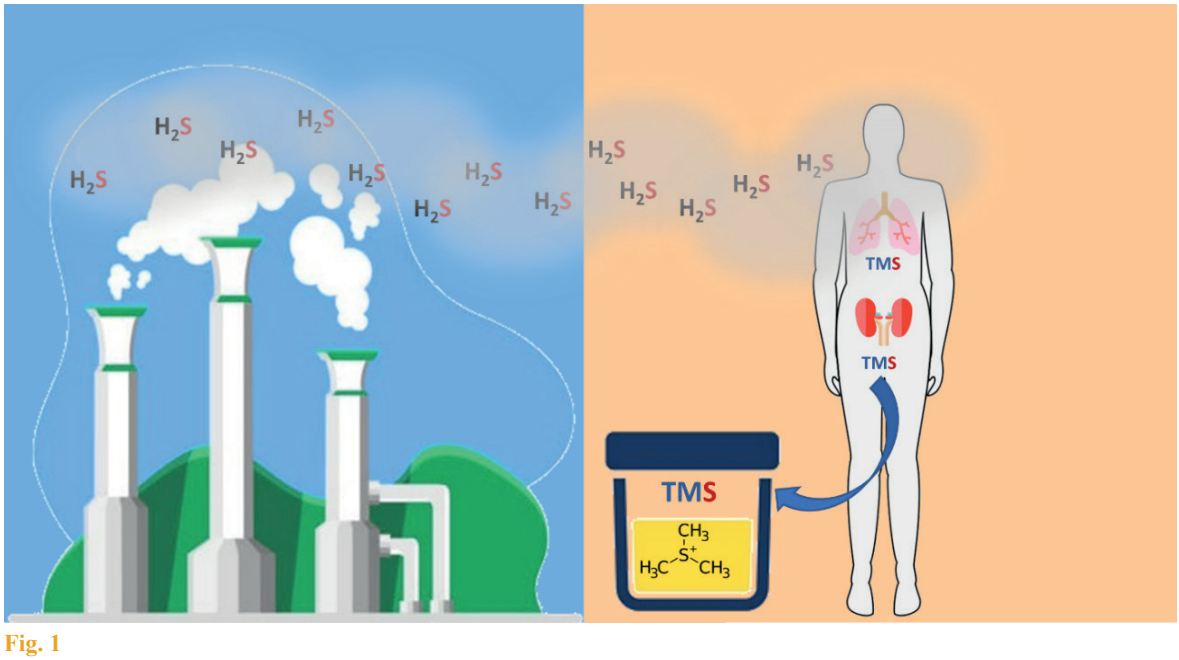

Fig. 1

Thiosulfate: the currently employed biomarker for hydrogen sulfide

As an enzymatic oxidation product, thiosulfate in blood and urine has been used as an indicator of acute hydrogen sulfide poisoning (6). However attempts to use urinary thiosulfate in human clinical studies as an indicator of the endogenously produced hydrogen sulfide have not found success (7). The failure of urinary thiosulfate as a clinical biomarker for endogenous hydrogen sulfide may not be surprising. The highest enzymatic activity of the key enzyme for thiosulfate production, namely thiosulfate sulfur transferase (rhodanese), is found in the colonic mucosa relative to other tissues (8, 9), where there is also a very high production rate of exogenous hydrogen sulfide by the sulfate-reducing bacteria in the gut (8, 10). Accordingly, it can be argued that urinary thiosulfate would heavily reflect this bacterial exogenous source of hydrogen sulfide, and therefore decrease the sensitivity of this biomarker to endogenously produced hydrogen sulfide produced in various organs and tissues.

Trimethylsulfonium production in humans

It follows that a metabolite that shows less dependency on the bacterial source of hydrogen sulfide may offer significant advantages in terms of reflecting the endogenously produced hydrogen sulfide. In our recent work, we identified for the first time the existence of the methylated metabolite trimethylsulfonium (TMS) in human urine (11). TMS is known to be produced by the enzyme thioether S-methyltransferase from dimethylsulfide (12, 13). Dimethylsulfide can be produced from successive methylation of hydrogen sulfide (14). Therefore, it is plausible to hypothesize that TMS can be a simple methylation biomarker of hydrogen sulfide. Unlike the enzyme that produces thiosulfate (rhodanese), the tissue expression profile of the enzyme that produces TMS (the thioether S-methyltransferase) indicates very low activity in the colonic mucosa relative to other tissues (9). Therefore, TMS production would be expected to show much less dependency on the large bacterial source of hydrogen sulfide in the colon in contrast with thiosulfate. Indeed, the urinary levels of TMS that we found in a group of human volunteers (median concentration 34 nM, range 2.7-505 nM) (11) are on average about 100-1000 times lower than the urinary levels of thiosulfate commonly reported (6.2-61 μM) (15), and are therefore noted to be closer to and likely more representative of the nanomolar levels of tissue hydrogen sulfide concentrations previously reported (4). These observations may imply a promising role for this new metabolite in humans as a new biomarker for endogenous tissue hydrogen sulfide. Furthermore, the expression of the thioether S-methyltransferase enzyme that produces TMS is highest in the lungs (9), which suggests this enzyme evolved in mammals as a defense mechanism against volatile toxic sulfur compounds.

Human exposure to hydrogen sulfide in air

The employment of the currently used biomarker of hydrogen sulfide, thiosulfate, under conditions of low exposure level to hydrogen sulfide was reported to show only small and inconsistent increase in the human volunteers (16). There is therefore a need for a new more sensitive biomarker for hydrogen sulfide at low levels of exposure and the significance of finding sensitive biomarkers for monitoring low sub-toxic and chronic exposure to hydrogen sulfide is highlighted by the increasing role of geothermal plants as an alternative source of energy (17) and the fact that there are numerous reports about high hydrogen sulfide concentrations in ambient air of heavily populated regions worldwide. The most commonly known example is the city of Rotorua in New Zealand, with a population of roughly 77,000, where geothermal activity leads to markedly elevated hydrogen sulfide levels in air that are consistently above characteristic odor threshold (>0.001 ppm). with levels exceeding 0.05 ppm in the mid-winter months (18). The village of Larderello in the Tuscany region in Italy, with a population of about 400 people, contains multiple geothermal power plants, contributing up to about 10% of the total world's entire supply of geothermal electricity with an output of 4,800 GWh/year. In this village, remarkably high concentrations of hydrogen sulfide within the range of 0.7-13 ppm were detected (19, 20). High concentrations of hydrogen sulfide in ambient air was also detected in Pozzuoli village in Italy with a population of about 82,000, particularly in residences around the Volcano Solfatara region (21). In the city of Thessaloniki, Greece, with a population of about 1 million mean hydrogen sulfide up to 0.02 ppm were reported on a daily basis in winter, and it was reported that traffic emission is a major source of the observed elevated hydrogen sulfide concentrations (22). Furthermore, a major contributor to anthropogenic hydrogen sulfide emission is the paper and pulp industry. For example, in close proximity to a pulp-mill in California, hydrogen sulfide concentrations peaked at around 0.15 ppm whereas the average monthly concentrations of hydrogen sulfide in a Finnish town close to a pulp-mill were reported at up to 0.1 ppm (18).

The variability in the human urinary excretion of trimethylsulfonium

It is noteworthy that the interpretation of trimethylsulfonium levels in humans must be approached with care. Following our recent identification of TMS as a natural metabolite in human urine (11), we performed a small study employing a total of 50 volunteers and we found a clear association between the urinary excretion of TMS and the urinary excretion of its selenium analogue trimethylselenonium (TMSe) (18). Our results indicated significant inter-individual variability in the production of TMS. Trimethylsulfonium and TMSe are known to be produced by the same enzyme thioether S-methyltransferase (12), which is encoded by the INMT gene, and this gene has been found to be genetically polymorphic, with a strong impact reported on TMSe production (23, 24). It is therefore likely that the genetic polymorphisms in the INMT gene can impact the production of TMS and result in significant inter-individual variability.

Concluding remarks

Trimethylsulfonium appears to be a simple methylated product of hydrogen sulfide and may serve as a biomarker for endogenous and exogenous (i.e. inhaled)

sources of this gas. However, plenty of research is needed to investigate the origin and etiology of the production of this metabolite in humans, as well as the applicability of this compound under various conditions in humans populations. We are currently investigating these aspects and future work will shed light on the significance of this human urinary metabolite.

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