

**H₂S and glucose metabolism, how does the stink regulate the sweet?**

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Received: October 16, 2015
Published online: December 15, 2015

Hydrogen sulfide (H₂S), once regarded as a toxic gas with a very bad smell of rotten eggs, now is recognized as an important gasotransmitter and regulates numerous physiological and pathophysiological processes in our body. Recent studies have demonstrated that H₂S is able to directly alter protein activity by modifying the free thiol groups in the target cysteine residue(s) to form persulfides, a process termed as protein S-sulfhydration, which mediates the major bioactivities of H₂S in cellular functions. Compared with all other tissues, liver generates huge amount of H₂S mainly from the enzyme cystathionine gamma-lyase. H₂S participates in the regulation of liver functions and attenuates fatty liver development. In this research highlight, I discuss the latest published findings on H₂S regulation of liver glucose generation and metabolism via posttranslational modification of gluconeogenic enzymes.

**Keywords:** H₂S; Cystathionine gamma-lyase; S-sulfhydration; Liver; Glucose

To cite this article: Guangdong Yang. H₂S and glucose metabolism, how does the stink regulate the sweet? Immunoendocrinology 2016; 3: e1066. doi: 10.14800/ie.1066.

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Hydrogen sulfide (H₂S) is traditionally known as a toxic gas predominantly present in the environment. Now we know H₂S can be endogenously produced in our body at a very small amount, and this small amount of H₂S help our health in many ways [1, 2]. Similar to nitric oxide and carbon monoxide, H₂S is recognized as a member of the growing family of gasotransmitter [1]. H₂S has been shown to be involved in the regulation of vascular tone, neurotransmission, insulin secretion, cell growth and differentiation, mitochondrial biogenesis, and energy generation, etc [1-3]. Three enzymes in the reverse transsulfuration pathway, including cystathionine beta-synthase, cystathionine gamma-lyase (CSE) and 3-mercaptopuruvate sulfurtransferase, contribute to the endogenous H₂S generation in a variety of cells and tissues [1]. Compared with all other tissues in the body, liver generates huge amount of H₂S, which is mainly attributed to CSE-catalyzed cysteine metabolism [4, 5]. The liver is the crucial organ in the maintenance of glucose homeostasis by balancing its uptake and storage via glycogenesis and the generation of glucose via gluconeogenesis and glycogenolysis, and hepatic H₂S has been shown to be involved in the development of diabetes and insulin resistance by affecting glucose metabolism [6]. In this research highlight, I discuss the latest discoveries on H₂S regulation of liver glucose generation and metabolism via posttranslational modification of gluconeogenic enzymes.
Under normal condition, glucose is stored in the liver in the form of glycogen, which can be broken down to yield glucose when energy is needed, such as in the status of starvation or fasting condition. Our recent papers discovered that H_2S impairs glucose uptake and increases glucose in liver cells \[5, 7, 8\]. NaHS, a well-known H_2S donor, significantly inhibited glucose consumption and resulted in a reduction in glycogen content in both liver hepatocellular carcinoma cell line (HepG2) and isolated mouse primary hepatocytes \[5\]. Overexpression of CSE in HepG2 cells stimulated H_2S generation, which subsequently attenuates glycogen storage. In contrast, CSE deficiency markedly induced liver glycogen content in mice under both normal and 6-h fasting conditions. Glycogen can be broken down to glucose-6-phosphate and then glucose through glycogenolysis. More directly, we observed H_2S increases the rate of glycogenolysis, which leads to the reduction of glycogen content. Furthermore, H_2S also enhanced glucose production when the substrates (pyruvate and lactate) were added into the HepG2 cells, indicating the participation of gluconeogenesis process \[5, 7\]. At the animal level, H_2S only increased blood glucose in nonfasting mice in a rapid fashion, indicating that H_2S plays a bigger role in glycogenolysis in comparison with gluconeogenesis (Figure 1) \[6\]. These findings will definitely help advance our understanding of H_2S regulation of glucose metabolism under both physiological and stress conditions and also help develop novel therapeutic avenue for treatment metabolic syndrome.

Glucokinase is the crucial enzyme in regulating liver glucose utilization through glycolysis pathway. Phosphoenolpyruvate carboxykinase (PEPCK) is the key enzyme involved in the metabolic pathway of gluconeogenesis. Interestingly, treatment of HepG2 cells with H_2S significantly enhanced PEPCK activity but reduced glucokinase activity, pointing the possibility that H_2S stimulates gluconeogenesis but shuts down glycolysis pathway synchronously \[5, 8\]. The increased PEPCK activity by H_2S was potentially due to higher glucocorticoid receptor (GR) activity and lower AMPK phosphorylation. Blockage of GR activity by its inhibitor RU-486 significantly reversed H_2S-stimulated PEPCK activity and glucose production \[8\]. Application of an AMPK agonist abolished the inhibitory effect of H_2S on glucose consumption \[5\]. In addition, H_2S-induced S-sulfhydration of PGC-1α also contributed to gluconeogenesis in liver cells \[8\]. PGC-1α is key gluconeogenic transcription factor, which induces the expressions of the rate-limiting gluconeogenic genes, including glucose-6-phosphatase and fructose-1,6-bisphosphatase. Not only acting on the transcriptional level, H_2S also directly induced the activities of PC, G6Pase and F1,6Pase through S-sulfhydration \[8, 9\]. Besides that, we provided more evidence showing that H_2S induces the activity of pyruvate carboxylase (PC), a crucial mitochondrial enzyme for controlling fuel partitioning toward gluconeogenesis \[7\]. All these findings demonstrated that H_2S induces glucose production by targeting at multiple signalling pathways (Figure 2).
The liver is the major organ generating endogenous H$_2$S in our body and is also likely exposed to high levels of exogenous H$_2$S from the gastrointestinal tract. Lower level of H$_2$S induces liver dysfunction and leads to hepatic fibrosis and cirrhosis, while higher level of H$_2$S stimulates insulin resistance and progression of diabetes [1, 4]. Maintenance of the normal level of liver H$_2$S through its generation and metabolism would be critical for modulating liver physiology and managing hepatic disorders. It is clear that abnormal glucose metabolism contributes to liver disease and metabolic syndrome. Future studies need to develop therapeutic targets for the prognosis, diagnosis, and treatment of liver disorders based on the interaction of H$_2$S and glucose metabolism, a stink and sweet symphony.

Conflict of interests

The authors have declared that no conflicts of interests exist.

Acknowledgment

This study was supported by a start-up funding from Laurentian University, Ontario, Canada.

Abbreviations

CSE: cystathionine gamma-lyase; F1,6Pase: fructose-1,6-bisphosphatase; G6Pase, glucose-6-phosphatase; GR: glucocorticoid receptor; H$_2$S: hydrogen sulfide; PC: pyruvate carboxylase; PEPCK: phosphoenolpyruvate carboxykinase.

References