Production of H$_2$S by 3-mercaptopyruvate sulphurtransferase

Received December 25, 2010; accepted January 24, 2011; published online February 15, 2011

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Hydrogen sulfide (H$_2$S) has been established as the third gaseous signaling molecule following nitric oxide and carbon monoxide and participates in a variety of cellular functions such as modulation of neuronal transmission, endothelium-dependent vasorelaxation, stimulation of angiogenesis and regulation of insulin release. Although cystathionine β-synthase and cystathionine γ-lyase have been regarded as the main producers of H$_2$S in many tissues including brain, liver and kidney, Kimura and his colleagues have recently communicated that 3-mercaptopyruvate sulphurtransferase coupled with cysteine (aspartate) aminotransferase is responsible for the production of H$_2$S in the vascular endothelium of the thoracic aorta [Shibuya et al. (2009) J. Biochem. 146, 623–626]. This finding provides a new insight into the production of the physiologically important signaling molecule.

Keywords: endothelium/hydrogen sulfide/3-mercaptopyruvate sulphurtransferase/smooth muscle/vasorelaxation.

Abbreviations: CAT, cysteine (aspartate) aminotransferase; CBS, cystathionine β-synthase; CSE, cystathionine γ-lyase; 3MST, 3-mercaptopyruvate sulphurtransferase.

Although hydrogen sulfide (H$_2$S), the so-called rotten egg gas, has been long known for its very high toxicity, studies over the past two decades have revealed that H$_2$S generated endogenously in mammalian tissues exhibits various physiological functions [for a recent review, see Ref. (1)]. Kimura and his colleague (2) first demonstrated that H$_2$S produced in the brain acts as a neuromodulator, which facilitates the induction of hippocampal long-term potentiation by enhancing the activity of NMDA receptors in neurons and increases the Ca$^{2+}$ influx into astrocytes (3). They also showed that H$_2$S produced in the thoracic aorta, portal vein and ileum plays as a smooth muscle vasorelaxant in synergy with nitric oxide (NO) (4). These pioneer findings by Kimura’s group facilitated numerous subsequent studies by other groups, which finally led to the establishment of H$_2$S as the third gaseous signaling molecule following NO and carbon monoxide (CO).

In an earlier study using the homogenates of rat liver and kidney (5), three enzymes present in mammalian tissues: (i) cystathionine β-synthase (CBS), (ii) cystathionine γ-lyase (CSE) and (iii) 3-mercaptopyruvate sulphurtransferase (3MST) in conjunction with cysteine (aspartate) aminotransferase (CAT), were reported to be possible H$_2$S-generators. CBS and CSE, which occur in many tissues including brain, liver, kidney, ileum, uterus and placenta, are both pyridoxal 5'-phosphate-dependent lyases (EC class 4) involved in the trans-sulphuration pathway and catalyse the synthesis of cystathionine from L-serine and L-homocysteine (β-replacement reaction) and the degradation of cystathionine into L-cysteine, 2-ketobutyrate and ammonia (γ-elimination reaction), respectively. Beside these main reactions, CBS and CSE can also catalyse the synthesis of cystathionine from L-cysteine (instead of L-serine) and L-homocysteine, generating H$_2$S (Scheme 1, reaction 1) (5, 6) and the β-elimination reaction with certain disulfides, including L-cysteine, respectively (5). CSE is known to prefer L-cysteine to L-cysteine for β-elimination and degrades it into pyruvate, ammonia and thiocysteine (reaction 2) (7), which may react non-enzymatically with L-cysteine or other thiols to form H$_2$S and L-cysteine or the corresponding disulfide (Scheme 1) (5). However, the significance of L-cysteine in the reducing intracellular environment remains to be clarified. Moreover, definitive evidence for the in vivo substrate directly used in the formation of H$_2$S is lacking for either of CBS and CSE. Nonetheless, it is widely assumed that desulphhydration of L-cysteine is the major source of H$_2$S in mammals and is catalysed by these trans-sulphuration pathway enzymes.

Recently, Kimura and his colleagues (8, 9) have found that the third enzyme, 3MST in conjunction with CAT, contributes significantly in generating H$_2$S from L-cysteine in the presence of α-ketoglutarate in the brain and in the vascular endothelium of thoracic aorta. CAT, which is identical with aspartate aminotransferase, efficiently catalyses the transamination between L-cysteine and α-ketoglutarate to produce 3-mercaptopyruvate and L-glutamate (Scheme 1, reaction 3). 3MST then transfers sulphur from 3-mercaptopyruvate to sulphurous acid to produce pyruvate and thiocysteine (reaction 4), which is finally reduced to H$_2$S by another sulphurtransferase in the presence of reduced glutathione (GSH). Both CAT and 3MST were found to be localized not only in the brain but also in the vascular endothelium of thoracic aorta (8, 9). Particularly, neither CSE nor CBS was found
in rat endothelial cells (9), although they were detected in mouse endothelial cells (10), suggesting that there may be a species/tissues difference for production of H$_2$S. The H$_2$S generation was not observed in the absence of α-ketoglutarate and suppressed in the presence of l-aspartate, a preferred CAT substrate to l-cysteine (9). Thus, the enzyme system consisting of 3MST and CAT significantly contributes in generating H$_2$S as a smooth muscle relaxant in the vascular endothelium. This finding provides a new insight into the production of the physiologically important signaling molecule.

Aside from some uncertainties in the substrates for enzymatic generation of H$_2$S, there is accumulating evidence for various physiological roles of H$_2$S. Yang et al. have recently shown that the CSE-knockout mice have markedly reduced H$_2$S levels in the serum, heart, aorta and other tissues, and display pronounced hypertension and diminished endothelium-dependent vasorelaxation, providing further evidence that H$_2$S is an endothelium-derived relaxation factor possibly regulating the systemic blood pressure (10). Like NO and CO, the production of H$_2$S is enhanced by muscarinic cholinergic stimulation of the vascular endothelium, which activates the major H$_2$S-generating enzyme CSE through binding to calcium-calmodulin (10). However, the mechanism of action of H$_2$S is thought to be different from those of NO and CO, both of which activate soluble guanylate cyclase and increase the intracellular cGMP (11). Presumably, H$_2$S opens the K$_{\text{ATP}}$ channel and thereby hyperpolarizes the membrane potentials of smooth muscle, leading to relaxation (12). Also, it should be noted that one gas regulates another to form intriguing feedback mechanisms among different gases (13, 14).

H$_2$S also plays as a cytoprotectant rescuing neurons and cardiac smooth muscle from oxidative stress mainly by enhancing the cellular production of GSH and preserving mitochondrial function (1, 15, 16). Furthermore, H$_2$S is involved in the regulation of insulin release from the pancreatic β-cells (17, 18) and in inflammatory reactions (19, 20), stimulates the endothelium-related angiogenesis and wound healing through a K$_{\text{ATP}}$ channel/MAPK pathway (21), and even brings small animals into a hibernation-like state by significantly down-regulating the energy metabolism (22). Due to such versatile activities, therapeutic exploitation of H$_2$S has been sought in clinical fields, expecting that administration of a low dose of H$_2$S or inhibitors for H$_2$S-generating enzymes would afford various clinical benefits (23, 24).

In summary, the studies related to H$_2$S physiology are now expanding explosively and receiving wide attention.

Conflict of interest
None declared.

References
Production of H\textsubscript{2}S by 3MST


