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Forum Editorial

Hydrogen Sulfide as a Biological Mediator

HIDEO KIMURA

HYDROGEN SULFIDE (H_2S) is a well-known toxic gas, and its toxic effect has been described for nearly 300 years. Recently, however, relatively high concentrations of endogenous sulfide have been measured in the brains of bovine, rats, and humans, suggesting a physiological function of H_2S (10, 22, 33). Responses of hippocampal neurons to *N*-methyl-D-aspartate are specifically enhanced by H_2S, and the induction of hippocampal long-term potentiation, a synaptic model for memory, is augmented by simultaneous application of H_2S (1, 16). In addition to the regulation of neurons, we recently found that H_2S induces glial Ca^{2+} waves, which may mediate glial signal transduction and regulate synaptic activity (19). Glial cells have been considered to be the nonexcitable and supportive elements in the nervous system, but they are now regarded as elements that respond to neuronal activity and modulate synaptic activity (12). There is accumulating evidence for reciprocal interactions between glial Ca^{2+} waves and neurons (5, 20). The multiple interactions between neurons and glia strongly suggest that glial cells are integral modulatory elements in synaptic transmission (2). H_2S may therefore be involved in the regulation of synaptic transmission by modulating the activity of both neurons and glia. Kimura *et al.* (16) review the recent progress in the involvement of H_2S in the regulation of synaptic transmission.

It is hard to imagine that H_2S protects neurons from oxidative stress (16, 17). Oxidative glutamate toxicity, recently renamed oxytosis, is a well-studied programmed cell-death pathway that is independent of excitotoxicity (18, 31). Glutamate shares the same amino acid transporter with cystine, and it competes with cystine for transport into cells (3). Therefore, elevated extracellular glutamate inhibits the transport of cystine, which is the primary source of intracellular cysteine necessary for glutathione synthesis. Cells can be rescued from oxidative stress by mechanisms that are either dependent on or independent of glutathione metabolism. For example, antioxidants such as vitamin E protect neuronal cells from oxytosis by acting directly as antioxidants even when the intracellular glutathione levels are decreased (23). Sulfur-containing substances, dimethylsulfoniopropionate (DMSP) and its enzymatic cleavage product dimethyl sulfide (DMS), have recently been identified as endogenous scavengers for hydroxyl radicals and other reactive oxygen species in marine algae (29). Kimura *et al.* (16) review the protection of neurons from oxidative stress by H_2S through the mechanism of producing a major and potent antioxidant, glutathione.

In addition to the function in the brain, we also demonstrated that H_2S functions as a relaxant in smooth muscle (13) like nitric oxide (NO) (9) and carbon monoxide (15, 27). There is a synergy between NO and H_2S to relax smooth muscle (13, 32). H_2S effectively relaxes aortic tissue precontracted by 20 m*M* KCl, and the effect is blocked by the K^+-channel blocker, tetraethylammonium (34). Glibenclamide, an ATP-dependent K^+ (K_{ATP})-channel blocker, also inhibits H_2S-induced relaxation of aortic smooth muscle, suggesting the involvement of the K_{ATP} channel in smooth muscle relaxation. Not only in mammals, but also in fish, H_2S can regulate smooth muscle tone (6). Here Olson reviews how H_2S produces a triphasic contraction–relaxation–contraction in pulmonary arteries in nonmammals (21). Phase-1 dilation has an endothelium-dependent component, and K_{ATP} channels may mediate part of the phase-3 relaxation. Both phases are apparently independent of cyclic GMP production as shown in the mammalian brain (1). Vasoregulatory function of H_2S is discussed based on the data obtained by the comparative physiology study.

Endogenous H_2S can be formed from cysteine by pyridoxal 5′-phosphate-dependent enzymes, including cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) (7, 26). CBS has been proposed as a candidate enzyme that produces H_2S in the brain (1). CBS is a well-known enzyme in the transsulfuration pathway, and most studies of CBS have been concentrated on its activity of converting homocysteine to cysteine (11, 25, 30). Here Jhee and Kruger review the structure–function relationship of CBS and the mutations of the CBS gene that are associated with homocystinuria, an autosomal recessive disorder characterized by atherosclerotic cardiovascular

National Institute of Neuroscience, Tokyo, Japan.

diseases, stroke, peripheral arterial occlusive diseases, and venous thrombosis (14). By using the yeast system to analyze CBS mutations, deletion of the C-terminal domain of CBS was discovered to suppress the functional defects caused by the CBS mutations (24). The possible development of drugs by using this analysis is also discussed.

The original article by Suematsu's group shows the modulatory function of H_2S in the liver (8). The administration of propargylglycine, an inhibitor of CSE, reduces the production of H_2S by 50% and induces choleresis by stimulating the basal excretion of biliary bicarbonate. The supplementation of NaHS abolishes the changes induced by the CSE inhibitor, suggesting that H_2S generated by CSE regulates biliary bicarbonate excretion. These observations suggest that H_2S can regulate biliary bicarbonate excretion.

Another original study by Suematsu's group shows that CBS and CSE are involved in the metabolism of sulfur-containing amino acids in testes exposed to cadmium stress (28). CBS is localized in Leydig cells and germ cells, and CSE in Sertoli cells and immature germ cells. Cadmium stress does not change the levels of CBS or CSE in testes, but significantly increases the amounts of methionine and cysteine. Stress also decreases the amount of oxidized glutathione without changing the level of the reduced form of glutathione. Suematsu suggests that cadmium stress induces metabolic changes in sulfur-containing amino acids and H_2S may be involved in this process.

The review articles and original articles in this *Forum* cover the most up-to-date research in the H_2S field.

Note: During the editing of the *Forum* reviews, Chen *et al.* published an article about the production of H_2S by CBS via the condensation mechanism.

ABBREVIATIONS

CBS, cystathionine β-synthase; CSE, cystathionine γ-lyase; H_2S, hydrogen sulfide; K_{ATP} channel, ATP-dependent potassium channel; NO, nitric oxide.

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Address reprint requests to:
Hideo Kimura, Ph.D.
National Institute of Neuroscience
4-1-1 Ogawahigashi
Kodaira
Tokyo 187-8502
Japan

E-mail: kimura@ncnp.go.jp

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