Translational Nephrology

Blood pressure control: hydrogen sulfide, a new gasotransmitter, takes stage∗

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Summary

Hydrogen sulfide (H2S) is the most recently characterized autocrine/paracrine messenger implicated in the control of vascular tone. A series of coherent observations now document that this gas is a strong vasorelaxant and a determinant of blood pressure in experimental models. Targeted deletion of the gene encoding cystathionine-lyase (CSE). CSE, a key enzyme for H2S biosynthesis, reduces serum H2S levels and determines age-dependent hypertension in mice. Hypertension in this model does not depend on central or on renal mechanisms or on compromised nitric oxide (NO) generation and rests solely on disturbed endothelium dependent vasorelaxation. Cholinergic stimulation of endothelial cells determines a marked increase in H2S levels which can be blocked by the anti-cholinergic drug atropine. H2S has in full the pharmacological properties which are considered characteristics of endothelium relaxing factors. Global endothelium dependent relaxing activity in the CSE knockout mice is reduced by about 60% suggesting that the lack of H2S is critical to explain impaired vasodilatation in these mice. Furthermore arterial pressure is similarly raised in NO synthase knockout and in CSE knockout mice indicating that H2S is a vasoregulator of potency comparable to that of NO. Defective synthesis of H2S may be involved in various human diseases including systemic and pulmonary hypertension and septic shock.

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H2S: basic biochemistry and experimental models

From an evolutionary perspective, the capacity of synthesizing H2S by living organisms antedates the development of the cardiovascular system. The biochemical pathways and enzymes linking this gas and sulphur amino acids [3] are depicted in Figure 1. In complex organisms, H2S synthesis is regulated by 2 pyridoxal-5'-phosphate-dependent enzymes, cystathionine beta synthase (CBS) and cystathionine-lyase...
It was known that H2S opens K+ channels in smooth muscle cells [4]. Initial studies suggested that this enzyme localizes mainly in smooth muscle cells. However, very recent observations (see below) have shown that CSE is also abundantly expressed in the endothelium where H2S acts as a major endogenous EDRF. Anti-atherosclerosis properties of H2S are well recognized [5]. Very recent observations by Yang et al. [6] now provide a series of coherent proofs documenting that this gasotransmitter is a strong vasorelaxant and a determinant of blood pressure. Genetic engineering studies in mice with a targeted deletion of the gene encoding CSE, i.e. homozygous (CSE−/−) and heterozygous (CSE+/−), show that these mutant mice have serum H2S levels by 50% and 20% lower than wild-type mice. In line with the hypothesis that H2S is a vasorelaxant, double knockout CSE−/− mice develop age-dependent hypertension starting from the 7th week of life. At the 12th week, systolic pressure is ~20 mmHg higher than in control, wild-type mice. Notably, heterozygous CSE+/− mice also show a distinct increase in BP that is initially similar to that observed in homozygous CSE−/− mutants, but halfway between CSE−/− and wild-type mice at later stages. Because CSE is not needed for the synthesis of H2S in the brain, cerebral concentration of this gas in CSE mutant mice is identical to that in wild-type mice, indicating that hypertension triggered by CSE deletion is not caused by a central mechanism. By the same token, endothelial NO synthase (NOS) is unchanged in CSE−/− mice, which speaks against the hypothesis that the BP rise depends on a concomitant loss of NO-mediated vasorelaxation. Furthermore, hypertension cannot be attributed to a renal alteration because kidney structure and function is well maintained in these animals.

**Pharmacologic insights on the vasoregulatory role of H2S**

It was known that H2S opens K+ channels in smooth muscle cells [4]. Building upon this consolidated knowledge, Yang et al. went to demonstrate that intravenous NaHS, an H2S donor, dose-dependently decreases systolic blood pressure in both CSE−/− and wild-type (CSE+/+) mice. Such an effect was more pronounced in the mutant mice (a model of H2S deficiency), pointing to a greater sensitivity to H2S, i.e. to receptor upregulation brought about by low levels of the agonist, H2S. Additional experiments in mesenteric arteries in vitro by adrenergic and cholinergic mediators and by NO donors definitively established a fundamental role of H2S in vasoregulation and in hypertension in CSE−/− mice. Thus, while phenylephrine (a smooth muscle cells contracting agent) and the NO donor nitroprusside (a smooth muscle cells relaxant) evoke responses of similar magnitude in wild-type and CSE−/− mice, H2S is a more potent vasorelaxant in mesenteric arteries in CSE−/− than in wild-type mice, which again points to H2S supersensitivity secondary to reduced formation of endogenous H2S. Of note, the response to metacholine in phenylephrine pre-constricted vessels was lower in CSE−/− than in wild-type mice, indicating that H2S is essential to reverse the potent increase in vascular tone induced by sympathetic stimulation. In other words, full activation of NOS by metacholine is insufficient to abolish the increase in smooth cells tone brought about by adrenergic stimulation. Separate immunohistochemistry studies of arterial vessels showed that CSE is highly expressed in the endothelium. Thus, H2S displays properties that are typical of EDRFs. Analogous to the other two gasotransmitters, NO and CO, which are regulated by enzymes (NOS and heme oxygenase-2) activated by calcium–calmodulin [7], CSE is also calcium-calmodulin dependent (Figure 2). H2S formation in endothelial cells is amplified by the calcium ionophore A23187, and this effect is prevented by the calcium chelator BAPTA [1, 2-bis (2-aminophenoxy) ethane-N, N, N′, N′-tetra acetic acid]. Remarkably, cholinergic stimulation regulates not only NOS but also CSE [8] (Figure 2). Indeed, stimulation of endothelial cells by acetylcholine or metacholine determines a marked increase in H2S levels that can be blocked by the anti-cholinergic drug atropine. H2S has in full the pharmacological properties that are considered characteristics of EDRFs. Global endothelium-dependent relaxing activity in mesenteric arteries of CSE knockout mice is reduced by ~60%, suggesting that the lack of H2S is critical to explain impaired vasodilatation in this vascular bed. Furthermore,
Potential relevance of H2S for human diseases

The primary role of CSE in disparate cell and organ functions makes it likely that deficient generation of the product of its activity, H2S, could be involved in human diseases. H2S deficiency is a feature of rats with experimentally induced hypoxic pulmonary hypertension [11]. Reduced NO synthesis is the major factor underlying pulmonary hypertension in humans [12]. Given the functional parallelism and complementarity of H2S and NO systems, a role of H2S deficiency in this disease seems likely. Spontaneously hypertensive rats, the most used animal model of primary hypertension, exhibit low CSE levels [13] suggesting that H2S deficiency can predispose to vasoconstriction and perhaps to hypertension. Conversely, CSE induction and excessive H2S generation play a role in hypotension in septic shock [14] in the rat and, again by analogy with NO, this gas may be a player in the corresponding human disease. A significant decrease in plasma H2S has been reported in children with hyperlipidaemia and in patients with coronary heart disease (quoted by Wang et al. [15]). The fact that CSE−/− mice do not develop renal damage would speak against this gas being involved in renal diseases. However, the complex and still scarcely characterized interaction of H2S with the NO system—a system of major importance for renoprotection—demands caution in dismissing a role of this gasotransmitter in kidney diseases. We are at a very early stage of knowledge of a new fundamental cell-signalling messenger. If a good morning is prelude to a gorgeous day, exciting findings by Yang and colleagues and initial clinical observations indicate that H2S research will shed new light on our understanding of human physiology and human diseases.

Conflict of interest statement. None declared.

References


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