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COMMENTARY

Hydrogen sulphide: an endogenous stimulant of capsaicin-sensitive primary afferent neurons?

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Hydrogen sulphide (H_2S) is a gas best known for its rotten egg smell. The toxic effects of high concentrations of H_2S have been extensively investigated. It is known that H_2S is generated in mammalian systems, but little is known of its effects in physiological concentrations. In the present issue of this journal, Patacchini *et al.* present evidence that H_2S stimulates capsaicin-sensitive primary afferent neurons to release tachykinins in the rat urinary bladder. The possible significance of this finding is discussed in this commentary.
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Abbreviations: CBS, cystathionine β-synthase; H_2S, hydrogen sulphide

Hydrogen sulphide (H_2S) is a gas with a characteristic rotten egg smell. It is a chemical hazard in certain industries and its toxic effects on the central respiratory centres have been extensively investigated (see Reiffenstein *et al.*, 1992). However, H_2S is also generated in considerable amounts enzymatically, and to a lesser extent nonenzymatically, by mammalian tissues (see Wang, 2002). The enzymes involved in the enzymatic production of H_2S are cystathionine β-synthase (CBS) and cystathionine γ-lyase. The expression of these enzymes is tissue specific. Using CBS knockout mice, Eto *et al.* (2002) established that in brain tissue the main enzyme involved is CBS. Furthermore, it was found that the production of H_2S was greatly enhanced by activation of glutamate receptors and by electrical stimulation. H_2S has also been shown to enhance long-term potentiation (LTP) in rat hippocampal slices by enhancing the NMDA-induced inward current (Abe & Kimura, 1996). These observations have led to the proposal that H_2S might be a third endogenous gaseous transmitter or modulator which, like nitric oxide and carbon monoxide, regulates synaptic activity (Eto *et al.*, 2002; Wang, 2002; Boehning & Snyder, 2003).

Zhao *et al.* (2001) studied the effect of physiologically relevant concentrations of H_2S on the rat cardiovascular system *in vivo* and showed that it had a vasorelaxant effect and caused a decrease in blood pressure that mimicked the K_{ATP} channel opener pinacidil, and was antagonized by the K_{ATP} channel blocker glibenclamide. Studies on vascular tissues *in vitro* and on isolated smooth muscle cells have established H_2S as a K_{ATP} channel opener in these cells (Zhao *et al.*, 2001). Interestingly, the relaxant effect of H_2S on nonvascular smooth muscle occurred by a mechanism independent of K_{ATP} channels (Teague *et al.*, 2002).

In the present issue, Patacchini *et al.* (2004) present evidence that in the detrusor muscle of the rat urinary bladder H_2S produced contractile responses. These responses exhibited marked tachyphylaxis similar to responses to capsaicin, the active principle from chillies that stimulates certain primary afferent neurons to release neuropeptides, in particular tachykinins and calcitonin gene-related peptide (CGRP) (Maggi, 1995). On investigation of this response to H_2S, they found that desensitization of capsaicin-sensitive primary afferent neurons by pretreatment with a high concentration of capsaicin, or pretreatment of tissues with a combination of tachykinin NK_1 and NK_2 receptor antagonists, abolished the response to H_2S. These results provide definitive evidence that in the detrusor muscle the dominant effect of physiologically relevant concentrations of H_2S involves stimulation of capsaicin-sensitive primary afferent neurons with consequent release of tachykinins, which in turn produce contractile responses of the detrusor muscle.

From the results reported by Patacchini *et al.* (2004), the site of action of H_2S cannot be determined with certainty. However, the observation that the responses to H_2S exhibited a similar resistance to tetrodotoxin as those to capsaicin indicates that H_2S predominantly activates the primary afferent nerve terminals directly rather than indirectly *via* axonal conduction, which involves fast tetrodotoxin-sensitive sodium channels. The intriguing possibility that H_2S activates the transient receptor potential vanilloid receptor 1 (TRPVR1) receptors that are activated by capsaicin (Caterina *et al.*, 1997) awaits future investigation.

The response to activation of capsaicin-sensitive primary afferent neurons in a tissue or organ depends upon the complement of neuropeptides in the primary afferent neurons in that tissue, and the effect of the released neuropeptides. Thus capsaicin may produce stimulation of some smooth muscles and relaxation of others. Therefore, previous studies on the actions of H_2S, such as its vasorelaxant effect, may need re-evaluation in light of the findings reported by Patacchini *et al.* (2004) that H_2S activates primary afferent neurons. Furthermore, the toxicology of H_2S may require further investigation in light of these new findings.

H_2S is a very potent stimulant of olfactory afferents. It is possible that it might also activate a number of other

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chemosensitive neurons. Indeed, one important aspect that remains to be investigated is the selectivity of H_2S for capsaicin-sensitive primary afferent neurons. The study of Patacchini *et al*. (2004) has opened a new field of research into the pharmacology of H_2S and of primary afferent neurons, which should lead to new advances in understanding the physiological and pathophysiological roles of this putative endogenous gaseous neurotransmitter.

References

ABE, K. & KIMURA, H. (1996). The possible role of hydrogen sulfide as an endogenous neuromodulator. *J. Neurosci.,* **16,** 1066–1071.

BOEHNING, D. & SNYDER, S.H. (2003). Novel neural modulators. *Annu. Rev. Neurosci.,* **26,** 105–131.

CATERINA, M.J., SCHUMACHER, M.A., TOMINAGA, M., ROSEN, T.A., LEVINE, J.D. & JULIUS, D. (1997). The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature,* **389,** 816–824.

ETO, K., OGASAWARA, M., UMEMURA, K., NAGAI, Y. & KIMURA, H. (2002). Hydrogen sulfide is produced in response to neuronal excitation. *J. Neurosci.,* **22,** 3386–3391.

MAGGI, C.A. (1995). Tachykinins and calcitonin gene-related peptide (CGRP) as co-transmitters released from peripheral endings of sensory nerves. *Prog. Neurobiol.,* **45,** 1–98.

PATACCHINI, R., SANTICIOLI, P., GIULIANI, S. & MAGGI, C.A. (2004). *Br. J. Pharmacol.,* **142,** 31–34.

REIFFENSTEIN, R.J., HULBERT, W.C. & ROTH, S.H. (1992). Toxicology of hydrogen sulfide. *Annu. Rev. Pharmacol. Toxicol.,* **32,** 109–134.

TEAGUE, B., ASIEDU, S. & MOORE, P.K. (2002). The smooth muscle relaxant effect of hydrogen sulphide *in vitro*: evidence for a physiological role to control intestinal contractility. *Br. J. Pharmacol.,* **137,** 139–145.

WANG, R. (2002). Two's company, three's a crowd: can H_2S be the third endogenous gaseous transmitter? *FASEB J.,* **16,** 1792–1798.

ZHAO, W., ZHANG, J., LU, Y. & WANG, R. (2001). The vasorelaxant effect of H_2S as a novel endogenous gaseous K_{ATP} channel opener. *EMBO J.,* **20,** 6008–6016.

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