#157 Hydrogen sulfide can be an endogenous relaxation factor in the rat bladder and prostate

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Aims of study

Hydrogen sulfide (H_2S) is the third endogenous gasotransmitter besides carbon monoxide and nitric oxide [1], and has a wide range of biological functions including neuromodulation, vasorelaxation and cytoprotection [2]. In the lower urinary tract, H_2S donors induce contraction of the rat detrusor [3] and relaxation of the pig bladder neck [4], suggesting a possibility that H_2S may have site-specific effects on the bladder. However, the detailed functions of H_2S in each part of the bladder are still unclear. In addition, there are no reports showing physiological roles of H_2S in the prostate.

Endogenous H_2S is produced from L-cysteine (L-Cys) by enzymes: cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), 3-mercaptopyruvate sulfurtransferase (MPST) and cysteine aminotransferase (CAT) (Fig. 1) [5]. CBS and CSE produce H_2S from L-Cys directly, and MPST produce H_2S from 3-mercaptopyruvate (3MP), which is produced by CAT from L-Cys (Fig. 1) [5]. Recently, a novel pathway for endogenous H_2S production from D-cysteine (D-Cys) is also reported [6], namely, D-Cys is metabolized by D-amino acid ocidase (DAO) to 3MP, which is a substrate for MPST to produce H_2S (Fig. 1).

In the present study, therefore, we investigated (1) pharmacological profile of exogenous H_2S-induced relaxation of the rat bladder dome and trigone (BL-D and BL-T) and dorsolateral and ventral prostate (PR-D and PR-V), and (2) expression levels of CBS, CSE, MPST, CAT and DAO in each site of these tissues.

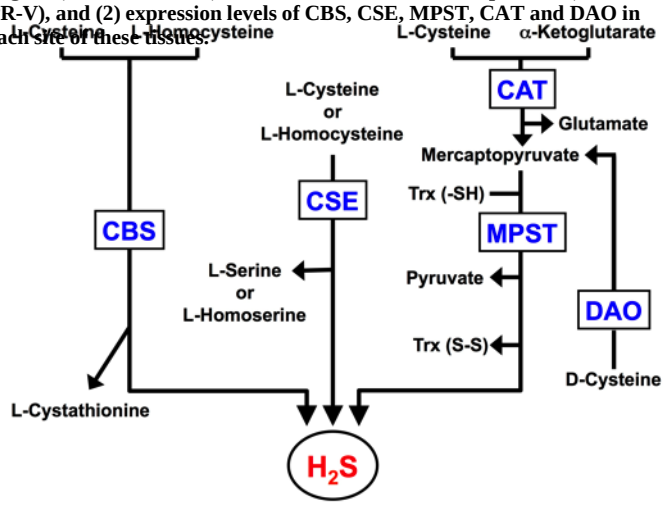


Fig. 1. Endogenous H_2S production. CAT; cysteine aminotransferase, CBS; cystathionine β-synthase, CSE; cystathionine γ-lyase, DAO; D-amino acid oxidase, MPST; 3-mercaptopyruvate sulfurtransferase, Trx; thioredoxin, Trx (-SH); reduced form of Trx, Trx (S-S); oxidized form of Trx.

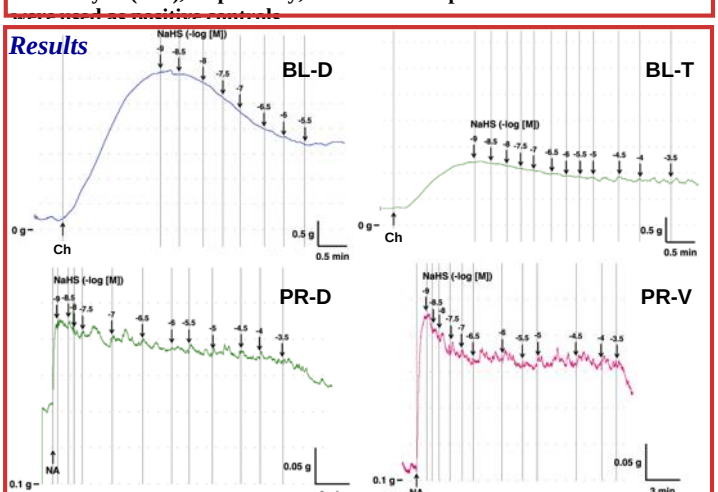
Materials and methods

BL-D, BL-T, PR-D, PR-V, liver and cerebellum (L and C) were prepared from male Wistar rats (300-400 g) sacrificed with an overdose of sodium pentobarbital (80 mg/kg, i.p.).

(1) By using 1 × 5 mm strips of bladder and prostate tissues, effects of NaHS (H_2S donor: 1 × 10^{-9} to 3 × 10^{-4} M) were evaluated on carbachol (1 × 10^{-5} M)-induced contractions of bladder and on noradrenaline (1 × 10^{-5} M)-induced ones of prostate. Prostate strips were pretreated with propranolol (1 × 10^{-6} M) 30 min before the pre-contraction.

(2) Gene and protein expression levels of CBS, CSE, MPST, CAT and DAO were investigated by quantitative real-time PCR (qPCR) and western blot analysis (WB), respectively, in bladder and prostate tissues. L and C were used as positive controls.

Results



Group	Relaxation rate (%)	EC_{50} (M)
BL-D	43.8 ± 3.4 (n=12)	9.64 ± 3.78 (× 10^{-8}) (n=14)
BL-T	38.5 ± 4.1 (n=14)	4.33 ± 1.19 (× 10^{-8}) (n=19)
PR-D	39.1 ± 2.9 (n=9)	10.13 ± 10.09 (× 10^{-6}) (n=18)
PR-V	42.7 ± 4.2 (n=14)	1.35 ± 1.29 (× 10^{-6}) (n=22)

Fig. 2. H_2S induced relaxation on pre-contracted bladder and prostate. BL-D and BL-T; bladder dome and trigone, PR-D and PR-V; dorsolateral and ventral prostate, Ch; carbachol, NA; noradrenaline. Values are means ± SEM.

- H_2S donor NaHS dose-dependently induced relaxation on the rat bladder and prostate

Conflict of interest

The first author has no conflict of interest to disclose with respect to this presentation.

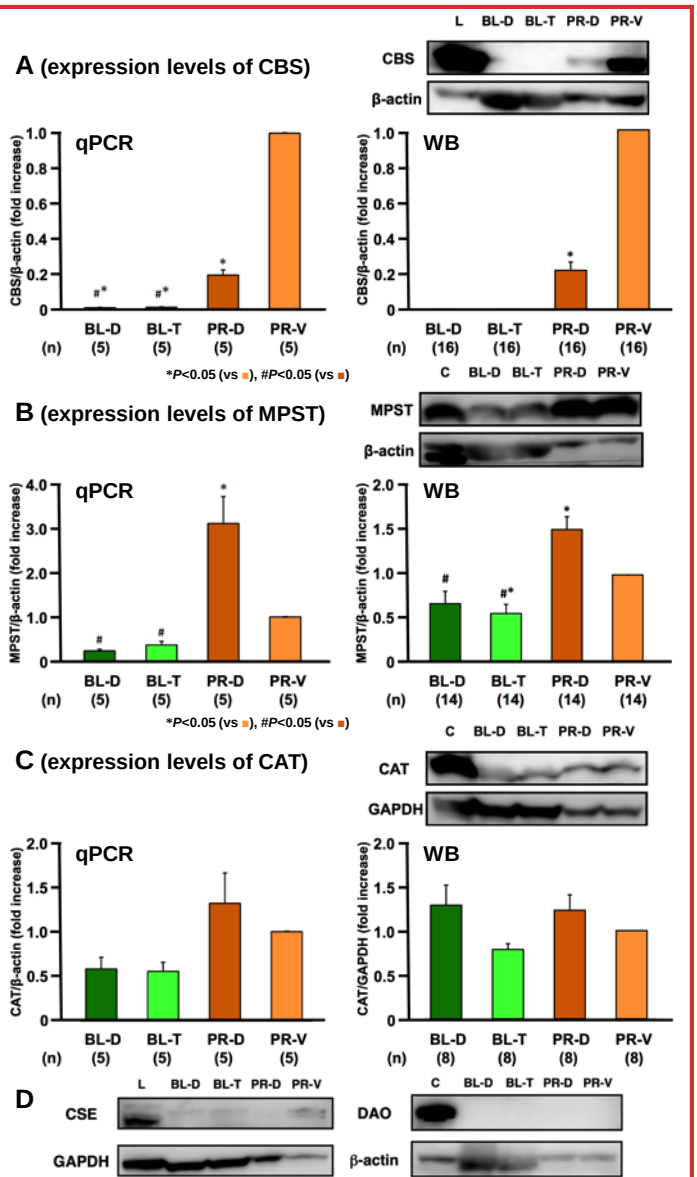


Fig. 3. Expression levels of H_2S synthases in the rat bladder and prostate. The amount of mRNA or protein for CBS (A), MPST (B) and CAT (C) was normalized to the amount of mRNA or protein for β-actin/GAPDH. Values are means ± SEM. *P<0.05, #P<0.05, significantly different from PR-V or PR-D, respectively (ANOVA with Bonferroni *post hoc* test). CAT; cysteine aminotransferase, CBS; cystathionine β-synthas, CSE; cystathionine γ-lyase, DAO; D-amino acid oxidase, GAPDH; glyceraldehyde-3-phosphate dehydrogenase, MPST; 3-mercaptopyruvate sulfurtransferase, BL-D and BL-T; bladder dome and trigone, PR-D and PR-V; dorsolateral and ventral prostate, L; liver, C; cerebellum (L and C, positive controls).

- CBS was expressed in the PR-D and PR-V (PR-V>PR-D), but not in the BL-D or BL-T
- MPST and CAT were expressed in all four tissues (MPST, PR-D>PR-V>BL-D=BL-T)
- CSE and DAO were not expressed in each bladder or prostate tissue

Interpretation of results

(1) H_2S can induce relaxation of rat bladder and prostate smooth muscle as evidenced by exogenous H_2S induced relaxation response to pre-contracted bladder and prostate strips.

(2) In the rat bladder, the MPST/CAT pathway is major for H_2S biosynthesis, while in the rat prostate, CBS and MPST/CAT pathways are involved in the biosynthesis. In the PR-D, the MPST/CAT pathway seems to be major for the biosynthesis, while in the PR-V, both CBS and MPST/CAT pathways seems to be involved in the biosynthesis.

Conclusions

H_2S can function as an endogenous relaxation factor in both bladder and prostate. Endogenous H_2S might open new avenues of therapeutic interventions for lower urinary tract dysfunction such as overactive bladder and benign prostatic hyperplasia.

Acknowledgements

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