THE ROLE OF SODIUM HYDROSULFIDE ON HYDROGEN SULFIDE GENERATING PATHWAY, NITRIC OXIDE PATHWAY, AND RENIN ANGIOTENSIN SYSTEM IN SPONTANEOUSLY HYPERTENSIVE RATS

You-Lin Tain[1] and Chien-Ning Hsu[2]
[1]Departments of Pediatrics and [2]Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

OBJECTIVES

1. The gasotransmitters, hydrogen sulfide (H_2S) and nitric oxide (NO), have been documented in hypertension.
2. Our previous reports showed that NO deficiency develops early in 4-week-old young spontaneously hypertensive rats (SHRs) and restoration of NO prevents the development of hypertension in young SHRs.
3. We examined whether sodium hydrosulfide, an exogenous H_2S donor, can regulate endogenous H_2S-generating pathway, mediate the balance between L-arginine and N^G monomethyl-L-arginine (L-NMMA, an inhibitor of NOS), and restore the RAS, to prevent the development of hypertension in SHR with a focus on the kidney.

METHODS

1. Rats aged 4 weeks are randomly assigned into three groups (N = 8 for each group): Group1, WKY rats without treatment; Group 2, SHRs without treatment; and Group 3, SHR+NaHS, SHRs were injected intraperitoneally with NaHS (14 μmol/kg/day) for 4 weeks.
2. Plasma L-arginine, L-NMMA, homocysteine, L-cysteine, and glutathione levels were measured using HPLC (HP series 1100, Agilent Tec., Inc.)

Table 1. Weights and functional parameters

Groups	WKY	SHR	SHR+NaHS
Mortality	0%	0%	0%
Body weight (g)	283 ± 5	290 ± 5	254 ± 5[a,b]
Left kidney weight (g)	1.16 ± 0.03	1.19 ± 0.02	0.98 ± 0.02[a,b]
Left kidney weight/100 g BW	0.41 ± 0.004	0.411 ± 0.007	0.394 ± 0.008[a]
Heart weight (g)	0.99 ± 0.03	1.21 ± 0.02[a]	1.05 ± 0.01[b]
Heart weight/100 g BW	0.354 ± 0.005	0.424 ± 0.096[a]	0.413 ± 0.005[a]
Systolic blood pressure (mm Hg)	153 ± 3	182 ± 3[a]	167 ± 2[a,b]
Diastolic blood pressure (mm Hg)	70 ± 3	96 ± 7[a]	87 ± 3[a]
Mean arterial pressure (mm Hg)	98 ± 3	125 ± 4[a]	113 ± 2[a,b]

N = 8/group; [a]P < 0.05 vs. WKY; [b]P < 0.05 vs. SHR

Table 2. Plasma L-arginine, L-NMMA, homocysteine, L-cysteine, and glutathione levels

Groups	WKY	SHR	SHR+NaHS
L-arginine	252 ± 30	319 ± 10	211 ± 4[b]
L-NMMA	511 ± 30	426 ± 52	260 ± 28[a,b]
Homocysteine	3.77 ± 0.26	2.55 ± 0.15[a]	2.33 ± 0.15[a]
L-cysteine	173.5 ± 9.9	186.6 ± 4.8	184.5 ± 7.4
Glutathione	27 ± 0.8	32.5 ± 1.4[a]	38.4 ± 3.4[a]

N = 8/group; [a]P < 0.05 vs. WKY; [b]P < 0.05 vs. SHR

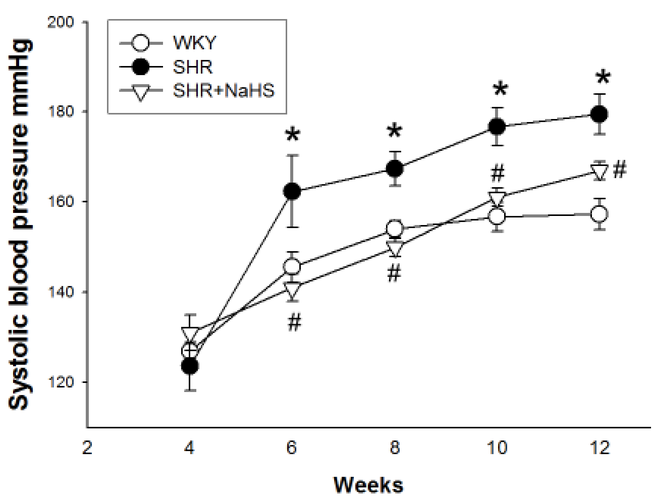

Figure 1. Effect of NaHS on systolic blood pressure in 12-wk-old Wistar Kyoto (WKY) rats and spontaneously hypertensive rats (SHRs), *P<0.05 vs. WKY; #P<0.05 vs. SHR.

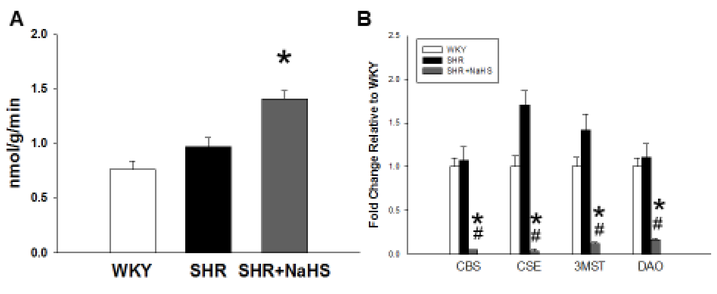

Figure 2. Effect of NaHS on (A) H_2S production and (B) mRNA expression of H_2S-generating enzymes in the kidney in 12-wk-old WKY rats and SHRs. *P<0.05 vs. WKY; #p<0.05 vs. SHR.

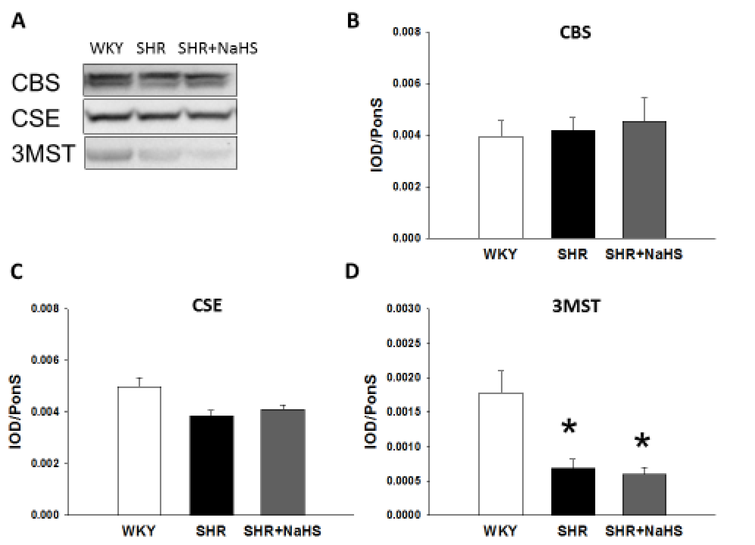

Figure 3. Representative western blots (A) show CBS (~61kDa), CSE (~45kDa), and 3MST (~52kDa) in WKY rats and SHRs at 12 wk of age. Relative abundance of renal cortical (B) CBS, (C) CSE, and (D) 3MST. *P<0.05 vs. WKY.

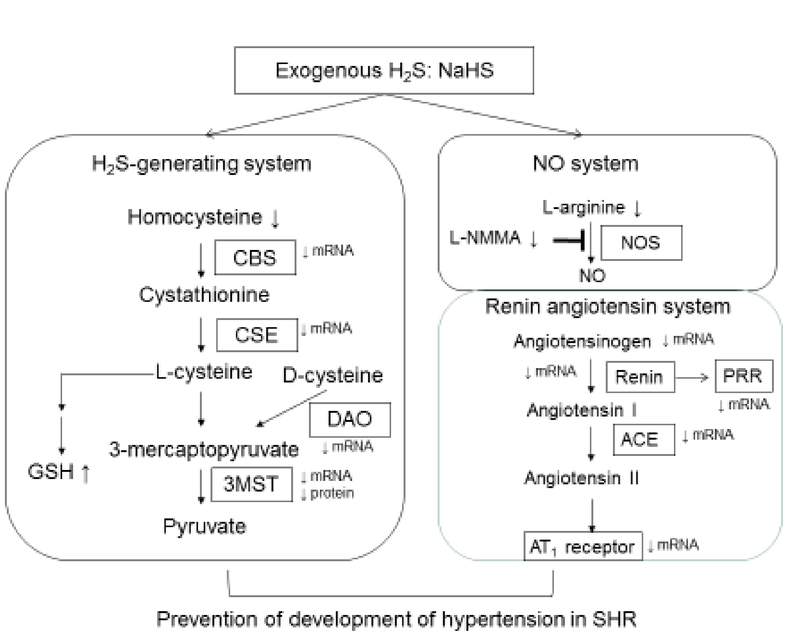

Figure 4. Simplified scheme of the interactions of H_2S, NO, and RAS in the kidney by which NaHS therapy prevents the development of hypertension in SHRs.

RESULTS

1. NaHS blocks the development of hypertension in SHRs (Table 1; Figure 1).
2. NaHS increased renal H_2S production in SHRs (Figure 2A).
3. NaHS reduces mRNA expression of 4 H2S-generating enzymes and decreased 3-mercaptopyruvate sulphurtransferase (3MST) protein level in SHR kidney. (Figure 2B; Figure 3D).
4. NaHS decreases plasma levels of L-arginine and L-NMMA in SHR (Table 2).
5. Figure 4 is a simple schematic summarizing our results.

CONCLUSIONS

1. We conclude that early exogenous H_2S therapy by NaHS increased renal H_2S production, restored the balance between L-arginine and L-NMMA, and inhibited the activation of RAS in the kidney, in favor of vasodilatation to prevent hypertension in SHRs.
2. The present study supports the assertion that early H_2S treatment in childhood might prevent the transition from prehypertension to hypertension in adult life.

ACKNOWLEDGMENTS

This work was supported by CMRPG8D0271 from Kaohsiung Chang Gung Memorial Hospital, Taiwan.