Hydrogen sulfide attenuates spatial memory disorder induced by cerebral anoxia via antioxidation in mice

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Abstract: OBJECTIVE To investigate effects of exogenous hydrogen sulfide (H_2S) on the spatial memory disorder induced by cerebral anoxia in mice and explore related mechanism. **METHODS** Sodium nitrite ($NaNO_2$) 120 mg·kg^{-1} was sc given to mice for 4 d in model group. Sodium hydrosulfide (NaHS) 1 mg·kg^{-1} was ip given and $NaNO_2$ 120 mg·kg^{-1} simultaneously was sc given to mice for 4 d in NaHS group. All drugs were given to mice immediately after Morris water maze experiment every day and escape latency. The number of crossings over the target area (NCTA) and search time in target quadrant (STTQ) were recorded. The activity of superoxide dismutase (SOD) and malondialdehyde (MDA) level in the brain was determined with colorimetry. The morphological alterations in hippocampus slices were assessed by microscope. **RESULTS** On the third and fourth days in Morris water maze experiment, compared with (16.1 ± 9.6) s and (11.1 ± 6.2) s in normal control group, the escape latency in model group was longer, (26.0 ± 7.3) s ($P < 0.05$) and (23.3 ± 8.7) s ($P < 0.01$). On the fifth day, compared with 7.2 ± 1.6 and (28 ± 8) s in normal control group NCTA and STTQ in model group were 4.1 ± 1.9 and (20 ± 8) s ($P < 0.05$), and they were obviously less. Compared with normal control group, SOD activity and MDA content of mice in model group were reduced by 12.6% ($P < 0.01$) and increased by 43.9% ($P < 0.01$), respectively. The neuron degenerative changes including karyopyknosis, dark cytoplasm and irregular pyramidal layer were observed in model group. On the third and fourth day, compared with model group, the escape latency in NaHS group was shorter, (17.9 ± 7.0) s and (15.8 ± 8.5) s ($P < 0.05$). Compared with model group, NCTA and STTQ in NaHS group increased to 6.7 ± 2.5 and (30 ± 9) s ($P < 0.01$). SOD activity and MDA content in NaHS group were increased by 8.9% ($P < 0.05$) and reduced by 29.6% ($P < 0.01$), respectively. Neuron degeneration was significantly attenuated in NaHS group ($P < 0.01$). **CONCLUSION** NaHS can attenuate the spatial memory disorder induced by cerebral anoxia and the mechanism may be related to the antioxidation effect and alleviation of neuron damage of H_2S.

Key words: sodium nitrite; hydrogen sulfide; learning and memory; neuron degeneration; hippocampus; antioxidation

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H_2S is now considered the third gaseous signal molecule along with NO and CO and possesses many important physiological functions. Previous studies showed that H_2S could enhance antioxidative ability[1], relax smooth muscle cells by opening K_{ATP} channels[2] and protect myocardial cells during hypoxia/reoxygenation injury[3-4]. So far, little has been reported, however, about the effect of exogenous H_2S on learning and memory disorder induced by cerebral anoxia. Alzheimer's disease (AD) and vascular dementia (VaD) are common types of senile dementia[5]. Some studies indicated that AD and VaD were related to hypoxic brain damage[6-7]. Besides, oxidative stress played an important role in brain parenchyma and cerebral microvascular injury under anoxia[8].

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Therefore, potential effects of exogenous H_2S on performance of mice subjected to anoxia in a spatial task and morphological changes in the hippocampus were investigated . Further more, the activity of superoxide dismutase (SOD) and malondialdehyde (MDA) level in the brain was determined to evaluate the oxidative stress mechanism by which H_2S affected learning and memory in mice.

1 MATERIALS AND METHODS

1.1 Chemicals and equipments

Sodium nitrite ($NaNO_2$) was purchased from Beijing Chemical Co., China. Sodium hydrosulfide (NaHS) was purchased from Sigma-Aldrich Co., USA. SOD and MDA reagent kit was purchased from Nanjing Jiancheng Bioengineering Institute, China. Video-tracking/computer-digitizing system (Coulbourn Instruments, USA), F25 homogenizer (FLUKO, Germany), Centrifuge 5804 R (Eppendorf, Germany), Olympus BX51 Microscope (Olympus, Japan), and ultraviolet spectrophotometer (Shanghai Third Analyses Instrument Factory, China)

1.2 Animals and treatment

Thirty male Kunming mice (28 ± 2) ($\bar{x}$ ± s) g were provided by the Experimental Animal Center of Xuzhou Medical College〔SYXK(Su) 2005-0018〕. Animals were housed in a temperature controlled room maintained on a 12-h light/12-h dark cycle and had access to the food and water *ad libitum*. All procedures and care of animals were approved by local veterinary authorities.

Animals were randomly divided into three groups: normal control group, saline 10 ml·kg^{-1} ip given; model group, $NaNO_2$ 120 mg·kg^{-1} sc given for 4 d; and NaHS group, NaHS 1 mg·kg^{-1} ip given and $NaNO_2$ 120 mg·kg^{-1} sc given simultaneously for 4 d. The NaHS dose was in the concentration range reported effective in protection of cardiomyocytes[9]. All drugs were given to mice immediately after the Morris water maze experiment each day.

1.3 Morris water maze test

The Morris water maze was a cylindrical, black painted pool (1 m in diameter, 0.6 m in height), filled with water〔0.3 m deep, (22 ± 1)℃〕, divided into 4 virtual quadrants with one starting point in each quadrant. A black painted platform (0.18 m diameter, 0.01 m below water surface) was placed in the determinate quadrant. The experimental room contained cues which remained unchanged throughout the study. The movements of mice were recorded by a video-tracking/computer-digitizing system.

The experiments were performed between 10 a. m. and 2 p. m. each day. One day before the training, all the animals were allowed to swim for 120 s without the platform in the pool. Four trials were performed in mice constantly every day, for 4 d. Each mouse was put into the water gently from one of the four starting points (in a random order) along the water maze perimeter with its face toward the wall of the pool. Mice were given 120 s to find the platform and were then left on the platform for 20 s. The intertrial interval was 30 s. If the mouse did not find the hidden platform within 120 s, then the researcher would guide it to the platform, and its escape latency to find the platform was then marked as 120 s. On the fifth day, the platform was removed and animals were allowed to search in the pool for 120 s (spatial probe test), the number of crossings over the target area(NCTA) and search time in target quadrant(STTQ) were recorded.

1.4 Measurement of MDA content and SOD activity

At the end of spatial probe test, the whole brain of mice was isolated, placed on an ice-cold plate, rinsed with ice-cold sterile saline and dissected along the midline between the two cerebral hemispheres. The right cerebral hemispheres were stored in a fixative containing 4% paraformaldehyde, the left ones were respectively homogenized at 10% (*W/V*) in normal saline (4℃), by F25 homogenizer. The supernatant fluid of cerebral homogenate was extracted by Centrifuge 5804 R. The activity of SOD and the level of MDA, following the instructions of SOD and MDA reagent kit were determined with colorimetry.

1.5 Histological observation

The right cerebral hemispheres were im-

mersed in the fixative over 24 h and paraffin-embedded, and 4 μm-thick coronal sections were sliced. The hippocampal sections were selected at the same layer from each mouse and stained with hematoxylin and eosin. The hippocampal CA1 region, which was regarded as closely related with memory[10], was evaluated by an examiner blind to experimental conditions.

1.6 Statistical analysis

All data were presented as $\bar{x} \pm s$. Statistical significance was assessed with one-way analysis of variance (ANOVA) followed by post hoc Fischer's LSD tests for multiple group comparison. The accepted level of statistical significance was $P<0.05$ or $P<0.01$. The experimental data were processed using the SPSS 13.0 statistical software package.

2 RESULTS

2.1 Effect of NaHS on spatial learning and memory in mice with cerebral anoxia induced by $NaNO_2$

For the first 4 d, the escape latency in normal control group decreased progressively. The escape latency in model group significantly declined and was longer than that in normal control group on the third and fourth days ($P<0.05$, and $P<0.01$). Compared with model group, the escape latency in NaHS group was shortened on the third and fourth days ($P<0.05$). No significant effect was observed in each group on the first and second days (Tab. 1). On the 5th day, NCTA and STTQ in model group were obviously less than in normal control group respectively ($P<0.01$) while NCTA and STTQ in NaHS group were markedly increased compared with model group ($P<0.01$, and $P<0.05$) (Tab. 2).

Tab. 2 Effect of NaHS on NCTA and STTQ in mice with cerebral anoxia induced by $NaNO_2$ in probe test

Group	NCTA	STTQ/s
Normal control	7.2 ± 1.6	28 ± 8
$NaNO_2$ (Model)	4.1 ± 1.9**	20 ± 8*
$NaNO_2$ + NaHS	6.7 ± 2.5##	30 ± 9#

See Tab. 1 for the treatment. On the fifth day, the platform was removed and animals were allowed to search in the pool for 120 s. The number of crossings over the target area (NCTA) and search time in target quadrant (STTQ) were recorded. $\bar{x} \pm s$, $n=10$. *$P<0.05$, **$P<0.01$, compared with corresponding normal control group; #$P<0.05$, ##$P<0.01$, compared with corresponding model group.

2.2 Effect of NaHS on SOD activity and MDA content in mice with cerebral anoxia induced by $NaNO_2$

There was significant difference between these groups in SOD activity [$F_{(2,27)}=9.179$, $P<0.01$] and the levels of MDA [$F_{(2,27)}=9.142$, $P<0.01$]. Compared with normal control group, SOD activity and MDA content in model group were reduced by 12.6% ($P<0.01$) and increased by 43.9% ($P<0.01$), respectively. Compared with model group, SOD activity and MDA content in NaHS group was increased by 8.9% ($P<0.05$) and reduced by 29.6% ($P<0.01$), respectively (Tab. 3).

Tab. 3 Effect of NaHS on superoxide dismutase (SOD) activity and malondialdehyde (MDA) content in mice with cerebral anoxia induced by $NaNO_2$

Group	SOD/kU·L^{-1}	MDA/mmol·L^{-1}
Normal control	145.1 ± 6.5	23.7 ± 4.5
$NaNO_2$ (Model)	126.8 ± 7.1**	34.1 ± 4.4**
$NaNO_2$ + NaHS	138.1 ± 13.7#	24.0 ± 8.6##

See Tab. 1 for the treatment. On the fifth day, the whole brain of mice was isolated and dissected along the midline between the two cerebral hemispheres at the end of spatial probe test. $\bar{x} \pm s$, $n=10$. **$P<0.01$, compared with corresponding normal control group; #$P<0.05$, ##$P<0.01$, compared with corresponding model group.

Tab. 1 Effect of NaHS on escape latency of mice with cerebral anoxia induced by $NaNO_2$

Group	Escape latency/s			
	1	2	3	4(d)
Normal control	54 ± 5	20 ± 8	16 ± 10	11 ± 6
$NaNO_2$ (Model)	55 ± 11	30 ± 16	26 ± 7*	23 ± 9**
$NaNO_2$ + NaHS	52 ± 8	23 ± 14	18 ± 7#	16 ± 8#

$NaNO_2$ 120 mg·kg^{-1} was given to mice for 4 consecutive days in model group. NaHS 1 mg·kg^{-1} ip and $NaNO_2$ 120 mg·kg^{-1} sc were given simultaneously for 4 consecutive days in NaHS group. All drugs were given immediately after Morris water maze experiment every day. $\bar{x} \pm s$, $n=10$. *$P<0.05$, **$P<0.01$, compared with corresponding normal control group; #$P<0.05$, compared with corresponding model group.

2.3 Effect of NaHS on hippocampal pathomorphology in mice with cerebral anoxia induced by $NaNO_2$

In normal control group, the pyramidal neuron had round and full nucleus as well as clear caryotheca in the CA1 region of hippocampus, with orderly arrangement (Fig. 1A). The neuron degenerative changes including karyopyknosis, dark cytoplasm and irregular pyramidal layer were observed in $NaNO_2$ model group (Fig. 1B). Compared with $NaNO_2$ model group, neuron degeneration was significantly attenuated by NaHS (Fig. 1C).

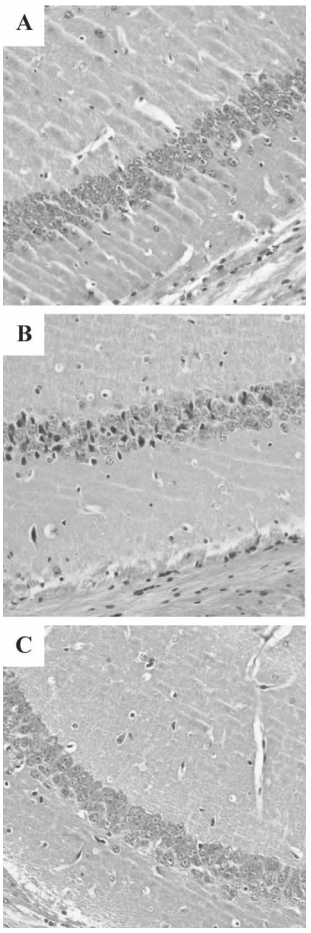

Fig. 1 Effect of NaHS on morphological changes in hippocampus of mice with cerebral anoxia induced by $NaNO_2$ (HE ×400). The hippocampal sections of right cerebral hemispheres were selected at from each mouse, stained with hematoxylin and eosin. A: normal control group; B: $NaNO_2$ model group; C: $NaNO_2$ + NaHS group.

3 DISCUSSION

The experiment results showed that $NaNO_2$ produced severe neuronal injury with degeneration in the hippocampus. Besides, $NaNO_2$ inhibited SOD activity and increased the MDA level in the brain. MDA level and SOD activity have been widely used as markers of oxidative stress. It was also found that exogenous H_2S improved neural functional performance in Morris water maze and markedly alleviated hippocampus injury by attenuating oxidative stress. The results above suggest that H_2S be a potential therapeutic agent for dysmnesia induced by cerebral anoxia.

Mice injected with $NaNO_2$ 120 $mg \cdot kg^{-1}$ are commonly used as a model of the consolidation impairment on memory[11]. When large amounts of $NaNO_2$ enter the body, hemoglobin is converted to methemoglobin and temporarily loses the oxygen-carrying capacity, so sodium nitrite is able to cause injury to the brain which is susceptible to anoxia[12]. The mechanism of hypoxic brain injury was complex, which was commonly thought to be caused by the disorder of energy metabolism[13]. Under the anoxic condition, the production of ATP decreased, glycolysis level was increased, pH value fell and the permeability of cell membrane was enhanced, which increased the inflow of Ca^{2+} and induced calcium overload[14]. The increase of intracellular Ca^{2+} could activate many enzymes such as phospholipase, ATPase and nuclease, which increased the production of free radicals and lipid peroxidation reaction[9]. Moreover, mitochondria swelling and crista fragmentation also aggravate neuronal injury[15]. In these pathophysiological processes above, the role of oxidative stress attracted more attention. Some researches showed that free radicals, lipid peroxidation reaction and mitochondrial injury were involved in the formation of brain aging and cognitive impairment[16-17]. In this study, SOD activity was inhibited and the MDA content was increased in model group, suggesting that oxidative stress is involved in hypoxic brain damage induced by $NaNO_2$.

H_2S is a novel endogenous neural active substance. Previous studies indicated that physiological concentration of H_2S facilitated the induction of long-term potential in CA1 region of hippocampus[18] and exogenous H_2S could

reversibly decrease metabolic level in the mouse[19-20]. In addition, it was reported that H_2S protects the mitochondria and inhibits the intracellular calcium overload in cardiomyocytes after ischemia-reperfusion[4,21]. In recent years, the function of H_2S on protecting several histiocytes by obvious antioxidant effect was paid attention[2,22-23]. These beneficial effects of H_2S could contribute to protecting against neuronal injury induced by anoxia. In present study H_2S was found to markedly improve the spatial memory ability in dysmnesia mouse induced by $NaNO_2$. It was also found that decline of SOD activity and increase in MDA production induced by $NaNO_2$ in brain were obviously attenuated. Besides, the neuron degenerative changes of hippocampus were greatly mitigated. The antioxidant effects of H_2S including anti-lipid peroxidation and scavenging free radical discovered in this study were compatible with previous study on lung ischemia-reperfusion injury[23].

In summary, the current study demonstrates that H_2S attenuates the spatial memory disorder induced by cerebral anoxia in mice and induces neuroprotection by antioxidative effects. These findings can stimulate us to further investigate the mechanisms by which H_2S improves dysmnesia induced by cerebral anoxia and provide a potential strategy for the prevention and treatment of learning and memory impairment.

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硫化氢通过抗氧化作用改善脑缺氧导致的小鼠空间记忆障碍

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摘要: 目的　观察外源性 H_2S 对缺氧性脑损伤小鼠空间学习记忆障碍的影响,并探究其作用机制。**方法**　连续 4 d sc 给予 $NaNO_2$ 120 mg·kg^{-1}·d^{-1}制备缺氧模型;氢硫化钠(NaHS)治疗组在制备模型的同时 ip 给予 NaHS 1 mg·kg^{-1}·d^{-1}。每天给药前进行 Morris 水迷宫实验,测定逃避潜伏期、原平台象限停留时间和穿越平台次数。比色法检测小鼠脑组织中超氧化物歧化酶(SOD)活性及丙二醛(MDA)含量。HE 染色观察海马组织切片 CA1 区神经元形态学改变。**结果**　水迷宫实验第 3 天和第 4 天,模型组小鼠逃避潜伏期分别为(26.0 ± 7.3)s和(23.3 ± 8.7)s,明显长于正常对照组的(16.1 ± 9.6)s($P < 0.05$)和(11.1 ± 6.2)s($P < 0.01$)。第 5 天,模型组小鼠穿越平台次数为 4.1 ± 1.9,在原平台象限停留时间为(20 ± 8)s,与正常对照组穿越平台次数(7.2 ± 1.6)次和在原平台象限停留时间(28 ± 8)s 比较明显减少($P < 0.01$)。与正常对照组相比,模型组小鼠脑组织中 SOD 活性降低 12.6%($P < 0.01$),MDA 含量升高 43.9%($P < 0.01$)。在模型组小鼠海马 CA1 区,锥体细胞出现明显的核固缩、胞浆深染和排列紊乱等变性改变。与模型组比较,NaHS 组小鼠在水迷宫实验的第 3 天和第 4 天逃避潜伏期明显缩短($P < 0.05$),分别为(17.9 ± 7.0)s 和(15.8 ± 8.5)s;在平台所在象限停留时间和穿越平台次数明显增加($P < 0.01$),分别为(30 ± 9)s 和(6.7 ± 2.5)次;SOD 活性升高了 8.9%($P < 0.05$),MDA 含量显著下降了 29.6%($P < 0.01$);海马 CA1 区神经元变性改变较模型组得到显著缓解。**结论**　NaHS 减轻了脑缺氧损伤诱发的小鼠学习记忆的损害,其作用机制可能与 H_2S 衰减海马区神经元损伤和抗氧化作用有关。

关键词: 亚硝酸钠; 硫化氢; 学习记忆; 神经元变性; 海马; 抗氧化作用

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