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Research Report

Sodium hydrosulfide prevents hypoxia-induced behavioral impairment in neonatal mice

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ABSTRACT

Hypoxic encephalopathy is a common cause of neonatal seizures and long-term neurological abnormalities. Endogenous hydrogen sulfide (H_2S) may have multiple functions in brain. The aim of this study is to investigate whether sodium hydrosulfide (NaHS), a H_2S donor, provides protection against neonatal hypoxia-induced neurobehavioral deficits. Neonatal mice were subjected to hypoxia (5% oxygen for 120 min) at postnatal day 1 and received NaHS (5.6 mg/kg) once daily for 3 d. Neurobehavioral toxicity was examined at 3–30 d after hypoxia. Treatment with NaHS significantly attenuated the delayed development of sensory and motor reflexes induced by hypoxia up to two weeks after the insult. Moreover, NaHS improved the learning and memory performance of hypoxic animals as indicated in Morris water maze test at 30 d after hypoxia. In mice exposed to hypoxia, treatment with NaHS enhanced expression of brain derived neurotrophic factor (BDNF) in the hippocampus. Furthermore, the protective effects of NaHS were associated with its ability to repress the hypoxia-induced nitric oxide synthase (NOS) activity and nitric oxide production in the hippocampus of mice brain. Taken together, these results suggest that the long-lasting beneficial effects of NaHS on hypoxia-induced neurobehavioral deficits are mediated, at least in part, by inducing BDNF expression and suppressing NOS activity in the brain of mice.

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1. Introduction

The developing brain is susceptible to hypoxic damage because of its high oxygen and energy requirements. Both experimental and human studies have shown that prenatal or neonatal hypoxia impairs normal development and results in long-term neurological deficits (Golan and Huleihel, 2006; Nyakas et al., 1996). For example, newborn rats subjected to hypoxia were delayed in the development of various sensory and motor reflexes during the first month (Grojean et al., 2003; Zhuravin et al., 2004). Furthermore, it reveals that perinatal hypoxia is an additional threat to neurodegeneration and

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decline of cognitive and other behaviors during the aging process (Decker et al., 2003; Grojean et al., 2003). There is evidence showing that chronic or acute hypoxia, the primary damage, which results in neuronal death, can affect the nearby cellular environment via the release of stress signals, including nitric oxide (NO) and cytokines. These stress signals cause secondary, delayed damage, resulting in a large area of tissue loss.

Hydrogen sulfide (H_2S) has been classified as the third novel gasotransmitter signaling molecule alongside nitric oxide and carbon monoxide (Wang, 2010). Endogenous H_2S is generated in mammalian tissues by two pyridoxal-5′phosphate-dependent enzymes, cystathionine β synthase (CBS) and cystathionine γ lyase (CSE). Both of these enzymes use L-cysteine as substrate. CBS and CSE are widely distributed in mammalian tissues; however, CBS activity is 30-fold greater than CSE in brain whereas CSE expression and activity are much higher than CBS in the cardiovascular system. It was also believed that CBS was responsible for H_2S production in the brain (Abe and Kimura, 1996). In human, rat and bovine brain, concentrations of H_2S were detected between 50 μM and 160 μM (Kimura and Kimura, 2004). Physiological concentrations of H_2S could potentiate the activity of the N-methyl-D-aspartate (NMDA) receptor and enhance the induction of hippocampal long-term potentiation (LTP) (Eto et al., 2002), which is associated with learning and memory. H_2S can also induce Ca^{2+} waves and increase intracellular concentrations of Ca^{2+} in both astrocytes and microglia (Lee et al., 2006; Nagai et al., 2004).

Interestingly, accumulating evidence suggests that H_2S acts as a powerful neuroprotective agent. Kimura et al. firstly demonstrated that H_2S protected primary rat cortical neurons from oxidative stress-induced injury (Kimura and Kimura, 2004). H_2S also protected PC12 cells against cobalt chloride-induced chemical hypoxia injuries. It is documented H_2S protected against cytotoxicity induced by beta-amyloid, 1-methy-4-phenylpyridinium ion, peroxynitrite, and hypochlorous acid in PC12 (Tang et al., 2008, 2011) and SH-SY5Y cells (Whiteman et al., 2004, 2005). Additionally, H_2S had protective effects against lipopolysaccharide (LPS)-induced inflammation in microglia (Hu et al., 2007), attenuated rotenone-induced apoptosis in SH-SY5Y cells (Hu et al., 2009), and inhibited H_2O_2 induced cytotoxicity in astrocytes (Lu et al., 2008). Importantly, it was reported that H_2S attenuated LPS-induced neuroinflammation both in vitro and in vivo and inhibited LPS-induced cognitive impairment and neuronal ultrastructure damage in rats (Gong et al., 2010, 2011). Li et al. reported that H_2S could improve impairment of learning and memory in brain-ischemic rats (Li et al., 2011).

However, the potential neuroprotective effects of H_2S against hypoxia-induced long-term neurobehavioral deficits and the mechanisms remain to be clarified. In the present study, administration of NaHS significantly attenuated the hypoxia-induced neurobehavioral deficits, at least in part, by increasing BDNF expression and suppressing neuronal and inducible nitric oxide synthases (nNOS and iNOS, respectively) activity in the brain of mice.

2. Results

2.1. *Short-term effects of NaHS on neurobehavioral deficits induced by hypoxia*

2.1.1. *Surface righting reflex*

The hypoxia group exhibited significantly delayed response latency in surface righting as compared with the sham group from post-hypoxia days 6 to 10 (Fig. 1A). NaHS treatment significantly shortened the hypoxia-induced increase in righting reflex latency.

2.1.2. *Negative geotaxis*

The response latency of mice decreased with age in the negative geotaxis (Fig. 1B). The hypoxia group exhibited significantly delayed response latency as compared with sham group from post-hypoxia days 6 to 10. NaHS treatment significantly accelerated negative geotaxis responses as compared with the hypoxia group.

2.1.3. *Wire hanging*

The wire hanging ability of mice increased with age (Fig. 2A). The mean duration of the hypoxia group was significantly shorter than that of the sham group from post-hypoxia days 3 to 14 (Fig. 2A). NaHS treatment significantly increased the duration of wire hanging from post-hypoxia days 4 to 14.

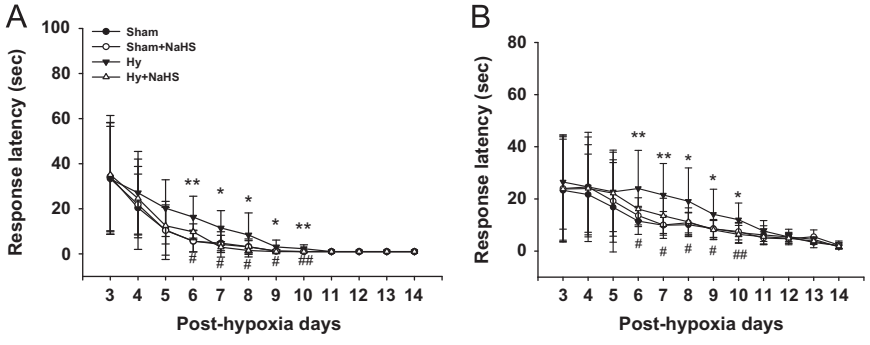

Fig. 1 – Effects of NaHS on righting reflex and negative geotaxis. (A) The mean latency time in righting reflex was measured at 3–14 d after hypoxia. (B) The mean latency time in negative geotaxis was measured at 3–14 d after hypoxia. The results are expressed as the mean ± SEM, $n = 10$, $^{*}p < 0.05$, $^{**}p < 0.01$, Hypoxia (Hy) VS Sham; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ Hypoxia+NaHS (Hy+NaHS) VS Hy.

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