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EXOGENOUS HYDROGEN SULFIDE ELIMINATES SPATIAL MEMORY RETRIEVAL IMPAIRMENT AND HIPPOCAMPAL CA1 LTD ENHANCEMENT CAUSED BY ACUTE STRESS VIA PROMOTING GLUTAMATE UPTAKE

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Abstract—Acute stress impairs the hippocampus-dependent spatial memory retrieval, and its synaptic mechanisms are associated with hippocampal CA1 long-term depression (LTD) enhancement in the adult rats. Endogenous hydrogen sulfide (H_2S) is recognized as a novel gasotransmitter and has the neural protective roles. However, very little attention has been paid to understanding the effects of H_2S on spatial memory retrieval impairment. We observed the protective effects of NaHS (a donor of H_2S) against spatial memory retrieval impairment caused by acute stress and its synaptic mechanisms. Our results showed that NaHS abolished spatial memory retrieval impairment and hippocampal CA1 LTD enhancement caused by acute stress, but not by glutamate transporter inhibitor L-*trans*-pyrrolidine-2,4-dicarboxylic (*t*PDC), indicating that the activation of glutamate transporters is necessary for exogenous H_2S to exert its roles. Moreover, NaHS restored the decreased glutamate uptake in the hippocampal CA1 synaptosomal fraction caused by acute stress. Dithiothreitol (DTT, a disulfide reducing agent) abolished a decrease in the glutamate uptake caused by acute stress, and NaHS eradicated the decreased glutamate uptake caused by 5,5′-dithio-bis(2-nitrobenzoic)acid (DTNB, a thiol oxidizing agent), collectively, revealing that exogenous H_2S increases glutamate uptake by reducing disulfide bonds of the glutamate transporters. Additionally, NaHS inhibited the increased expression level of phosphorylated c-Jun-N-terminal kinase (JNK) in the hippocampal CA1 region caused by acute stress. The JNK inhibitor SP600125 eliminated spatial memory retrieval impairment, hippocampal CA1 LTD enhancement and the decreased glutamate uptake caused by acute stress, indicating that exogenous H_2S exerts these roles by inhibiting the activation of JNK signaling pathway. **© 2017 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: hydrogen sulfide, acute stress, memory retrieval, long-term depression, glutamate transporters.

INTRODUCTION

The brain is the central organ in the adaptation to stress, as it regulates the behavioral and physiological responses to the stressor (McEwen and Gianaros, 2011). The brain is also a key target of stress, as stress causes synaptic plasticity in the brain, such as dendritic atrophy and loss of dendritic spines (Vyas et al., 2002; Liston et al., 2006). Acute and chronic stress affects glutamatergic neurotransmission including glutamate release, glutamate receptor trafficking and function, and glutamate clearance and metabolism (Popoli et al., 2012). Severe stress induces dysfunction of glutamatergic neurotransmission which is associated with the onset and exacerbation of several neuropsychiatric disorders (Popoli et al., 2012).

The hippocampus is the main brain region to be recognized as a target of stress hormones (Vyas et al., 2002). Acute stress impairs hippocampus-dependent spatial memory retrieval (de Quervain et al., 1998; Wong et al., 2007), but the underlying mechanisms are still not completely understood.

Hippocampal long-term depression (LTD), a long-lasting decrease of synaptic transmission efficacy, is induced by prolonged periods of low-frequency stimulation (LFS) and may be involved in some types of learning and memory. Recent studies reveal that hippocampal LTD has a critical role in mediating the consolidation of long-term spatial memory (Brigman et al., 2010; Ge et al., 2010).

Acute stress causes hippocampal CA1 LTD enhancement in the slices of adult rats (Xu et al., 1997; Yang et al., 2005). Acute stress also induces the release of corticosterone, which then increases glutamate concentration in the synaptic clefts through the increased

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Abbreviations: H_2S, hydrogen sulfide; MWM, Morris water maze; LTD, long-term depression; fEPSP, field excitatory postsynaptic potential; LFS, low-frequency stimulation; *t*PDC, L-*trans*-pyrrolidine-2,4-dicarboxylic; DTT, dithiothreitol; DTNB, 5,5′-dithio-bis(2-nitrobenzoic) acid; JNK, c-Jun-N-terminal kinase.

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glutamate release (Karst et al., 2005) and the decreased glutamate uptake (Yang et al., 2005) in the hippocampus. Glutamate accumulated in the synaptic clefts diffuses into the extrasynaptic spaces and activates extrasynaptically localized GluN2B-containing N-methyl-D-aspartate receptors (NMDARs), thereby leading to hippocampal CA1 LTD enhancement and spatial memory retrieval impairment (Wong et al., 2007).

Endogenous hydrogen sulfide (H_2S) is recognized as a novel gasotransmitter and can be produced from cysteine by two pyridoxal-5′-phosphate (PLP)-dependent enzymes, namely cystathionine-β-synthase (CBS) (Abe and Kimura, 1996) and cystathionine-γ-lyase (CSE) (Hosoki et al., 1997), and a newly identified enzyme, 3-mercaptopyruvate sulfurtransferase (3-MST) (Shibuya et al., 2009). CBS is highly expressed in the brain and thus believed to be the main enzyme to produce endogenous H_2S in the brain (Abe and Kimura, 1996; Eto et al., 2002a,b). CBS mRNA and protein are localized in most areas of the brain, especially in hippocampus and cerebellum (Robert et al., 2003).

Increasing evidence has shown that H_2S has important physiological and pathological functions in the brain. H_2S serves as a neuromodulator in physiological conditions. For example, H_2S specifically potentiates the activity of NMDA receptors and facilitates the induction of hippocampal long-term potentiation (LTP) (Abe and Kimura, 1996). H_2S increases intracellular Ca^{2+} concentration in neurons and astrocytes, and induces Ca^{2+} waves in astrocytes as well as hippocampal slices (Nagai et al., 2004; Yong et al., 2010). Additionally, H_2S produces anti-inflammatory, antioxidant and antiapoptotic effects in some pathological conditions which may lead to neurodegenerative disorders (Kimura and Kimura, 2004; Tang et al., 2008; Yin et al., 2009; Hu et al., 2010; Tiong et al., 2010). Of note, the level of endogenous H_2S is severely decreased in the brains of Alzheimer's disease (AD) patients (Morrison et al., 1996; Eto et al., 2002a,b). The endogenous H_2S level is also declined in the rat model of Parkinson's disease, and exogenously applied H_2S is demonstrated to have potential neuroprotective value (Hu et al., 2010).

Previous studies show that exogenously applied H_2S reverses H_2O_2-induced cellular injury in primary cultured rat cortical astrocytes, this effect is attenuated by a specific glutamate uptake inhibitor (Lu et al., 2008). Exogenous H_2S also increases glutamate uptake in astrocytes treated with H_2O_2 (Lu et al., 2008). Considering that acute stress impairs the spatial memory retrieval by blockade of glutamate uptake (Yang et al., 2005; Wong et al., 2007), it is possible that exogenous H_2S has potential protective effects against the memory retrieval impairment caused by acute stress.

Exogenous H_2S is a highly reactive molecule and easily reacts with reactive oxygen and nitrogen species (Lowicka and Beltowski, 2007). Exogenous H_2S also prevents oxidative damage in the brain by scavenging $HOCl^-$ and peroxynitrite (Whiteman et al., 2004, 2005). It is reported that oxidation or reduction of sulfhydryl (—SH) groups within the glutamate transporters cause the decrease or increase of glutamate uptake, respectively (Trotti et al., 1997a,b). Therefore, it will be significant to investigate whether exogenous H_2S promotes the activity of the glutamate transporters by keeping —SH groups of the glutamate transporters in reducing conditions.

Moreover, acute stress activates the c-Jun-N-terminal kinase/stress-activated protein kinase (JNK/SAPK) signaling pathway in many brain regions (Shen et al., 2004; Zheng et al., 2008). In a transgenic animal model of Alzheimer's disease (AD) and cell apoptosis model of Parkinson disease (PD), exogenous H_2S inhibits activity of JNK kinases to slow down the progression of these diseases (Hu et al., 2009; Giuliani et al., 2013). Intrahippocampal injection of JNK inhibitors reduced activity of hippocampal JNK kinases and deficits in contextual fear induced by acute stress (Sherrin et al., 2010). However, it remains unclear whether exogenous H_2S inhibits the JNK signaling pathway to eliminate spatial memory retrieval impairment caused by acute stress.

In the present studies, we investigated the protective effects of exogenous H_2S on the spatial memory retrieval and hippocampal CA1 LTD disrupted by acute stress, and we lay emphasis on the involvement of glutamate transporters and the inhibition of JNK signaling pathway in these protective roles. Moreover, we also observe whether reduction of the disulfide bonds within glutamate transporters and inhibition of the JNK signaling pathway are contributed to the increase of glutamate uptake. Our findings showed that exogenous H_2S eradicated spatial memory retrieval impairment induced by acute stress by increasing the glutamate uptake. Exogenous H_2S also blocked hippocampal CA1 LTD enhancement in the slices from previously stressed rats.

EXPERIMENTAL PROCEDURES

Animals and stress protocol

Healthy adult male Sprague–Dawley rats (9–13-week-old, Grade II, Certificate No 26-001 conferred by Medical Animal Management Committee, Guangdong Province) were obtained from the Experimental Animal Center of Sun Yat-sen University. Animals were housed in groups of five in a rearing cage with a 12-h light–dark cycle (lights on at 7:00 a.m.), 50–60% humidity. Sufficient food and water were available. Ambient temperature was controlled at 25 °C. All experiments were conducted between 9:00 a.m. and 3:00 p.m. Animals were allowed to acclimate to the laboratory for 7 days before the beginning of experiments. Acute stress was evoked by 60 tail shocks (1 mA for 1 s, 30–90 s apart) while rats were restrained in a Plexiglas tube, as described previously (Yang et al., 2004).

Drugs

NaHS, pentobarbital sodium, aminooxyacetic acid (AOAA), L-*trans*-pyrrolidine-2,4-dicarboxylic (*t*PDC), SP600125, dithiothreitol (DTT), 5,5′-dithio-bis(2-nitrobenzoic) acid (DTNB), Na_2S and L-glutamate were obtained from Sigma–Aldrich (St. Louis, MO, USA). L-[^{3}H]

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