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HYDROGEN SULFIDE INHIBITS GIANT DEPOLARIZING POTENTIALS AND ABOLISHES EPILEPTIFORM ACTIVITY OF NEONATAL RAT HIPPOCAMPAL SLICES

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Abstract—Hydrogen sulfide (H_2S) is an endogenous gasotransmitter with neuroprotective properties that participates in the regulation of transmitter release and neuronal excitability in various brain structures. The role of H_2S in the growth and maturation of neural networks however remains unclear. The aim of the present study is to reveal the effects of H_2S on neuronal spontaneous activity relevant to neuronal maturation in hippocampal slices of neonatal rats. Sodium hydrosulfide (NaHS) (100 μM), a classical donor of H_2S produced a biphasic effect with initial activation and subsequent concentration-dependent suppression of network-driven giant depolarizing potentials (GDPs) and neuronal spiking activity. Likewise, the substrate of H_2S synthesis L-cysteine (1 mM) induced an initial increase followed by an inhibition of GDPs and spiking activity. Our experiments indicate that the increase in initial discharge activity by NaHS is evoked by neuronal depolarization which is partially mediated by a reduction of outward K^+ currents. The subsequent decrease in the neuronal activity by H_2S appears to be due to the rightward shift of activation and inactivation of voltage-gated Na^+ currents, thus preventing network activity. NaHS also reduced N-methyl-D-aspartate (NMDA)-mediated currents, without essential effect on AMPA/kainate or $GABA_A$-mediated currents. Finally, H_2S abolished the interictal-like events induced by bicuculline. In summary, our results suggest that through the inhibitory action on voltage-gated Na^+ channels and NMDA receptors, H_2S prevents the enhanced neuronal excitability typical to early hippocampal networks.

Key words: hydrogen sulfide, neonatal hippocampus, giant depolarizing potentials, membrane potential, interictal-like events, NMDA-mediated currents.

INTRODUCTION

Hydrogen sulfide (H_2S) has been recently identified as an important intra- and intercellular messenger, regulating various physiological and pathological processes (Kimura, 2010; Hermann et al., 2012a; Wang, 2012). In the central nervous system H_2S induces long-term potentiation in the hippocampus (Abe and Kimura, 1996), modulates neuronal excitability of the subfornical organ, the nucleus of the solitary tract (Kuksis et al., 2014; Kuksis and Ferguson, 2015; Malik and Ferguson, 2016) and trigeminal neurons (Feng et al., 2013) and mediates central inhibition of the respiratory rhythm (Chen et al., 2013). In the peripheral nervous system H_2S modulates transmitter release as well as exo- and endocytosis of synaptic vesicles in motor nerve endings (Sitdikova et al., 2011; Gerasimova et al., 2013, 2015; Mitrukhina et al., 2013). H_2S also exerts neuro-protectant effects by preventing oxidative stress (Kimura and Kimura, 2004) and by increasing glutathione levels (Kimura et al., 2010). Furthermore, H_2S participates in the pathophysiology of central nervous system diseases such as epilepsy, stroke, neurodegenerative diseases and hyper-homocysteinemia (Wang, 2012; Luo et al., 2014). Neurotoxic or neuroprotective action of H_2S is critically dependent on its concentration and cellular location (Wedmann et al., 2014).

H_2S can change neuronal excitability through modulation of Na^+ channels (Khademullah and Ferguson, 2013; Kuksis and Ferguson, 2015) and different types of K^+ channels (Pan et al., 2010; Sitdikova

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Abbreviations: 3-MST, 3-mercaptopyruvate sulfurtransferase; ACSF, artificial cerebrospinal fluid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CAT, cysteine aminotransferase; CBS, cystathionine beta-synthase; CNQX, 6-cyano-7-nitroquinoxaline-2,3dione; CSE, cystathionine gamma-lyase; DAO, d-amino acid oxidase; d-APV, d-2-amino-5-phosphopentanoate; EGTA, ethylene glycol-bis(2-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid; GABA, γ-aminobutyric acid; GDPs, giant depolarizing potentials; H_2S, hydrogen sulfide; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; MUA, multi-unit activity; NaHS, sodium hydrosulfide; NMDA, N-methyl-D-aspartate; TEA, tetraethylammonium; TTX, tetrodotoxin.

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