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COMMENT

Involvement of hydrogen sulfide in the pathogenesis of ischemic stroke-induced paroxysmal sympathetic hyperactivity

Randa Salah Gomaa Mahmoud [1]

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Paroxysmal sympathetic hyperactivity (PSH) is a common clinical feature secondary to ischemic stroke (IS) due to the loss of sympathetic nervous system (SNS) inhibition without parasympathetic involvement [1]. The paraventricular nucleus (PVN) of the hypothalamus controls the sympathetic tone and hypothalamic injury can be accompanied by sympathetic overactivity [2]. Hydrogen sulfide (H_2S) is an endogenous gaseous signaling molecule with a neuroprotective function. It was found that Inhalation of H_2S attenuates IS-induced injury in rats via inhibition of oxidative stress, inflammation, apoptosis, and regulation of cerebral blood flow [3].

In the present study, Sun et al. [4] hypothesized that H_2S could ameliorate the PSH induced by IS in both humans and rats, and its alteration was involved in the pathogenesis of PSH.

They investigated IS patients who were divided into malignant (MCI) and non-malignant cerebral infarction (NMCI) groups and the authors found that PSH was associated with the severity of IS and more plasma norepinephrine (NE) was positively correlated with levels of creatine kinase, glutamate transaminase, and creatinine respectively. The 1-year survival rate of patients with high plasma NE levels was lower. Moreover, the cerebrospinal fluid H_2S levels were negatively associated with PSH. The plasma NE level as a predictor for neurological outcomes and survival in IS patients is controversial. Some studies have supposed that plasma NE does not predict the neurological outcome at one month in IS patients [5]. However, others proved that plasma NE predicts autonomic dysfunction and risk of death in IS patients [6, 7].

In the present study, IS in rats was induced by the right middle cerebral artery occlusion (MCAO). H_2S donor (NaHS) or inhibitor (aminooxy-acetic acid, AOAA) were microinjected into the hypothalamic paraventricular nucleus (PVN). The authors found that the hypothalamus of rats with MCAO showed increased activity, especially in the PVN region. The levels of H_2S in PVN of the rats with MCAO were reduced, while the blood pressure and renal sympathetic discharge were increased, that ameliorated by NaHS and exacerbated by AOAA. These findings are supported by Coletti et al. who fund that hypothalamic H_2S is involved in the hypothalamic control of blood pressure, HR, and temperature [8].

The present study shows that NaHS completely reduced the disulfide bond of NMDAR1 in PC12 cells. The inhibition of NMDAR by MK-801 microinjected in PVN of rats with MCAO lowered blood pressure and renal sympathetic discharge. The neuroprotective effect of NMDAR signaling inhibitors is previously demonstrated in various IS animals [9] and the antioxidant effect of H_2S was reported as it cleaves the disulfide bond of VEGFR2 [10], TGF-β1 [11], CD36 [12], and PX-12 [13].

The current study could conclude that PSH may be associated with disease progression and survival in patients with IS. Abnormal activity, NMDAR signaling, and the H_2S level of PVN were involved in regulating sympathetic activity after cerebral infarction. Modulating the hypothalamic active state or H_2S release/supplementation may be beneficial in treating PSH. These findings might provide a new strategy for the prevention and treatment of IS-induced PSH patients.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

✉ Randa Salah Gomaa Mahmoud
rsgomaa@medicine.zu.edu.eg

[1] Physiology Department, Faculty of Human Medicine, Zagazig University, Zagazig, Egypt

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