Hydrogen sulfide

Along with nitric oxide (NO) and carbon monoxide (CO), hydrogen sulfide (H2S) is regarded as the third gasotransmitter and endogenous neuromodulator and plays multiple roles in the central nervous system under physiological and pathological states, especially in secondary neuronal injury.

There is growing evidence that H2 S has a promising future in the treatment of central nervous system diseases. In a review, Lu et al. focus on the effects of H2 S in experimental SAH and elucidate the underlying mechanisms. They demonstrated that H2 S has neuroprotective effects and significantly reduces secondary damage caused by SAH via antioxidant, antiinflammatory, and anti-apoptosis mechanisms, and by alleviating cerebral edema and vasospasm. Based on these findings, they believe that H2 S has great potential in the treatment of SAH and warrants further study to promote its early clinical application [1)]

Merz et al. explored the potential mediating role of hydrogen sulfide (H2S) and the oxytocin (OT) systems in hemorrhagic shock (HS) and/or traumatic brain injury (TBI). Morbidity and mortality after trauma mainly depend on the presence of HS and/or TBI. Rapid “repayment of the O2 debt” and prevention of brain tissue hypoxia are cornerstones of the management of both HS and TBI. Restoring tissue perfusion, however, generates an ischemia/reperfusion (I/R) injury due to the formation of reactive oxygen (ROS) and nitrogen (RNS) species. Moreover, pre-existing medical conditions (PEMC's) can aggravate the occurrence and severity of complications after trauma. In addition to the “classic” chronic diseases (of cardiovascular or metabolic origin), there is growing awareness of psychological PEMC's, e.g., early life stress (ELS) increases the predisposition to develop post-traumatic-stress-disorder (PTSD) and trauma patients with TBI show a significantly higher incidence of PTSD than patients without TBI. In fact, ELS is known to contribute to the developmental origins of cardiovascular disease. The neurotransmitter H2S is not only essential for the neuroendocrine stress response but is also a promising therapeutic target in the prevention of chronic diseases induced by ELS. The neuroendocrine hormone OT has fundamental importance for brain development and social behavior, and, thus, is implicated in resilience or vulnerability to traumatic events. OT and H2S have been shown to interact in physical and psychological trauma and could, thus, be therapeutic targets to mitigate the acute post-traumatic effects of chronic PEMC's. OT and H2S both share anti-inflammatory, anti-oxidant, and vasoactive properties; through the reperfusion injury salvage kinase (RISK) pathway, where their signaling mechanisms converge, they act via the regulation of nitric oxide (NO) [2)].

The endogenous level of H2S in the brain is significantly higher than that in peripheral tissues and is mainly formed by cystathionine β-synthase (CBS) in astrocytes and released in response to neuronal excitation. The mechanism of secondary neuronal injury exacerbating the damage caused by the initial insult includes microcirculation failure, glutamate-mediated excitotoxicity, oxidative stress, inflammatory responses, neuronal apoptosis and calcium overload. H2S dilates cerebral vessels by activating smooth muscle cell plasma membrane ATP-sensitive K channels (KATP channels). This modification occurs on specific cysteine residues of the KATP channel proteins which are S-sulfhydrated. H2S counteracts glutamate-mediated excitotoxicity by inducing astrocytes to intake

more glutamate from the extracellular space and thus increasing glutathione in neurons. In addition, H2S protects neurons from secondary neuronal injury by functioning as an anti-oxidant, anti-inflammatory and anti-apoptotic mediator. However, there are still some reports suggest that H2S elevates neuronal Ca(2+) concentration and may contribute to the formation of calcium overload in secondary neuronal injury. H2S also elicits calcium waves in primary cultures of astrocytes and may mediate signals between neurons and glia. Consequently, further exploration of the molecular mechanisms of H2S in secondary neuronal injury will provide important insights into its potential therapeutic uses for the treatment of acute neuronal insult events [3].

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