Potential role of hydrogen sulfide in central nervous system tumors: a narrative review

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Abstract
Central nervous system tumors are classified as diseases of special clinical significance with high disability and high mortality. In addition to cerebrovascular diseases and craniocerebral injuries, tumors are the most common diseases of the central nervous system. Hydrogen sulfide, the third endogenous gas signaling molecule discovered in humans besides nitric oxide and carbon monoxide, plays an important role in the pathophysiology of human diseases. It is reported that hydrogen sulfide not only exerts a wide range of biological effects, but also develops a certain relationship with tumor development and neovascularization. A variety of studies have shown that hydrogen sulfide acts as a vasodilator and angiogenetic factor to facilitate growth, proliferation, migration and invasion of cancer cells. In this review, the pathological mechanisms and the effect of hydrogen sulfide on the central nervous system tumors are introduced.

Key words: central nervous system; clinical research; experimental research; glioblastoma multiforme; hydrogen sulfide; hypoxia inducible factor-1α; p38 mitogen-activated protein kinase; pituitary tumor; therapeutic implications

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Introduction
Central nervous system (CNS) tumors are classified as nervous system diseases characterized by high disability and mortality. They are the most common diseases of the CNS except for cerebrovascular diseases and craniocerebral injuries, including meningiomas, gliomas, pituitary tumors and so on. Among them, glioblastoma multiforme (GBM) is the most malignant brain tumor, with a strong ability to spread and invade the surrounding parenchyma. The number of treatment options is increasing; however, the prognosis is still poor. Pituitary tumors are a group of tumors originated from the residual cells of anterior and posterior pituitary and craniopharyngeal epithelium, accounting for 10–20% of intracranial tumors, most of which are benign.

Hydrogen sulfide (H₂S) is usually considered an environmental pollutant with its smell of rotten eggs. However, with continuously furthering research in recent years, H₂S has been discovered as a gaseous chemical messenger with regulatory roles in neurotransmission, cardiovascular regulation, cell metabolism and other physiological processes in mammalians. Recently, it has been reported that H₂S plays a role in a wide range of physiological and pathophysiological properties on cancer progress. Previous results have evidenced that H₂S may act as a vascular relaxant and angiogenetic factor to promote the growth, proliferation, migration and invasion of cancer cells. H₂S is extremely fat-soluble, can freely pass through cell membranes, widely presenting in various parts of the human body, with a variety of production and transformation methods. Generally speaking, on the one hand, H₂S can be synthesized by cystathionine β-synthetase and cystathionine c-lyase extracted with sulfur-containing amino acids as substrates, in pyridoxal-50-phosphate-(PLP-)dependent reactions. On the other hand, it can produce through nonenzymatic reduction of elemental sulfur in the blood using reduction equivalents provided by glycolysis, or in the form of sodium bisulfide. Changes in H₂S metabolism and/ or signal transduction are closely related to human diseases, especially cancer. An increasing number of studies have reported that cystathionine β-synthetase, cystathionine c-lyase and 3-mercaptoppyruvate sulfurrtransferase are overexpressed in tumor cell lines and tumor tissues, with colorectal cancer, ovarian cancer, breast cancer, and glioma involved. In this review, the potential role of endogenous and exogenous H₂S in CNS tumors is described and the implications of H₂S on future treatment strategies are discussed.

Experimental Finding About the Roles of Hydrogen Sulfide in Central Nervous System Tumors
The mechanisms underlying the roles of H₂S in the CNS tumors have not been fully elucidated. As is known to all, a therapeutic method must be verified by a large amount of basic experiments before being applied to clinic. However, not all studies can reach the same result. We collected several experiments related to CNS tumors and H₂S and summarized the outcomes (Table 1), in which the researchers detected the effects of H₂S on brain tumors and explored the potential mechanisms by which this gas can promotes tumor cells growth.

Li et al. reported that H₂S serves as a stimulator in the development of rat glioblastoma and exogenous H₂S strongly promotes the tumor growth. It was observed that the H₂S
and with the growth of tumors, endogenous H\textsubscript{2}S production in the brain of tumor-bearing mice increased, in the control group. Compared with normal rats, endogenous H\textsubscript{2}S production further increased. Furthermore, exogenous H\textsubscript{2}S promoted the expression of hypoxia inducible factor-1\textalpha (HIF-1\textalpha) in GBM tissues, while increased HIF-1\textalpha further stimulates tumor growth. HIF-1\textalpha can be activated in a variety of factors (including hypoxia, inflammation, adenosine triphosphate levels, and isocitrate dehydrogenase (IDH) mutation status), as well as in gliomas and immune cell infiltrating tumors.\textsuperscript{27} HIF-1\textalpha increases the expression of inducible nitric oxide synthase in cancer cells, which impairs the recruitment of tumor immune cells and produces immunosuppression.\textsuperscript{28} Similarly, HIF-1\textalpha’s increased activity promotes the production of vascular endothelial growth factor by endothelial cells, which can modulate chemotactic properties of immune cell-mediated tumor infiltration.\textsuperscript{29} Vascular endothelial growth factor binds to its receptor neuropilin-1 to attract regulatory T cells to the tumor site, and malignant cells secrete transforming growth factor-\beta to attract regulatory T cells to GBM, preventing the killing of cancer cells.\textsuperscript{27,30} There is increasing evidence that IDH1, closely related to the carcinogenesis mediated by HIF-1\textalpha, is the most common mutated gene in GBM.\textsuperscript{31-33} The mutated IDH1 increases its level by protecting HIF-1\textalpha from degradation. In the midst of IDH1 mutant gliomas, the transcriptional activity of HIF-1\textalpha increases, intensifying the growth of gliomas.\textsuperscript{34,35} Besides, under normal oxygen conditions, the degradation of HIF-1\textalpha is promoted by prolyl hydroxyylase domain-containing proteins with its transcriptional activity being inhibited by HIF-1\textalpha inhibitor protein (encoded by Hif-1\textalpha).\textsuperscript{36,37} A typical feature of HIF-1\textalpha-dependent signaling is hypoxia, a condition in which tissue oxygen supply is in reduction.\textsuperscript{37,38} Since hypoxic conditions are characteristic of the tumor microenvironment, the effects of both are inhibited. Therefore, HIF-1\textalpha is often upregulated in solid malignant tumors (such as GBM).\textsuperscript{38} Lactic acid accumulation caused by hypoxia can lead to an acidic tumor microenvironment and induction local inflammation. Lactic acid can promote the polarization of macrophages’ expression of immunosuppressive arginase 1 through HIF-1\textalpha-mediated mechanism and promotion of tumor growth.\textsuperscript{27,39} In addition, the tumor-specific T cell effector functions can be impacted by HIF-1\textalpha via an increase of glycolysis and promotion of T cell differentiation.\textsuperscript{40,41} This study provides evidence for the angiogenic effect of H\textsubscript{2}S mediated by promoting and stabilizing HIF-1\textalpha protein expression under hypoxic conditions.

In 2015, Zhen et al.\textsuperscript{23} found that H\textsubscript{2}S induced C6 glioma cell proliferation through utilizing its two-fold cytoprotective and anti-apoptosis functions via decrease of the expression of caspase-3. Within the range of physiological dose of H\textsubscript{2}S (0.2–1 mM), different doses of NaHS (100–1600 \textmu M) promoted cell proliferation. The optimal concentration of NaHS for inducing maximum proliferation and markedly diminished cell apoptosis was 400 \textmu M. On the other hand, Zhao et al.\textsuperscript{24} reported NaHS failed to act as a mitogen to promote proliferation of C6 cells but succeeded in functioning as a stimulus to activate the apoptosis of C6 cells. They showed that the application of NaHS significantly increased the phospho-p38/p38 protein expression rate in C6 cells, indicating that p38 mitogen-activated protein kinase (MAPK) activation is linked to Na\textsubscript{2}S-mediated apoptosis of C6 cells. Different research results are related to different conditions, such as time and concentration of cell treatment. The latter treated C6 cells with NaH\textsubscript{2}S (100–1000 \textmu M) for 48 hours. MAPK, a serine threonine protein kinase, evolutionarily conserved in all eucaryotes that can be activated by different extracellular stimuli, such as cytokines, neurotransmitters, hormones, cell stress and cell adhesion,\textsuperscript{7,24} and plays significant roles in gene expression regulation and cytoplasmic function activities. Moreover, MAPK takes part in the regulation of many important cell physiology/pathology processes such as cell growth and proliferation, differentiation, adaption to the environment, and inflammation response.\textsuperscript{45} Researches have found that MAPKs (p38 MAPK and extracellular signal-regulated protein kinase 1/2) also activate cyclooxygenase-2 signal pathway and other signaling cascades in various tumor cell types.\textsuperscript{46-49} Cyclooxygenase-2 is a kind of inducible enzyme whose expression is enhanced under the conditions of tissue damage and inflammation, closely related to the growth of tumor as an important molecule in the process of tumor proliferation, angiogenesis, anti-apoptosis and invasion.\textsuperscript{50-53} Besides, previous studies have emphasized that the activation of cyclooxygenase-2 in the glioma depends on the extracellular signal-regulated protein kinase 1/2 pathway.\textsuperscript{7,46} p38 MAPK and extracellular signal-regulated protein kinase 1/2 pathway can be activated by Na\textsubscript{2}S to induce proliferation.

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**Table 1: Experimental studies regarding hydrogen sulfide in brain tumor**

| Study          | Year | Cell          | Cancer model     | Results                                                                 |
|---------------|------|---------------|------------------|-------------------------------------------------------------------------|
| Li et al.\textsuperscript{22} | 2012 | C6 glioma cell | Glioblastoma     | Hydrogen sulfide serves as a stimulator in the development of rat glioblastoma by the increase of hypoxia-inducible factor-1\textalpha expression and neovascular formation. |
| Zhen et al.\textsuperscript{23} | 2015 | C6 glioma cell | Glioblastoma     | Exogenous hydrogen sulfide promotes C6 glioma cell growth through activation of the p38 mitogen-activated protein kinase/extracellular signal-regulated protein kinase1/2-cyclooxygenase-2 pathways.               |
| Zhao et al.\textsuperscript{24} | 2015 | C6 glioma cell | Glioblastoma     | Exogenous hydrogen sulfide effectively reduces cell number of C6 cells by triggering the apoptosis via Caspase-dependent pathway.                                                |
| Sidikova et al.\textsuperscript{25} | 2010 | Rat pituitary tumor cell GH3 | Pituitary tumor | Hydrogen sulfide increases calcium-activated potassium channel activity of rat pituitary tumor cells in a concentration-dependent manner.                                                     |
| Mustafina et al.\textsuperscript{26} | 2015 | Rat pituitary tumor cell GH3 | Pituitary tumor | Hydrogen sulfide induces hyperpolarization of GH3 cells with dose-dependent, resulting in a decrease of hormone release.                                                               |

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and anti-apoptosis.\textsuperscript{23}

In addition, some studies have discovered the potential role of H\textsubscript{2}S in pituitary tumor cells. The one major discover of these studies is that the NaHS induces a dose-dependent hyperpolarization and truncation of spontaneous action potentials in rat pituitary GH3 cells via activating ofadenosine triphosphate-sensitive potassium channels as H\textsubscript{2}S donor, resulting in decrease of secretion.\textsuperscript{26} NaHS increases the magnitude of adenosine triphosphate-sensitive potassium currents, as well as whether in GH3 cells at rest or in a depolarization reaction, NaHS can reduce the exocytosis of secreted particles.\textsuperscript{26} This effect is exerted in a dose-dependent manner.\textsuperscript{26} Sitdikova et al.\textsuperscript{25} found H\textsubscript{2}S promotes the activation of calcium-activated potassium (BK) channels in rat pituitary tumor (GH3) cells, which is probably related to the reduction of sulfhydryl groups of the channel protein. BK channels mediate or regulates many physiological functions and pathophysiological conditions.\textsuperscript{37} As is known to all, the activity of BK channels in the channels protein is regulated by the redox state of the key sulfhydryl group, with the exchange of free mercaptan and disulfide involved.\textsuperscript{54,59} Under oxidation conditions, activity of BK channels is enhanced in both reduction and inhibition.\textsuperscript{60} H\textsubscript{2}S as a reducing agent may increase the channel open probability by redox regulation of cysteine or other residues of channel protein.\textsuperscript{25}

It is concluded that H\textsubscript{2}S is fully involved in the pathological process of CNS tumors, especially in that of gliomas and pituitary tumors, indicating that the clinical application of H\textsubscript{2}S has great prospects, which can be further examined as a potential neuroprotective gas for CNS tumors, according to experimental results above.

**Clinical Findings About the Roles of Central Nervous System Tumors**

Currently, research on H\textsubscript{2}S in CNS tumors is still at the cells experimental stage and has not yet been applied clinically. However, there is ample evidence to show that \textit{in vivo}, H\textsubscript{2}S is produced mainly by two key enzymes, cystathionine \( \beta \)-synthetase and cystathionine \( \gamma \)-lyase, which are primarily present in the CNS. Although there is no direct evidence indicating that H\textsubscript{2}S has neuroprotective effect in clinical trials, the close touch with brain injury caused by CNS tumors is no doubt, which needs us to make great efforts to the study.

**Perspectives**

According to the data of the current research, H\textsubscript{2}S plays a role in promoting growth of brain tumors. Although some studies have found that the role of H\textsubscript{2}S is somewhat inconsistent with those mentioned above, which may be caused by differences in dose, mode of action, and type of disease. Although we have not fully understood its mechanism, we will continue to do a lot of research in the future. Finally, we believe that H\textsubscript{2}S will open up a new path into the treatment of the CNS tumors.

**Author contributions**

WP and MLZ were responsible for writing the manuscript. JZ was responsible for its revision. JZ and GC were responsible for its drafting and revision. All authors read and approved the final version of the manuscript for publication.

**Conflicts of interest**

The authors declare that they have no competing interests.

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