Submitted: 05 June, 2025 Accepted: 08 July, 2025 Published: 08 August, 2025 DOI:10.22514/sv.2025.118

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ORIGINAL RESEARCH

Hydrogen sulfide regulates NLRP3 to inhibit pyroptosis and protect against hypoxic-ischemic brain injury in neonatal rats

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Abstract

Background: Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal mortality and long-term neurological deficits. This study investigated whether sodium hydrosulfide (NaHS), an exogenous donor of hydrogen sulfide (H_2S) could protect against HIE by inhibiting microglial activation and pyroptosis in brain tissue. **Methods**: A neonatal hypoxic-ischemic encephalopathy (NIE) model was established in rats via hypoxia combined with ligation of the left common carotid artery. Exogenous hydrogen sulfide (NaHS) and the nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain- containing receptor 3 (NLRP3) inhibitor CY-09 were administered post-injury. Cognitive function was assessed using the Morris water maze. Hippocampal injury was examined using Nissl staining. Microglial activation was assessed by immunofluorescence detection of Iba-1 expression. Pyroptosis-related proteins expression levels in brain tissue were measured using Western blotting. **Results**: Treatment with exogenous hydrogen sulfide significantly reduced neuronal injury, inhibited microglial activation, enhanced memory and spatial learning (as demonstrated by a decrease in escape latency, an increase of platform crossings, and time spent in the target quadrant). Furthermore, it suppressed the expression of NLRP3 inflammasome, Gasdermin D N-terminal domain (GSDMD-N), cleaved caspase-1, Interleukin (IL)-1β, and IL-18 proteins. **Conclusions**: Exogenous hydrogen sulfide mitigates neuronal damage, improves cognitive outcomes, and suppresses pyroptosis and microglial activation in neonatal rats with hypoxic-ischemic encephalopathy.

Keywords

Hypoxic-ischemic encephalopathy; Exogenous hydrogen sulfide; Cognitive dysfunction' microglial activation; NLRP3

1. Introduction

Neonatal hypoxic-ischemic encephalopathy (NIE) is a form of brain injury resulting from perinatal asphyxia, posing a serious threat to neonatal survival. It is associated with a markedly increased risk of complications such as cerebral palsy and cognitive dysfunction [1]. Therefore, the development of new neuroprotective drugs aimed at improving the long-term outcomes of infants with hypoxic-ischemic encephalopathy (HIE) has become a major focus in neonatal medicine.

Neuroinflammation is the key pathological mechanism of neonatal hypoxic-ischemic brain injury. Studies have shown that hypoxia-ischemia can trigger a systemic inflammatory cascade, which in turn significantly affects the development and myelination of oligodendrocytes by activating neuroinflammatory processes such as microglia, ultimately leading to white matter damage. When it comes to treating neonatal brain injury, this pathway is a crucial therapeutic target [2]. In hypoxic-ischemic brain injury, activated microglia continuously release a variety of pro-inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and complement system components, which together constitute the key molecular network of neuroinflammatory response [3]. The classical pyroptosis pathway involves the nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain- containing receptor 3 (NLRP3)/caspase-1/gasdermin D (GSDMD) axis. Recent studies have highlighted the importance of microglial pyroptosis mediated by this NLRP3/caspase-1/GSDMD pathway in the pathogenesis of neonatal brain injury [4], indicating that the development of hypoxic-ischemic encephalopathy (HIE) in neonates may be significantly influenced by pyroptosis.

Hydrogen sulfide (H_2S) has been reported to regulate various functions of the central nervous system. In neonatal mice, exogenous H_2S derived from L-cysteine has been shown to protect neurons from hypoxic-ischemic injury via a phosphatidylinositol 3-kinase (PI3K)/protein kinase

B (Akt)-dependent pathway [5]. Sodium hydrosulfide (NaHS), a widely used donor of exogenous H_2S, has been reported to reduce neuronal apoptosis in models of hypoxic-ischemic encephalopathy [6] and to protect against diabetic cardiomyopathy by enhancing cell viability and reducing cardiomyocyte pyroptosis [7].

It is yet unknown, nevertheless, how NaHS affects pyroptosis in relation to HIE. This study is the first to demonstrate that NaHS inhibits cellular pyroptosis and alleviates neuronal injury and cognitive deficits associated with neonatal HIE.

2. Methods

2.1 Animals

7-day-old newborn rats were anesthetized with isoflurane, and their left common carotid artery was ligated with 5-0 silk sutures. After a 1-hour recovery period, the rats were exposed to a hypoxic environment consisting of 8% oxygen and 92% nitrogen at 37 °C for 2 hours to induce NIE. The animals were randomly divided into 4 groups. Control group (control group without any treatment); NIE group (ischemic hypoxia); NIE + NaHS (100 μmol/kg of NaHS solution was administered intraperitoneally into ischemia hypoxic mice); NIE + CY-09 (NLRP3 inhibitor) (A dose of 10 mg/kg of CY-09 was administered intraperitoneally to ischemia hypoxic mice). NaHS and CY-09 were administered once daily via intraperitoneal injection for 14 consecutive days post-surgery. At designated time points, rats were anesthetized with isoflurane and euthanized by decapitation to collect brain tissue for subsequent analyses. All animal procedures were approved by the Ethics Committee of the Animal Facility at Zhejiang Provincial People's Hospital (Approval No. 20250121218107) and were carried out in compliance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH).

2.2 Water maze experiment

Neonatal rats were tested for spatial learning and memory using the Morris water maze test. The circular pool was filled with water that was kept at 25 °C and separated into four equal sections. In one quadrant, a concealed platform was positioned two centimeters below the water's surface. During each trial, rats facing the wall were let go into the pool, and they had ninety seconds to find the secret platform. Rats were gently led to the platform and left there for 30 seconds if they could not find it in the given amount of time. Training trials were conducted once daily for five consecutive days to assess spatial learning ability, during which escape latency (the time taken to reach the platform) was recorded. To control for motor deficits, swimming speed was also measured. On the sixth day, the platform was removed for the probe trial. To evaluate memory recall, rats were given 90 seconds to swim freely. The number of platform crossings and the amount of time spent in the target quadrant were noted.

2.3 Nissl staining

After being removed, hippocampal tissues were preserved for 24 hours in 4% paraformaldehyde. After that, the samples were dehydrated using a series of graded ethanol (70% to 100%), with each step lasting 2 hours, followed by clearing in xylene for 1 hour. The tissues were cut into thin slices after being fixed in paraffin. After being dewaxed in xylene, paraffin sections were rehydrated using a gradient of decreasing ethanol. After that, the slices were kept out of the light and stained with toluidine blue solution for five minutes at room temperature. Following a quick rinse with distilled water, the sections underwent ethanol dehydration and differentiation, xylene clearing, and neutral gum mounting. For histological examinations, stained sections were viewed and photographed under a light microscope.

2.4 Immunofluorescence

After removing all the brain tissue, the hippocampus was separated and preserved for six hours at 4 °C in 4% paraformaldehyde. The tissue was transferred to 30% sucrose solution until it sank to the bottom. After embedding the samples in an optimal cutting temperature (OCT) compound, coronal slices 10 μm thick were made with a cryostat and placed on anti-slip microscope slides. The sections were equilibrated at room temperature for 30 minutes and washed with phosphate-buffered saline (PBS, pH 7.4). At room temperature, permeabilization was carried out for 15 minutes using 0.3% Triton X-100. 5% bovine serum albumin (BSA) was used to prevent non-specific binding for one hour at room temperature. The sections were incubated overnight at 4 °C with a primary antibody against Iba-1. Sections were cleaned with PBS and then incubated for one hour at room temperature in the dark with a fluorophore-conjugated secondary antibody. Using 4′,6-diamidino-2-phenylindole (DAPI, 1 μg/mL), nuclei were counterstained for 5 minutes. Following thorough PBS rinse, the sections were mounted using an anti-fade fluorescence mounting medium and imaged using a fluorescence microscope.

2.5 Western-blot

Hippocampal tissues were snap-frozen in liquid nitrogen and lysed using radioimmunoprecipitation assay (RIPA) buffer, followed by ultrasonic homogenization on ice. Samples were mixed with 5× sodium dodecyl sulfate (SDS) loading buffer and boiled at 95 °C for 5–10 minutes to denature the proteins. Equal amounts of total protein (20 μg per well) were loaded and separated via SDS-polyacrylamide gel electrophoresis (PAGE). Proteins were then transferred onto a polyvinylidene fluoride (PVDF) membrane, which was pre-activated by soaking in methanol for 1 minute. The membrane was blocked with 5% skim milk in TBST (Tris-buffered saline with 0.1% Tween-20) for 1 hour at room temperature with gentle shaking. Membranes were incubated overnight at 4 °C with the following primary antibodies: NLRP3 (Affinity, Cincinnati, OH, USA, DF15549, 1:1000). Cleaved-caspase1 (Affinity, Cincinnati, OH, USA, AF4022, 1:1000). GSDMD-N (Affinity, Cincinnati, OH, USA, DF13758, 1:1000). IL-1β (Abcam, Cambridge, UK, ab234437, 1:1000). IL-18 (Affinity, Cincinnati, OH, USA, DF6252, 1:1000). β-Actin (Abcam, Cambridge, UK, ab8226, 1:1000). Following washing, membranes were incubated for one hour at room temperature

with a goat anti-rabbit Immunoglobulin G (IgG) secondary antibody coupled with horseradish peroxidase (HRP). Protein bands were visualized using enhanced chemiluminescence (ECL) detection reagents (mixed 1:1 from solutions A and B) and exposed in the dark for 1 minute.

2.6 Statistical analysis

Data were analyzed using SPSS 22.0 (IBM, Armonk, NY, USA). The differences between several groups were compared using one-way analysis of variance (ANOVA). The Tukey's Honestly Significant Difference (HSD) test was used for *post hoc* comparisons. A p-values < 0.05 were regarded as statistically significant.

3. Results

3.1 NaHS enhances cognitive function in NIE rats

To evaluate cognitive function, all groups of rats underwent the Morris water maze test (Fig. 1A). Rats in the NIE group exhibited significant impairments, characterized by reduced time spent in the target quadrant, fewer platform crossings, and prolonged escape latency, indicating spatial learning and memory deficits. In NIE rats, NaHS and NLRP3 inhibitors decreased escape latency, increased platform crossings, and lengthened duration in the target quadrant. Importantly, there were no significant differences in swimming speed among the groups, suggesting that motor function did not influence the observed cognitive outcomes (Fig. 1B–E).

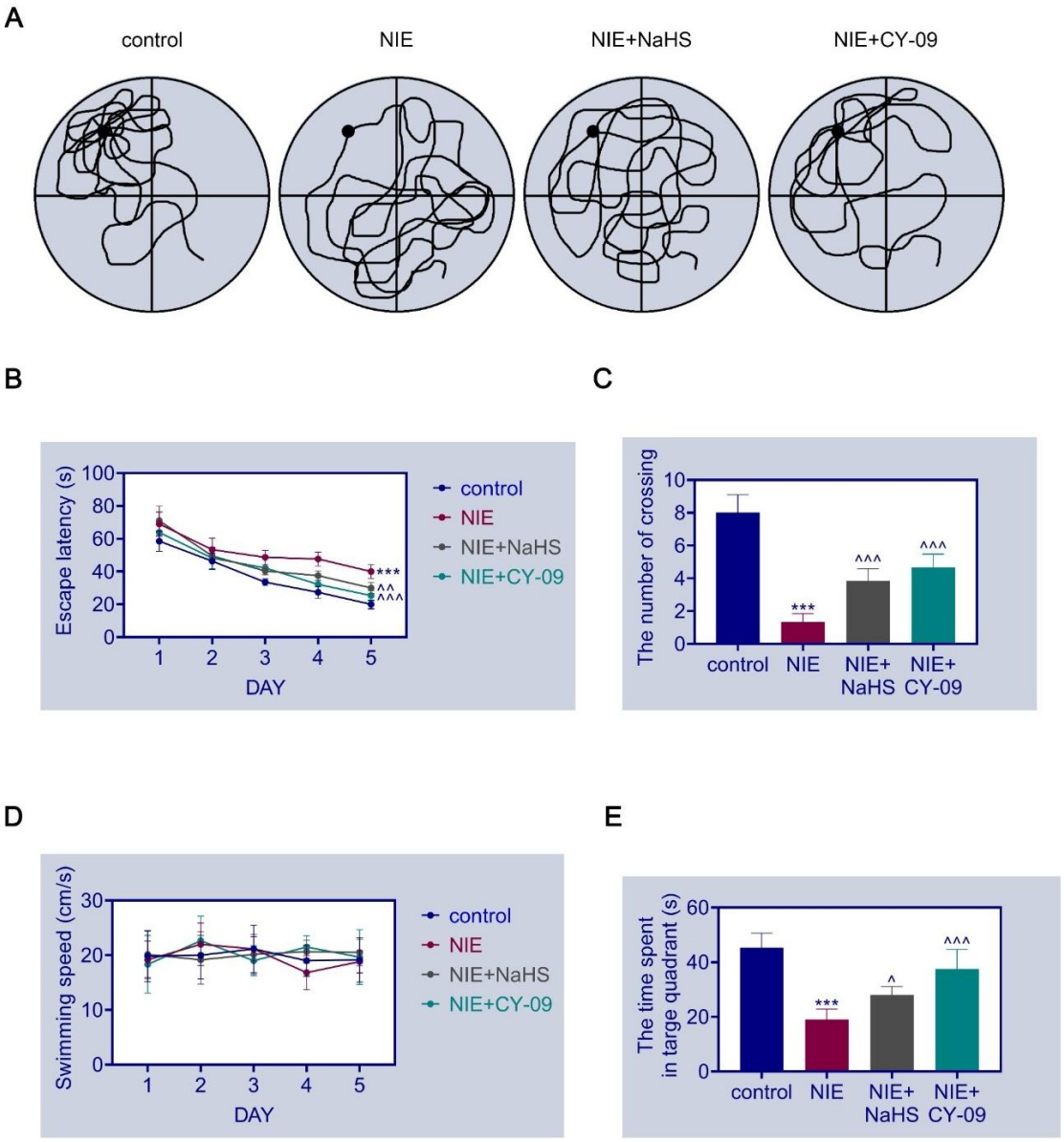

FIGURE 1. NaHS enhances cognitive function in NIE rats. The water maze experiment was used to detect the movement trajectory (A), escape latency (B), number of platform crossings (C), swimming speed (D), and residence time (E) in the target quadrant of each group of rats. *vs.* Control, ***$p < 0.001$. *vs.* NIE, ^$p < 0.05$, ^^$p < 0.01$, ^^^$p < 0.001$. NIE: Neonatal hypoxic-ischemic encephalopathy; NaHS: Sodium hydrosulfide.

3.2 NaHS reduces the neuronal damage in NIE rats

The neurons in the control group had bigger cell bodies and more cytoplasm, and their shape and organization were unaltered. In contrast, neurons in the NIE group exhibited pronounced damage, including nuclear condensation, darkly stained (deep blue) nuclei, and loss of normal neuronal architecture. However, treatment with NaHS or the NLRP3 inhibitor CY-09 markedly reduced these pathological changes, indicating a protective effect against neuronal damage (Fig. 2).

3.3 NaHS and CY-09 suppress microglial activation in NIE rats

In the hippocampus of NIE rats, immunofluorescence detection of Iba-1 and microglial activation revealed that Iba-1 fluorescence increased while CY-09 and NaHS prevented microglial activation. However, treatment with NaHS and the NLRP3 inhibitor CY-09 significantly reduced Iba-1 expression, suggesting that both agents effectively suppressed microglial activation (Fig. 3).

3.4 NaHS inhibits pyroptosis-related protein expression in NIE rats

The expression of the proteins NLRP3 (Fig. 4A), Cleaved Caspase-1, GSDMD-N, IL-1β, and IL-18 (Fig. 4B) was elevated in the brain tissue of rats in the NIE group, indicating ischemia and hypoxia caused pyroptosis of rat brain tissue cells. In contrast, treatment with CY-09 and NaHS reduced the expression of these proteins, demonstrating an inhibitory effect on the pyroptosis of brain tissue cells in NIE rats.

4. Discussion

This research is the first to show that sodium hydrosulfide (NaHS), an exogenous hydrogen sulfide donor, significantly improves cognitive function in neonatal hypoxic-ischemic encephalopathy (NIE) rats. NaHS administration reduced neuronal damage, inhibited microglial activation, and suppressed pyroptosis-related pathways in brain tissue. These findings suggest a neuroprotective role for hydrogen sulfide in hypoxic-ischemic brain injury and highlight its potential as a novel therapeutic strategy for neonatal encephalopathy.

Given the lack of effective clinical interventions for the complex pathological mechanisms underlying neurological injury following NIE, there is a crucial need to explore new strategies and establish theoretical foundations to address the neurological sequelae of neonatal HIE, particularly cognitive impairment [8]. In this study, although NIE injury did not affect swimming speed but can cause severe long-term cognitive impairment, as evidenced by increased escape latency, reduced platform crossings, and decreased times spent in the target quadrant in the Morris water maze test. Treatment with NaHS or the NLRP3 inhibitor significantly ameliorated these impairments.

In addition to reduced or disrupted blood and oxygen supply, hypoxia-ischemia leads to neuronal energy depletion, cell death, and excessive neuroinflammatory responses that exacerbate brain injury [9]. NIE induced damage also triggers infiltration of peripheral leukocytes and immune cells, and activation of resident brain immune cells, particularly microglia [10]. Tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 are among the proinflammatory cytokines released by these activated immune cells, which contribute to secondary neuronal injury and disease progression [11]. Early interruption of this neuroinflammatory cascade has been shown to reduce brain damage [12]. Modulating neuroinflammation is therefore considered a promising therapeutic approach to mitigate neurological deficits and brain injury associated with hypoxic-ischemic events [13]. Therefore, targeting neuroinflammation is a novel therapeutic target for NIE. Microglial activation was reduced in this study by NLRP3 and NaHS inhibitors, suggesting that NaHS inhibits neuroinflammation.

Nucleotide-binding oligomerization domain-like receptor (NLR) family is an important regulator of neuroinflammation, among which NLRP3 inflammasome (NLR family pyrin domain-containing protein 3) plays a core role in the inflammatory response [14]. Activation of the NLRP3 inflammasome, a major contributor to neuroinflammation, can greatly increase the release of proinflammatory cytokines, thereby amplifying the inflammatory cascade [15]. Interestingly, NLRP3 inflammasome expression is mostly seen in microglia, the central nervous system's primary defense cells [16].

Inflammasomes are formed during pyroptosis, a recently identified kind of programmed cell death that is dependent on the activation of cysteine-dependent aspartate-specific proteases (caspases). In this process, Gasdermin-D (GSDMD) is cleaved into an active GSDMD-N-terminal fragment (GSDMD-N), which then forms cell membrane pores, ultimately leading to cell rupture and the release of a large number of proinflammatory factors [17]. Recent studies have shown that targeted inhibition of the pyroptosis pathway can significantly reduce the inflammatory cascade, thereby alleviating ischemic brain damage [18]. Among them, the NLRP3/Caspase-1/GSDMD signaling axis is a classic pathway for regulating pyroptosis [19]. The NLRP3/Caspase-1/Gasdermin-D axis was suppressed in this study, suggesting that NaHS prevents pyroptosis in NIE rats.

However, this study has several limitations. The specific molecular target of NaHS whether it directly interacts with NLRP3 remains unclear. Although CY-09 was used as a pharmacological inhibitor of NLRP3, we did not employ more definitive methods such as gene knockdown or RNA interference to confirm the critical role of NLRP3 in mediating NaHS's effects. This limits the ability to draw strong conclusions regarding the target specificity of NaHS. Future studies should incorporate NLRP3 knockdown models or siRNA-based approaches to clarify this interaction. All experiments were conducted in animal models, and the clinical translatability of the findings requires further investigation. In addition, the behavioral test methods we used in cognitive assessment were relatively simple and may not fully reflect the complexity of cognitive function. Finally, although we explored the activation mechanism of NLRP3 inflammasome, the potential role of other inflammasome pathways has not been fully studied. These limitations warrant more refined experimental designs

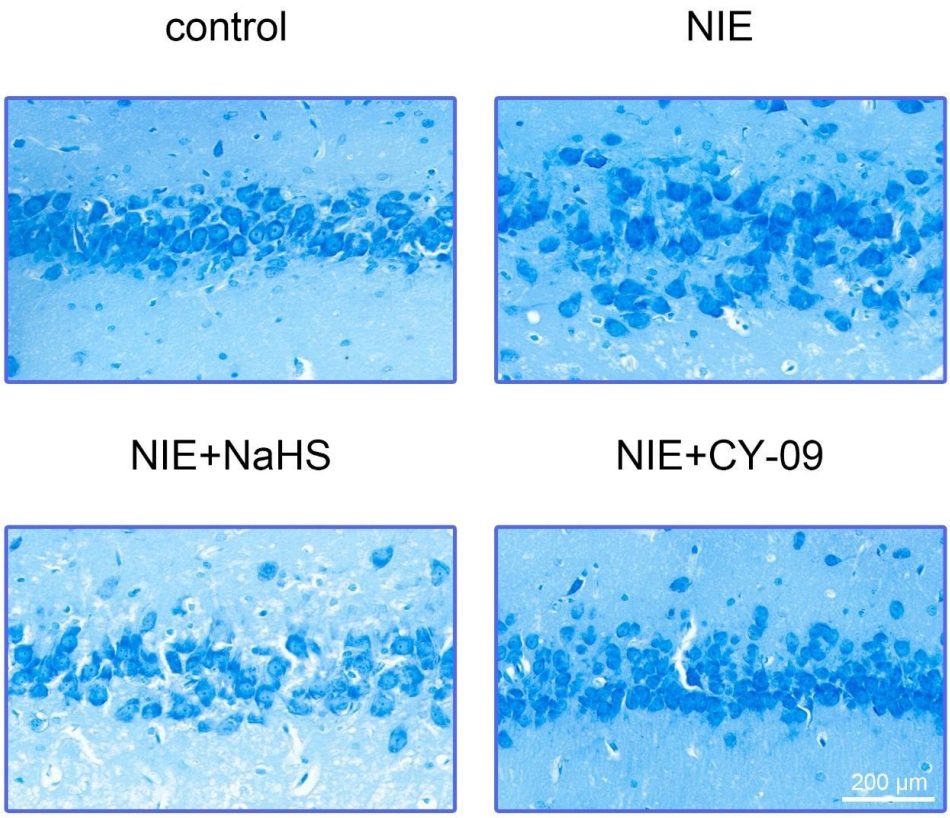

FIGURE 2. NaHS reduces the neuronal damage in NIE rats. Nissl staining to assess each group's hippocampus neuron damage. NIE: Neonatal hypoxic-ischemic encephalopathy; NaHS: Sodium hydrosulfide.

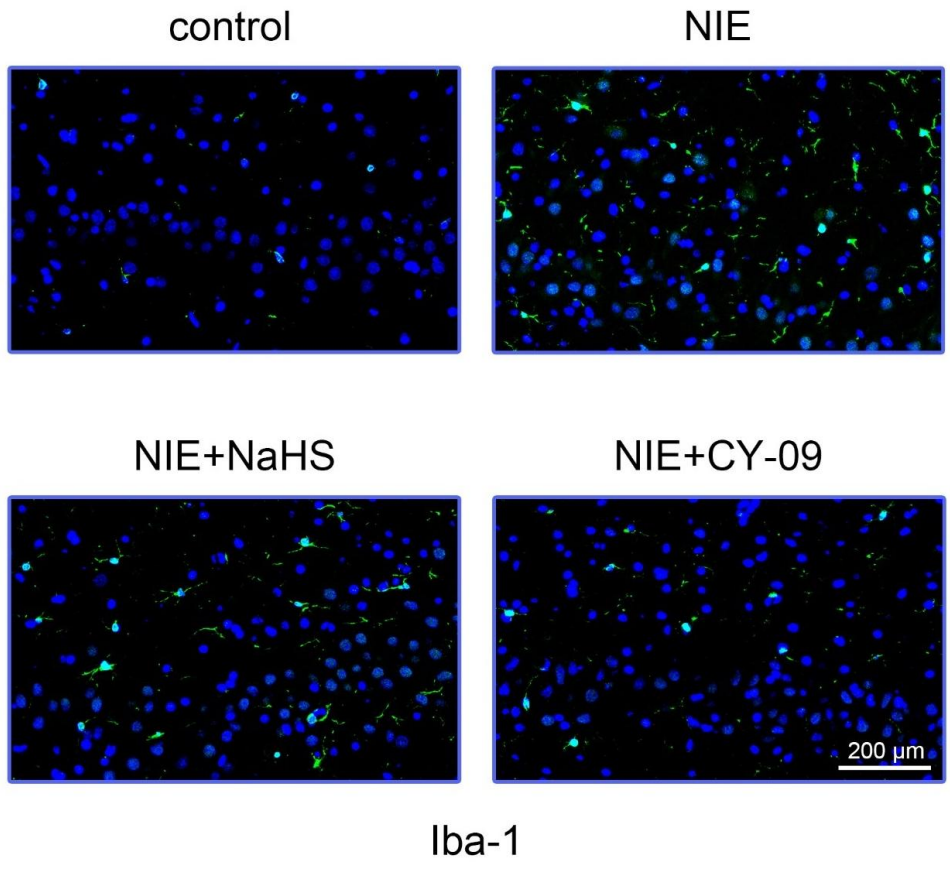

FIGURE 3. NaHS and CY-09 suppress microglial activation in NIE rats. Iba-1 expression in rat hippocampus tissue was detected by immunofluorescence in each group. NIE: Neonatal hypoxic-ischemic encephalopathy; NaHS: Sodium hydrosulfide.

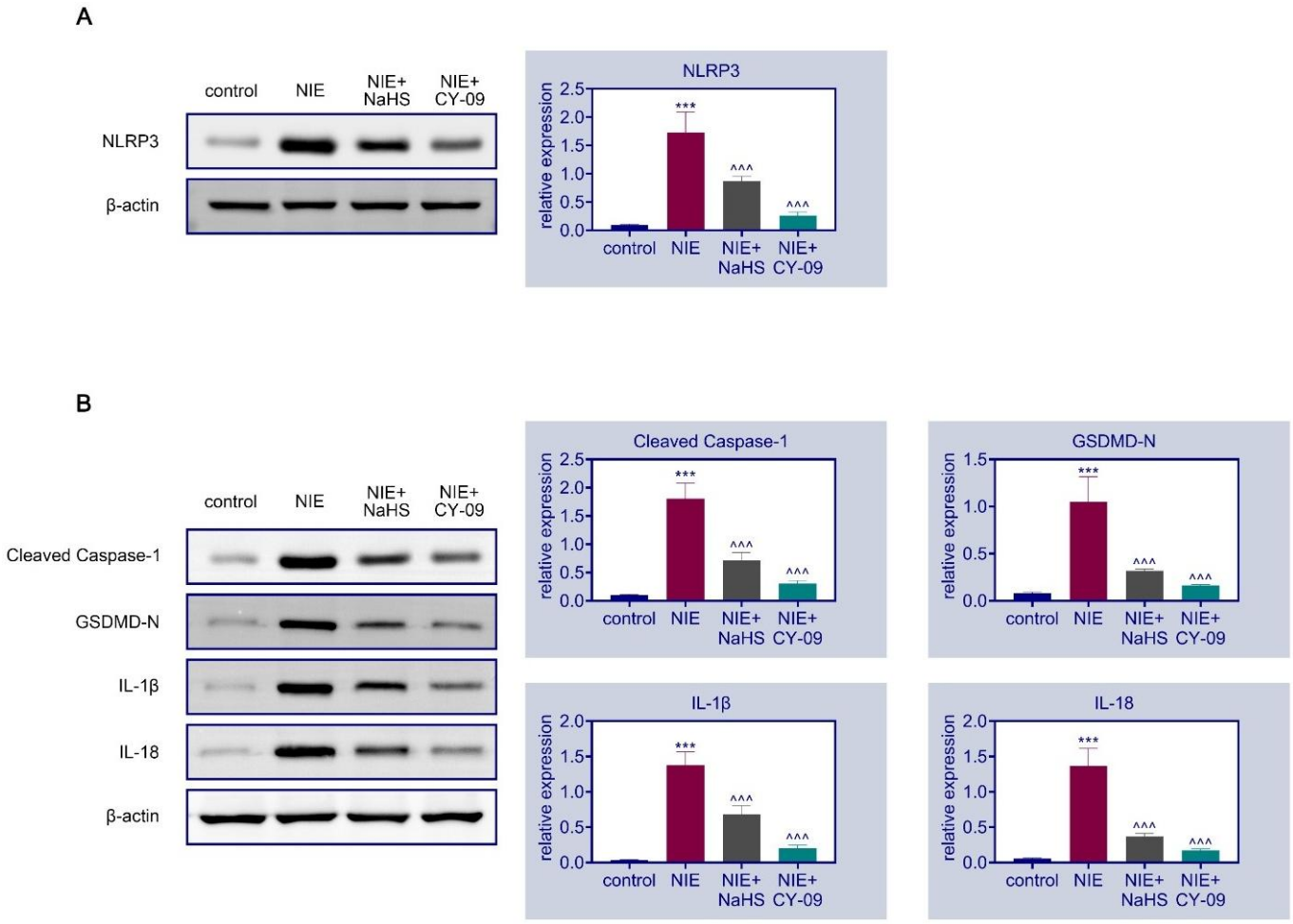

FIGURE 4. NaHS inhibits pyroptosis-related protein expression in NIE rats. (A) Identification of NLRP3 protein expression in brain tissue using Western blot. (B) Identification of Cleaved Caspase-1, GSDMD-N, IL-1β, and IL-18 protein expression in brain tissue using Western blot. *vs.* Control, ***$p < 0.001$. *vs.* NIE, ^^^$p < 0.001$. NIE: Neonatal hypoxic-ischemic encephalopathy; NaHS: Sodium hydrosulfide; NLRP3: the nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain- containing receptor 3; GSDMD: gasdermin D; IL-1β: interleukin-1β; IL-18: interleukin-18.

with enhanced behavioral and mechanistic evaluations.

5. Conclusions

This study is the first to connect the suppression of pyroptosis with the neuroprotective effect of NaHS, offering a novel perspective on the mechanisms underlying hypoxic-ischemic brain injury. In summary, NaHS alleviates cognitive impairment and neuronal damage caused by ischemia and hypoxia by inhibiting microglia-mediated neuroinflammation and cell pyroptosis. This study provides an experimental basis for the development of hydrogen sulfide-based neuroprotection strategies in neonatal hypoxic-ischemic encephalopathy.

AVAILABILITY OF DATA AND MATERIALS

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

AUTHOR CONTRIBUTIONS

XLJ and GQC—designed the study and carried them out; analyzed the data, interpreted the data. XLJ, GQC and FG—supervised the data collection. XLJ, GQC, FG and WWW—prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of the Animal Room of Zhejiang Provincial People's Hospital (Approval no. 20250121218107).

ACKNOWLEDGMENT

Not applicable.

FUNDING

This work was supported by Zhejiang Province Health Science and Technology Project (2023KY465).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Xiaoli Jin, Guoqing Chen, Fang Gu, Wenwen Weng. Hydrogen sulfide regulates NLRP3 to inhibit pyroptosis and protect against hypoxic-ischemic brain injury in neonatal rats. Signa Vitae. 2025; 21(8): 91-97. doi: 10.22514/sv.2025.118.