ARTICLE IN PRESS

Kafkas Universitesi Veteriner Fakultesi Dergisi
Journal Home-Page: http://vetdergikafkas.org
E-ISSN: 1309-2251

Kafkas Univ Vet Fak Derg
x (x): x-x, 2026
DOI: 10.9775/kvfd.2025.35579

Research Article

Dexmedetomidine Up-Regulates UCP2 via Modulation of the AMPK Pathway Is Associated with Reduced ROS and Neuroprotection in Neonatal Mice with Hypoxic-Ischemic Brain Damage

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How to cite this article?

Nie B, Zhu M, Hu S, Tan L, Wang J: Dexmedetomidine Up-Regulates UCP2 via Modulation of the AMPK Pathway is Associated with Reduced ROS and Neuroprotection in Neonatal Mice with Hypoxic-Ischemic Brain Damage. *Kafkas Univ Vet Fak Derg*, 2026 (Article in Press).
DOI: 10.9775/kvfd.2025.35579

Article ID: KVFD-2025-35579
Received: 05.11.2025
Accepted: 25.02.2026
Published Online: 05.03.2026

Abstract

We aimed to investigate whether dexmedetomidine (Dex) alleviates hypoxic-ischemic brain damage (HIBD) in neonatal mice and to explore the potential involvement of AMPK-related mechanisms. C57BL/6 neonatal mice were randomly assigned into a sham group, an HIBD group, an HIBD + Dex group, and an HIBD + Dex + Compound C (CC) group. Neurological deficits were scored, brain water content was detected and cerebral infarction areas were determined via 2,3,5-triphenyltetrazolium chloride staining. Hematoxylin-eosin staining was performed to detect the pathological changes in brain tissues. Compared with the sham group, HIBD mice showed markedly increased neurological deficit scores, brain water content, infarct area, ROS, and MDA levels, accompanied by reduced GSH-Px, SOD activity, a lower p-AMPK/AMPK ratio, and decreased UCP2 expression ($p<0.05$). Dex treatment significantly improved neurological function, reduced cerebral edema and infarction, decreased oxidative stress markers, and enhanced antioxidant enzyme activity, together with increased AMPK phosphorylation and UCP2 expression compared with HIBD ($p<0.05$). Notably, co-administration of Compound C partially attenuated the neuroprotective and antioxidative effects of Dex, supporting the involvement of AMPK-dependent mechanisms. Although UCP2 expression was altered in parallel with AMPK activity, the present data do not directly establish UCP2 as a causal mediator. Overall, these findings suggest that Dex mitigates oxidative stress and neuronal injury in neonatal HIBD, potentially through AMPK-associated pathways, with UCP2 representing a putative downstream component.

Keywords: AMPK, Brain damage, Dexmedetomidine, Neonate, Oxidative stress

Introduction

Hypoxic-ischemic brain damage (HIBD), a common brain lesion in neonates in the perinatal period, is mainly characterized by deficiency in oxygen supply or reduction in blood perfusion to brain tissues. The clinical manifestations of HIBD include a series of neurological dysfunction, and some child patients may experience sequelae including mental retardation, motor dysfunction and even cerebral palsy, posing substantial impacts on the long-term quality of life of these patients. Such a serious nervous system injury not only brings lifelong health risks to the child patients, but also imposes a heavy care burden and economic pressure on the family and society [1]. Neuronal damage serves as the kernel mechanism of HIBD development and progression, which directly affects the process and outcome of diseases. Hence, the protection of neurons has become a key strategy for HIBD treatment [2].

As a crucial pathological feature of HIBD, oxidative stress stimulates the excessive accumulation of reactive oxygen species (ROS) to attack neurons and destroy the structure and function of brain tissues [3]. Although oxidative stress has been widely recognized as a central contributor to neuronal injury in HIBD, the upstream regulatory pathways that coordinate mitochondrial redox homeostasis under hypoxic-ischemic conditions remain incompletely understood. Based on this pathological mechanism, seeking drugs that can effectively intervene in HIBD from the perspective of anti-oxidative stress has emerged as an important direction of clinical research at present.

Dexmedetomidine (Dex) is a highly specific α2 adrenergic receptor agonist, which is frequently applied to sedation and analgesia in perioperative period [4]. It possesses anti-oxidant, anti-inflammatory, anti-apoptotic and many other neuroprotective effects [5]. Previous evidence has linked Dex to the regulation of oxidative stress and energy-sensing pathways, including AMPK signaling, in different neurological injury contexts [6]. In neonatal rat model of HIBD, Dex has been shown to mitigate neuronal injury and improve neurological outcomes by relieving pathological damage, modulating inflammatory responses, and suppressing neuronal cell death [7,8]. However, how Dex integrates mitochondrial oxidative stress control with cellular energy-sensing mechanisms in neonatal HIBD remains largely unexplored.

Uncoupling protein 2 (UCP2) is a protein localized in the inner mitochondrial membrane, which can reduce ROS production by lowering the mitochondrial membrane potential, thereby exerting an anti-oxidant effect [9]. Adenosine 5'-monophosphate-activated protein kinase (AMPK) is a key metabolic sensor that responds to cellular energy stress and has been reported to influence mitochondrial function and oxidative balance [10]. Recent study suggests that AMPK may modulate UCP2 expression or activity as part of a coordinated response to metabolic and oxidative stress [11]; however, the relevance of this regulatory relationship in neonatal hypoxic-ischemic brain injury has not been established. Notably, whether AMPK-associated regulation of UCP2 contributes to Dex-mediated neuroprotection under hypoxic-ischemic conditions remains unknown.

Therefore, the present study was designed to explore the involvement of AMPK-dependent mechanisms, with a particular focus on the AMPK-UCP2 axis, in the antioxidative and neuroprotective effects of Dex in neonatal mice with HIBD.

Material and Methods

Ethical Approval

This study has been approved by the ethic committee of Tongji Hospital (Approval No. TJH-202111026), and great efforts have been made to minimize the animals' suffering.

Experimental Animals

SPF-grade C57BL/6 neonatal mice (n=40, 7 days old, no restriction in sex) were purchased from Hainan Pharmaceutical Research Institute Co., Ltd. [Animal License No. SCXK (Hainan) 2020-0007]. All mice weighing 4-5 g were uniformly raised in a sterile animal room with a temperature of 22-25°C, relative humidity of 60%, and a 12 h/12 h light/dark cycle. They were fed adaptively for 7 d before experiments, without deprivation of water and food. Sex was not treated as an independent biological variable due to the limited sample size.

Reagents and Apparatus

Dex was supplied by Beijing Kaishiyuan Biotechnology Co., Ltd. ROS detection kit was purchased from US Everbright Inc. Compound C (CC), an AMPK inhibitor, was offered by MCE (USA). Enzyme-linked immunosorbent assay (ELISA) kit sourced from Shanghai ZCi Biotech Co., Ltd. RIPA lysis buffer, bicinchoninic acid (BCA) protein assay kit, and ECL solution were provided by Beijing Solarbio Science & Technology Co., Ltd. Antibodies against phosphorylated (p)-AMPK, AMPK, and UCP2 were procured from CST (USA). A microscope (model: DM2000LED) was supplied by Leica (Germany). A microplate reader (model: Infinite M200) was bought from BioTek.

Grouping and Modeling Methods

Forty mice were allocated to a sham operation group (sham group, n=10) and a model group (n=30) in a random manner. After all mice were anesthetized with 3% pentobarbital sodium (100 μL in volume) through intraperitoneal injection. The same anesthetic protocol was applied across all experimental groups to minimize potential confounding effects. Pentobarbital was used solely for surgical anesthesia and was not considered an experimental variable in this study. After anesthesia, the neck was routinely disinfected and a median incision was made to expose the left common carotid artery. In the model group, the left common carotid artery was double ligated using surgical sutures, and the incision was sutured layer by layer. A thermostatic (37°C) pad was employed to maintain body temperature throughout the operation. After surgery, mice in the model group were placed in a customized hypoxic chamber, and exposed to a gas mixture of 8% O_2 and 92% N_2 at a flow rate of 2.5-3.5 L/min for 2 h once oxygen concentration stabilized below 10%. In the sham group, only vessel exposure was performed without arterial ligation or hypoxia intervention. The neonatal mouse model of HIBD was successfully prepared when the mice manifested toddling, limb paralysis, and other phenomena.

Totally 2 mice died during modeling, and 1 mouse failed. Thus, 27 successfully modeled mice were randomly assigned to the HIBD group (n=9), an HIBD + Dex group (n=9), and HIBD + Dex + CC group (n=9). The sample size was determined based on previous HIBD studies using similar experimental designs and outcome measures [12]. Given the exploratory nature of this study and ethical considerations regarding animal use, a formal a priori power analysis was not performed. The mice in the HIBD + Dex group were intraperitoneally injected with 50 μg/kg Dex for intervention immediately after modeling [13]. The mice in the HIBD + Dex + CC group were intraperitoneally injected with 50 μg/kg Dex immediately after modeling,

followed by intraperitoneal injection of CC (10 mg/kg) [14]. The intraperitoneal injection of 0.9% sodium chloride solution in the same volume was conducted in the sham and HIBD groups. All subsequent assessments were performed at a predefined early time point to evaluate acute pathological and biochemical changes following hypoxic-ischemic injury.

Scoring of Severity of Neurological Deficits

After the completion of drug intervention, the neurological function of neonatal mice in all experimental groups was evaluated using the neurological deficit score (NDS) system [15], with the specific scoring criteria listed in *Table 1*. All behavioral assessments were conducted by investigators blinded to group allocation. Neurological deficit scoring was conducted 24 h after hypoxic-ischemic injury and pharmacological intervention.

Sample Collection

After the NDS evaluation, 6 mice randomly selected from each group were decapitated, and craniotomy was performed rapidly to remove the brain tissues on the left side and isolate the hippocampus. Following rinsing with precooled PBS buffer, the tissue samples were immediately stored at -80°C for later use. The remaining 3 mice were fixed in the supine position, perfused with 0.9% normal saline followed by 4% paraformaldehyde, and whole brains were collected for histological examination. All tissue collection procedures for biochemical assays, Western blotting, and histological analyses were performed at the same time point.

Measurement of Brain Water Content

The whole brain tissues were immediately measured as wet weight, and the brain tissue was baked in a 100°C oven for 72 h to obtain the dry weight. The ratio of the difference between wet weight and dry weight to wet weight was determined as brain water content (%).

2,3,5-Triphenyltetrazolium Chloride (TTC) Staining

The brain tissues frozen in -20°C refrigerator were sliced to uniform sections (2 mm-thick) along the coronal plane using a microtome, followed by 30 min of incubation with ice-cold 2% TTC solution. Thereafter, the sections were taken out and immersed in 4% paraformaldehyde solution for 24 h, and the images were captured to measure and calculate the cerebral infarction area in each group of mice through ImageJ v1.8.0.

Table 1. *Neurological function scoring criteria*

Score	Symptom
0 point	No nerve damage
1 point	Inability of the left forelimb to bend inward
2 points	Rotation of the left forelimb to the left or walking toward the left side
3 points	Rotation of the mouse to the left side like chasing the tail

Hematoxylin-Eosin (HE) Staining

The 4% paraformaldehyde-fixed brain tissues were embedded in paraffin, dehydrated in a gradient of ethanol (70-100%), and transparentized using xylene solution. Later, the treated tissue blocks were prepared into 5 μm-thick serial sections *via* the microtome. After double staining with hematoxylin and eosin, the sections were mounted with drops of neutral balsam. Finally, the sections were observed under a light microscope and analyzed for pathological-morphological changes in the brain tissues.

ELISA for Levels of Oxidative Stress Indicators in Brain Tissues

The brain tissues were obtained from the mice in each group, cut into pieces (1 mm in size) with ophthalmic scissors, and transferred to a centrifuge tube on ice. Then the supernatant was discarded after the tissues were precipitated, which were digested into tissue homogenates using 0.25% trypsin. Afterward, the suspension was centrifuged at 3.000 rpm for 10 min in a centrifuge, so as to harvest the supernatant. The levels of ROS, glutathione peroxidase (GSH-Px), malondialdehyde (MDA), and superoxide dismutase (SOD) in the supernatant were measured by means of ELISA.

Determination of Protein Expressions Through Western Blotting

The hippocampal tissues homogenized and lysed using RIPA lysis buffer supplemented with protease and phosphatase inhibitors on ice for 30 min. After centrifugation at 10.000 rpm for 10 min at 4°C, the supernatant was collected as total protein extract. Protein concentration was determined using the BCA kit. Equal amounts of protein (30 μg per lane) were subjected to SDS-PAGE gel and transferred to polyvinylidene fluoride (PVDF) membranes. After blocking with 5% non-fat milk for 1 h, the membranes were incubated with primary antibodies against p-AMPK, AMPK, UCP2, and GAPDH (1:500) overnight at 4°C. ON the next day, the membranes were incubated with HRP-labeled secondary antibodies (1:1000) for 3 h at room temperature. Protein band intensities were quantified using ImageJ software. p-AMPK levels were normalized to total AMPK, and UCP2 expression was normalized to GAPDH.

Statistical Analysis

GraphPad Prism 8.0 software was employed to conduct the statistical analysis of experimental data. Data were expressed by mean ± standard deviation (Mean ± SD). One-

way ANOVA was used for comparisons among multiple groups. Post hoc multiple comparisons were performed using Tukey's test to reduce the risk of type I error. P<0.05 suggested a difference of statistical significance.

Results

The NDS of mice in the HIBD group was significantly higher than that in the sham group (p<0.05). The mice in the HIBD + Dex group had reduced NDS compared to those in the HIBD group (p<0.05) and the HIBD + Dex + CC group (p<0.05) *(Fig. 1)*.

When contrasted with the sham group, the HIBD group presented significantly raised brain water content (p<0.05). The brain water content in mice was significantly lower in the HIBD + Dex group than in the HIBD group (p<0.05) and the HIBD + Dex + CC group (p<0.05) *(Fig. 2)*.

Compared with the sham group, the cerebral infarction area was significantly increased in the HIBD group (p<0.05). In contrast, the cerebral infarction area was significantly reduced in the HIBD + Dex group compared with the HIBD group (p<0.05) and the HIBD + Dex + CC group (p<0.05) *(Fig. 3)*.

In the sham group, the hippocampal neurons were tightly and orderly arranged, with complete and regular cell morphology. The HIBD group manifested remarkable pathological changes such as obvious neuron swelling, evident reduction in cell density, and widespread neuronal damage. The density of neurons was notably elevated, the cell arrangement tended to be regular, and the swelling was apparently improved in the HIBD + Dex group by comparison to those in the HIBD group. In contrast, the HIBD + Dex + CC group showed similar severity of neuronal damage to the HIBD group, without significant protective effect *(Fig. 4)*.

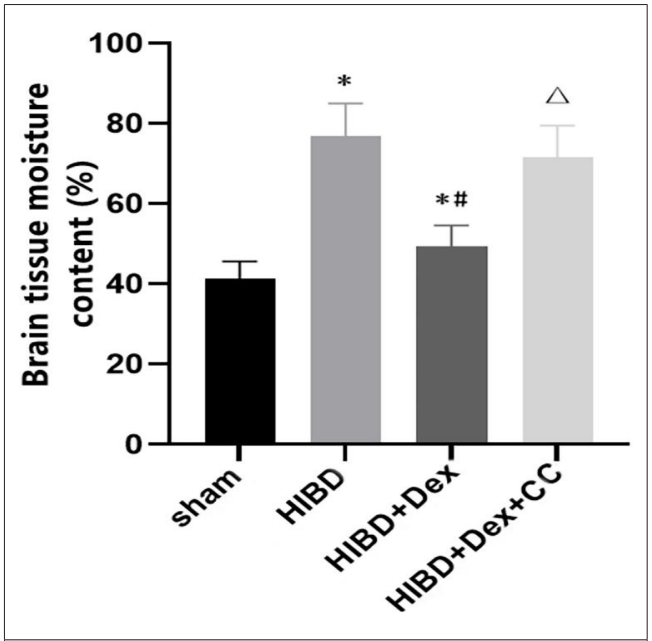

Fig 1. NDS of mice. *p<0.05 vs. Sham Group, #p<0.05 vs. HIBD Group, and △p<0.05 vs. HIBD + Dex Group

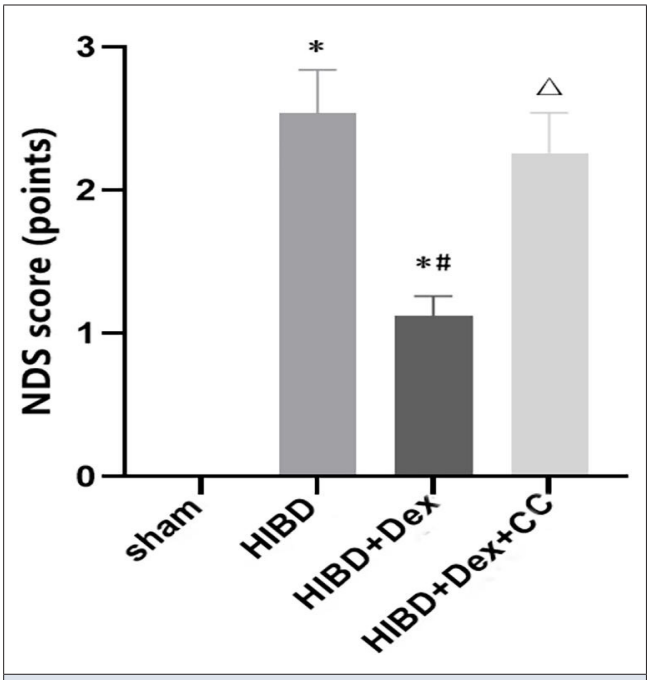

Fig 2. Brain water content in different groups of mice. *p<0.05 vs. Sham Group, #p<0.05 vs. HIBD Group, and △p<0.05 vs. HIBD + Dex Group

Compared with those in the sham group, the relative ROS level and MDA content in murine brain tissues rose significantly, whereas the GSH-Px content and SOD activity dropped significantly in the HIBD group (p<0.05). The HIBD + Dex group, when contrasted with the HIBD group, presented significant decreases in relative ROS level and MDA content, together with significant increases in GSH-Px content and SOD activity in the brain tissues of mice (p<0.05). The relative ROS level and MDA content in the brain tissues of mice in the HIBD + Dex + CC group were significantly higher, but the GSH-Px content and SOD activity were significantly lower than those in the HIBD + Dex group (p<0.05) *(Fig. 5)*.

The p-AMPK/AMPK ratio and UCP2 protein expression were significantly decreased in the brain tissues of mice in the HIBD group compared with the sham group (p<0.05). Dex treatment was associated with a significant increase in the p-AMPK/AMPK ratio and UCP2 protein expression compared with the HIBD group (p<0.05). These increases were attenuated in the presence of Compound C, indicating that the observed changes in UCP2 expression occurred in parallel with alterations in AMPK phosphorylation (p<0.05) *(Fig. 6)*.

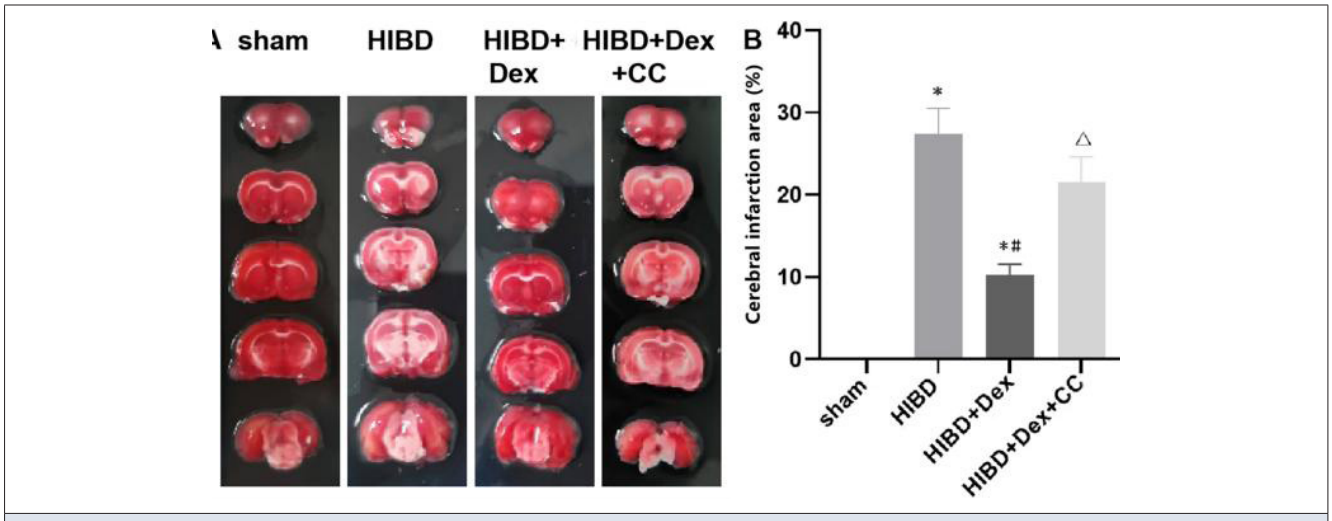

Fig 3. Cerebral infarction area in various groups of mice. A: Cerebral infarction area detected via TTC staining, B: Cerebral infarction area in diverse groups of mice. *p<0.05 vs. Sham Group, #p<0.05 vs. HIBD Group, and △p<0.05 vs. HIBD + Dex Group

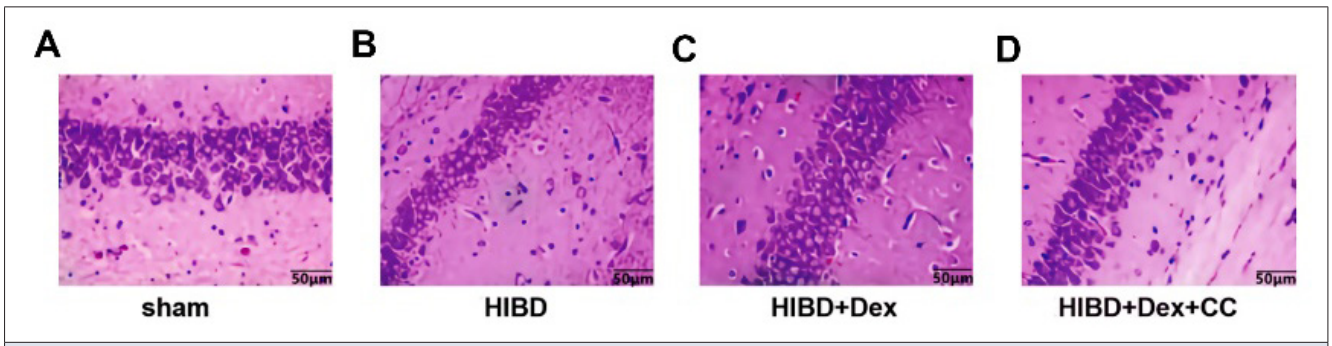

Fig 4. HE staining results of mouse brain tissues (×200). A- Sham, B- HIBD, C- HIBD + Dex, D- HIBD + Dex + CC. Neuronal injury was evident in the HIBD group, alleviated by Dex treatment, and partially reversed by CC

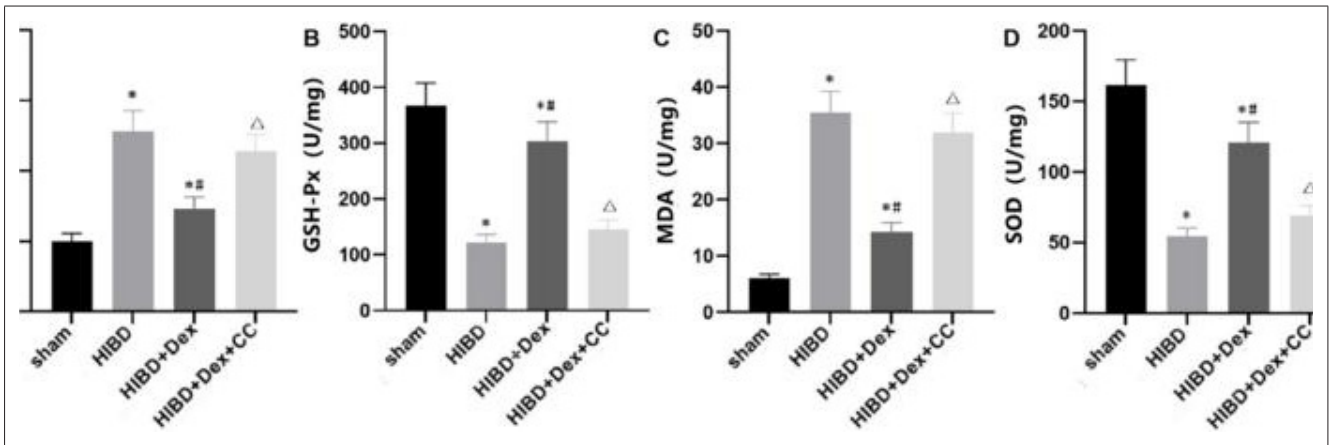

Fig 5. Oxidative stress indicators in murine brain tissues from different groups. A: Relative ROS level in brain tissues, B: GSH-Px content in brain tissues, C: MDA content in brain tissues, D: SOD activity in brain tissues. *p<0.05 vs. Sham Group, #p<0.05 vs. HIBD Group, and △p<0.05 vs. HIBD + Dex Group

Discussion

Pathologically, HIBD is typically featured with brain tissue edema, selective neuronal necrosis, marble-like pathology in the basal ganglia, neuronal damage in the parasagittal region of the brain, periventricular leukomalacia, *etc* [16]. The clinical manifestations of HIBD mainly include sudden hyperthermia, chills, and severe headache accompanied by projectile vomiting. Infants and young children suffering from this disease may present alternating dysphoria and lethargy, bilateral gaze, abnormal crying, food refusal, irritability, and other symptoms, and they may rapidly

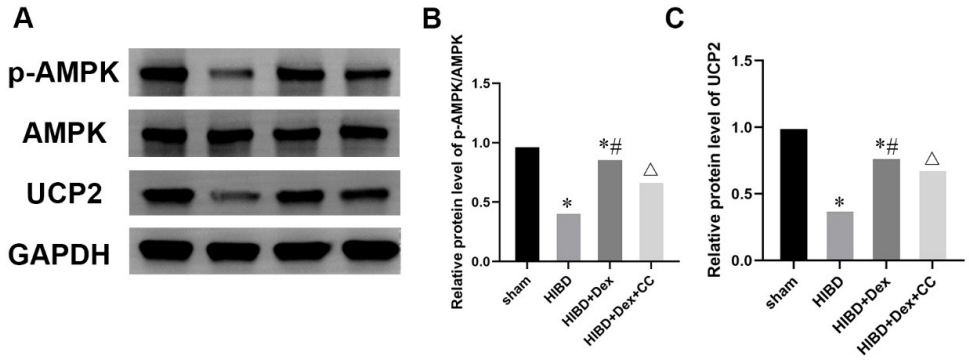

Fig 6. Protein expressions of p-AMPK, AMPK, and UCP2 in murine brain tissues from various groups. A: Protein bands of p-AMPK, AMPK, and UCP2 in murine brain tissues from diversified groups, B: p-AMPK/AMPK ratio in brain tissues of mice in each group, C: UCP2 protein expression in murine brain tissues from different groups. *p<0.05 vs. Sham Group, #p<0.05 vs. HIBD Group, and △p<0.05 vs. HIBD + Dex Group

progress to a coma state in severe cases [17]. At present, there is a lack of targeted therapeutic drugs capable of effectively relieving brain damage and preventing and treating neurological sequelae in neonates. Dex is a potent and highly specific α2 adrenergic receptor agonist, which performs the major neuroprotective mechanisms like the modulation of glutamatergic neurotransmitter release, the attenuation of inflammatory cascades, the blockade of neuronal apoptosis pathways, the scavenging of oxygen free radicals, and the enhancement of synaptic plasticity. These action mechanisms are jointly implicated in mitigating secondary damage to brain tissues and prominently improving neurological function score, and thus exerting significant neuroprotective effects [18]. As reported in the study of Hu et al.[19], Dex could markedly enhance the cognitive function in rat models of traumatic brain damage, effectively inhibit programmed nerve cell death, and substantially relieve structural damage in neurons, demonstrating distinct neuroprotective efficacy. Chen *et al.* [20] corroborated that Dex could lower NOX4 expression to reduce ROS generation in brain tissues, thus ameliorating neurological damage after cerebral hemorrhage in mice by alleviating oxidative stress. Through controlling the PPARγ/STAT3 signaling pathway, Dex pretreatment can efficiently relieve oxidative stress injury and interrupt the process of cell apoptosis, thereby producing a significant neuroprotective effect against HIBD [21]. Obvious decreases were detected in the NDS, brain water content, and cerebral infarction area in the HIBD + Dex group of the present study, suggesting that Dex can mitigate brain damage and exert a neuroprotective effect on HIBD mice, which is consistent with the results of the aforementioned studies.

Under physiological conditions, the ROS generated in brain tissues activates the anti-oxidant defense system in the body, in which SOD and catalase (CAT) are pivotal components of the enzymatic anti-oxidant system in nerve cells, capable of effectively removing ROS and maintaining GSH at a high level [22]. In the context of HIBD, however, excessive ROS rapidly overwhelms the anti-oxidant and scavenging capacities of nerve cells, disrupting the oxidant-anti-oxidant balance in brain tissues and leading to apparent oxidative stress in nerve cells. When HIBD induces persistent chronic oxidative stress, the activities of SOD and CAT decrease significantly in brain tissues, and large amount of GSH is consumed [23]. Meanwhile, the intensified lipid peroxidation in brain tissues causes the production of massive MDA, triggers abnormal aggregation of proteins, nucleic acids, and other macromolecules in nerve cells, and arouses neurotoxicity, further exacerbating mitochondrial dysfunction and ultimately resulting in nerve cell injury and apoptosis [24]. It was discovered in this study that the HIBD + Dex group had overtly reduced ROS level and MDA content and notably incremented SOD activity and GSH-Px content, implying that Dex can alleviate oxidative stress in HIBD mice and thus protect the neurological function, but the specific action mechanism needs in-depth research.

In the pathological process of HIBD, the activation of the AMPK-UCP2 signaling pathway is a crucial link for regulating ROS generation and maintaining mitochondrial function [25]. Once hypoxia and ischemia occur in brain tissues, the elevated intracellular AMP/ATP ratio can activate the AMPK signaling pathway. Such an energy metabolism regulatory hub not only promotes fatty acid β-oxidation to maintain energy supply, but also up-regulates UCP2 expression to improve mitochondrial function [26]. With the help of the induced mild uncoupling of the inner mitochondrial membrane, UCP2 can effectively decrease the overproduction of superoxide anions in the process of electron transport chain, thus significantly reducing the ROS accumulation. In the meantime, the activated AMPK also strengthens the activities of anti-oxidant enzymes, such as SOD and CAT, and coordinates with UCP2 in maintaining the oxidant-anti-oxidant balance in cells. This neuroprotective mechanism of the AMPK/UCP2

axis is particularly important in HIBD because it can attenuate oxidative stress injury of nerve cells, hinder the deterioration of mitochondrial dysfunction, and finally reduce neuronal apoptosis. Zeng et al.[27] proved that pterostilbene had a protective effect on neonatal rats with HIBD through the mechanism possibly highly associated with the up-regulated expression of the LKB1/AMPK/Nrf2 signaling pathway and the repressed oxidative stress responses. According to the results of the present study, the p-AMPK/AMPK ratio and UCP2 protein expression were markedly increased in the brain tissues of the HIBD + Dex group. These findings indicate that Dex treatment is associated with concurrent activation of AMPK signaling and upregulation of UCP2 expression under hypoxic-ischemic conditions. Furthermore, co-administration of the AMPK inhibitor Compound C attenuated the antioxidative and neuroprotective effects of Dex, supporting the involvement of AMPK-dependent mechanisms in Dex-mediated protection.

Several limitations should be noted. First, although changes in AMPK phosphorylation and UCP2 expression were observed after Dex treatment, direct evidence for a causal role of UCP2 is lacking, as UCP2-specific interventions were not performed. Second, sex-specific analyses were not conducted due to the limited sample size, despite potential sex differences in HIBD outcomes and AMPK-related signaling. Third, all assessments were performed at a single early time point after hypoxic-ischemic injury, which may not fully reflect the dynamic progression of HIBD. Future studies incorporating genetic approaches, sex stratification, and multiple time points are warranted.

In conclusion, Dex alleviates oxidative stress and improves neurological outcomes in neonatal mice with HIBD. These protective effects are likely associated with activation of AMPK signaling and downstream mitochondrial redox regulation, including altered UCP2 expression.

Declarations

Availability of Data and Materials: The datasets used and/or analyzed during the current study are available from the corresponding author (JW) on reasonable request.

Acknowledgments: None.

Financial Support: This study was financially supported by the Hubei Natural Science Foundation (No. No. 2023ABF707).

Conflict of Interest: The authors declared that there is no conflict of interest.

Declaration of Generative Artificial Intelligence (AI): The authors declare that the article, tables and figures were not written/ created by AI and AI-assisted Technologies

Authors Contributions: B.N. and M.Z. conceived and designed the study. S.H. performed the animal experiments and data collection. L.T. conducted the statistical analysis and prepared the figures. J.W. supervised the study, interpreted the data, and revised the manuscript.

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