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SPECIALTY SECTION

This article was submitted to Neonatology, a
section of the journal Frontiers in Pediatrics

RECEIVED 05 July 2022

ACCEPTED 20 September 2022

PUBLISHED 10 October 2022

CITATION

Chen A, Chen X, Deng J and Zheng X (2022)
Research advances in the role of endogenous
neurogenesis on neonatal hypoxic-ischemic
brain damage.
Front. Pediatr. 10:986452.
doi: 10.3389/fped.2022.986452

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Research advances in the role of endogenous neurogenesis on neonatal hypoxic-ischemic brain damage

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Hypoxic-ischemic brain damage (HIBD) is the main cause of perinatal mortality and neurologic complications in neonates, but it remains difficult to cure due to scarce treatments and complex molecular mechanisms remaining incompletely explained. Recent, mounting evidence shows that endogenous neurogenesis can improve neonatal neurological dysfunction post-HIBD. However, the capacity for spontaneous endogenous neurogenesis is limited and insufficient for replacing neurons lost to brain damage. Therefore, it is of great clinical value and social significance to seek therapeutic techniques that promote endogenous neurogenesis, to reduce neonatal neurological dysfunction from HIBD. This review summarizes the known neuroprotective effects of, and treatments targeting, endogenous neurogenesis following neonatal HIBD, to provide available targets and directions and a theoretical basis for the treatment of neonatal neurological dysfunction from HIBD.

KEYWORDS

neonates, hypoxic-ischemic brain damage, neurogenesis, neural stem cell, subventricular zone, subgranular zone

Introduction

Neonatal hypoxic-ischemic brain damage (HIBD), which is caused by perinatal asphyxia, is a primary etiology for acute neonatal mortality and long-term infant neurological dysfunction (1–3). The incidence of neonatal HIBD is 1–3 per 1,000 in developed countries, while in developing countries the rate can be as high as 25 per 1,000 (4, 5). HIBD can lead to irreversible neurological injuries including cerebral palsy, audiovisual impairment, memory difficulties, and cognitive dysfunction (6, 7). At present, standard global treatments for neonatal HIBD are focused on alleviating symptoms (e.g., hyperbaric oxygen therapy, therapeutic hypothermia, rehabilitation training); thus, there remains marked room for improved treatments (8–10).

Endogenous neurogenesis is the process by which neural stem cells (NSCs) undergo symmetric and asymmetric divisions, after which they proliferate and subsequently differentiate into directed progenitor cells that gradually migrate to functional brain areas while undergoing uninterrupted plastic changes and establishing synaptic

connections to produce neurological functions (11) (Figure 1). Under normal conditions, NSCs at neurogenesis sites remain in a resting state. When the brain is damaged by hypoxia and ischemia, they can be stimulated to proliferate, migrate, differentiate and integrate, activating brain neurogenesis. While neonatal HIBD has been shown to activate endogenous brain neurogenesis, spontaneous endogenous brain neurogenesis is limited and insufficient to fully compensate for neurons lost to injury (12). Thus, therapeutic techniques to promote endogenous neurogenesis would be of great clinical value for ameliorating neurological dysfunction from neonatal HIBD. This review summarizes the known neuroprotective effects and treatments targeting endogenous neurogenesis in neonatal HIBD, to provide available targets and directions and a theoretical basis for the treatment of neurological dysfunction from neonatal HIBD.

Overview of endogenous neurogenesis

Over recent years, our understanding of spontaneous endogenous neurogenesis shifted from its existence exclusively during embryonic and prenatal mammalian development (13) to be present within the adult mammalian brain, NSCs concentrated primarily in the subgranular zone (SGZ) of the hippocampal dentate gyrus and the subventricular zone (SVZ) of the lateral ventricle (14). NSCs are a class of primitive “mother” cells that can give rise to neurons and glial cells, with the potential for multidirectional differentiation and the ability to maintain self-renewal (15). The NSCs population is represented by radial glial-like cells that produce proliferating intermediate progenitor cells with transient expansion characteristics, which then differentiate into neuronal cells and finally develop into mature dentate granule neurons that integrate into neural circuits of the brain to perform neurological functions (16). Due to the asymmetric division of NSCs, two cellular pools exist in the progeny of a single clone of NSCs: mature neurons and undifferentiated neural progenitor cells. The latter retains the potential for multidirectional differentiation (17). Thus, asymmetric NSCs division allows the possibility of endogenous neurogenesis.

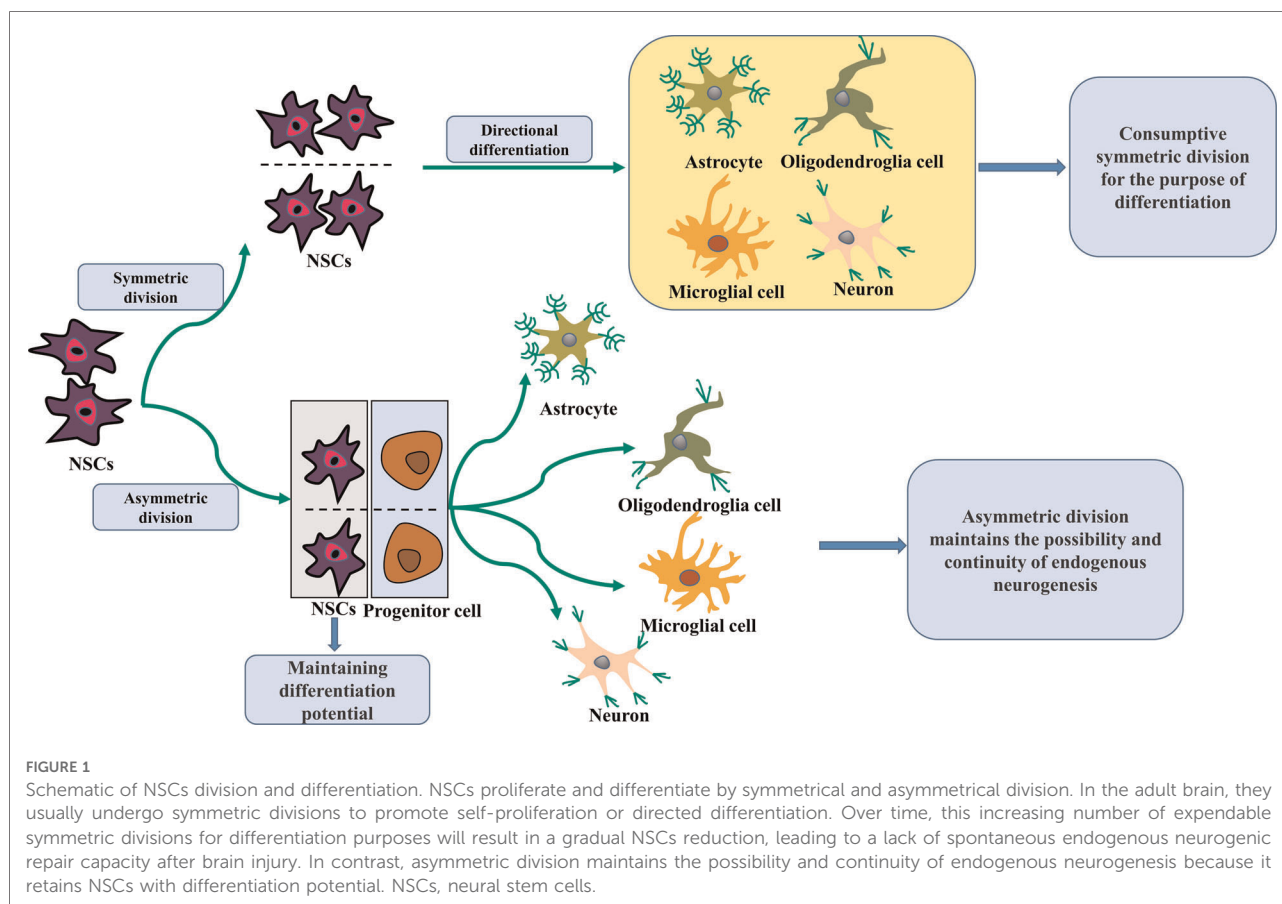
NSCs differentiation depends mainly on the components of their microenvironment, including neuronal cells, stromal cells, and the extracellular matrix. Based on these factors, NSCs of the same origin can differentiate into different cell types, including astrocytes, oligodendrocytes, and neurons (18). Next, the migration of progenitor cells differentiated from NSCs also depends on their brain location. In the SGZ, they migrate to the molecular layer of the hippocampal dentate gyrus and eventually integrate into the neural circuits of the hippocampus, playing an important role in learning and memory (19, 20). In the SVZ, they form migratory streams in

the surrounding astroglial precursor structures, and subsequently, migrate to the olfactory bulb and differentiate into intermediate neurons, ultimately participating in olfaction processes and influencing plasticity of olfactory-related behaviors (14, 21). After brain injury, progenitor cells from the neurogenesis sites migrate to damaged areas (e.g., striatum, cerebral cortex, hypothalamus) to repair damaged neurological functions by transforming into new neurons within these areas (22). This self-healing brain mechanism is enormously significant for the recovery of neurological functions after brain injury.

Although endogenous neurogenesis can improve neurological dysfunction by replacing neurons lost to injury, this is not always the case. As endogenous neurogenesis is a highly regulated process, exposure to a hypoxic-ischemic environment may lead to abnormalities in its course. In some cases, neurodevelopmental dysplasia may be a secondary process leading to brain dysfunction (23), like dysfunction of endogenous neurogenesis in hippocampal SGZ is a major factor in the development of dementia after a stroke in older adults. Current studies on the side effects of endogenous neurogenesis have focused on brain exposure to different pathological conditions in which new hippocampal SGZ granule neurons may develop abnormal morphology, leading to changes in hippocampal structure and thus ongoing exacerbation of neurological damage (24). Therefore, considering both the advantageous and deleterious effects of endogenous neurogenesis, clinical treatment of neonatal HIBD should promote endogenous neurogenesis to improve the intracranial microenvironment to facilitate the repair of damaged neurological function.

Endogenous neurogenesis after neonatal HIBD

It was recently shown that post-neonatal HIBD can induce NSCs proliferation in neurogenesis sites, with subsequent migration of proliferating progenitor cells to a damaged brain region where they acquire the desired phenotype; furthermore, in the damaged brain region, new neurons differentiated from NSCs can integrate into functional neural loops and repair damaged nerves (25). Plane et al. (26) used 5-Bromodeoxyuridine (BrdU) as a marker of proliferating cells in the Rice-Vannucci neonatal rat model of brain hypoxia-ischemia, in which they demonstrated a significant increase in BrdU-positive cells in damaged brain areas, mainly the SVZ. Others (27, 28), using a perinatal model of severe asphyxia to investigate neurogenesis in the neonatal rat brain, noted that 3H-deoxythymidine (3H-T)-labeled brain cells revealed specific upregulation of proliferation, but only in the injured hippocampus at five days post-injury. In contrast, at two weeks post-injury, there was a large increase in the number of



3H-T proliferating cells in the brain, with accompanying hippocampal weight increases. Both studies suggest that neonatal brain injury (e.g., hypoxia, ischemia) activates endogenous neurogenesis in the brain and promotes the repair of neurological damage, specifically in the SGZ and SVZ. However, literature (29) pointed out that the capacity for spontaneous endogenous neurogenesis is limited and insufficient for replacing neurons lost to brain damage. Therefore, it is of great clinical value and social significance to seek therapeutic techniques that promote endogenous neurogenesis, to reduce neonatal neurological dysfunction from HIBD.

Molecular mechanisms involved in endogenous neurogenesis after neonatal HIBD

HIF-1

Hypoxia-inducible factor (HIF-1) is a major transcriptional activator induced by hypoxia and ischemia. In hypoxic conditions, HIF-1 acts as the main mediator of a series of *in vivo* pathophysiological responses, including angiogenesis, cell

proliferation, and transcriptional induction of survival genes (30). The main function of the HIF-1 nucleoprotein is to coordinate the organism's homeostatic balance of developmental and pathological oxygen states; it does so as a heterodimer with α and β subunits. HIF-1 β is stably expressed intracellularly, whereas HIF-1 α contains a transcription-binding domain and is regulated by hypoxic signals. α subunits determine the biological activity of HIF-1 β , whereas cellular oxygen concentration strictly regulates the expression of HIF-1 α (31). Some studies (32–34) have shown that HIF-1 gene expression is enhanced in neonatal rats after the onset of hypoxic-ischemic encephalopathy, mainly manifesting as enhanced HIF-1 expression at both the mRNA and protein levels in brain tissue. Further, immunohistochemical results suggest that enhanced expression is more pronounced in vascular endothelial cells. These cumulative findings suggest that HIF-1 may be a primary mediator following neonatal HIBD.

Erythropoietin (EPO) is the first protein that has been identified downstream of HIF-1 to activate erythropoiesis (35). In hypoxic conditions, elevated EPO expression promotes erythropoiesis, enhancing oxygen transport and thus adaptation to the hypoxic environment (36). Though it was previously thought that EPO was solely a key gene in the maturation and proliferation of red lineage progenitors, later

studies showed that it is widely expressed in mammalian brain cells, including neurons and glial cells, which also express EPO receptors (37). Additionally, HIF-1 activates increased EPO expression, to induce expression of brain-derived neurotrophic factor (BDNF) and promote hippocampal neurogenesis (27). This cumulative evidence indicates that following injury from neonatal HIBD, the brain activates HIF-1-mediated factors, which promote endogenous neurogenesis.

Shh signaling pathway

The sonic hedgehog (Shh) signaling pathway plays an important role in endogenous neurogenesis (38) and can play a neuroprotective role in ischemia-exposed brain injury through the activation of pathway proteins (39). This pathway regulates NSCs growth, survival, and differentiation by upregulating the expression of the transcription factor *Gli1* in the SVZ. *Gli1*, which exerts a neuroprotective effect, induces the production of ganglionic neurons in the medial and lateral forebrain. In the midbrain and hindbrain, it induces the production of 5-hydroxytryptaminergic and dopaminergic neurons (40). It also plays an important role in NSCs renewal and migration (41). During normal development, Shh signaling pathway activation can establish homologous domains in the dorsal-ventral axis, to organize neural tube development across regions and maintain brain functional integrity (42). After brain injury, the Shh signaling pathway induces SVZ progenitor cells to produce large amounts of transcription factors, which determine cell differentiation types through time-dependent mechanisms and concentration gradients, compensating for brain cell losses (43). Thus, Shh signaling pathway expression upregulation may be a primary mechanism of endogenous neurogenesis following neonatal HIBD.

Notch pathway

The Notch signaling pathway is a highly conserved signaling pathway that plays a critical role in the process of endogenous neurogenesis (44). Under normal conditions, the Notch signaling pathway is relatively inhibited and is activated when ischemic changes occur, playing an active role in immune inflammation, neurogenesis, and apoptosis (45). A study (46) showed that after neonatal HIBD, the expression levels of Notch1 and its downstream signaling molecule *Hes1* were found to be upregulated and the number of newborn neurons in the SGZ region of the brain increased; while the number of newborn neurons in this region decreased after the application of Notch signaling pathway inhibitors, suggesting that the activation of the Notch signaling pathway can promote the process of endogenous neurogenesis induced by HIBD.

PI3K pathway

The Phosphatidylinositol-3-kinase (PI3K) pathway has already been identified to play an important role in cell survival of endogenous neurogenesis and many studies have focused on use of the PI3K pathway to treat brain injury after stroke (47). A recent study (48) has shown that PI3K activating its downstream effector protein kinase B (Akt) can improve hippocampal brain injuries and restore neuronal development after neonatal HIBD, which demonstrates that the activation of PI3K/Akt pathway can promote endogenous neurogenesis induced by HIBD.

Wnt/ β -catenin pathway

Wingless-type mouse mammary tumor virus integration site/ β -catenin (Wnt/ β -catenin) signaling is a vital pathway for endogenous neurogenesis and an essential signaling system during embryonic development and aging (49). Most studies demonstrate that Wnt/ β -catenin regulates progenitor self-renewal but others suggest it can also promote differentiation (50). A recent study (51) has shown that some treatments could alleviate the neurological deficits after neonatal HIBD by up-regulation of β -catenin protein in the brain. Taken together, the Wnt/ β -catenin pathway also plays a crucial role in the endogenous neurogenesis after neonatal HIBD.

Other influencing factors

The process of neurogenesis after HIBD is made up of multiple signaling molecules and pathways that are interconnected, coordinated, and work together to regulate the continuous process of neurogenesis. Several other modulators have been found to promote neurogenesis, reduce the size of infarcts and promote neurological recovery in the brain after HIBD, as follows: Vascular endothelial growth factor (VEGF) binds to the VEGFR2 receptor and activates the Rho/Rok pathway, promoting synaptic growth and playing a crucial role in neuroprotection and neurogenesis (52, 53). BDNF activates glutamatergic neurons and subsequently promotes endogenous neurogenesis after HIBD *via* the BDNF-TrkB-CREB signaling pathway (54).

Therapeutic measures for neonatal HIBD to promote endogenous neurogenesis

The ability of spontaneous endogenous neurogenesis after neonatal HIBD to repair damaged neurological functions is markedly limited. Therefore, developing therapeutic techniques

(Table 1) to promote endogenous neurogenesis to repair neurological deficits after neonatal HIBD is an urgent priority.

Therapeutic hypothermia

Several clinical studies have shown that hypothermia initiated at less than 6 h after birth reduces death or disability for infants with HIBD at 36 weeks or later gestation (8) and hypothermia treatment could improve patients' neurodevelopment two years after HIBD (7); however, whether therapeutic hypothermia facilitates neonatal endogenous neurogenesis after HIBD remains uncertain. One study (55) indicated that prolonged (>24 h) sub-hypothermia reduces cell proliferation in the SGZ, but not the SVZ, in neonatal rats. In contrast, a newer study (56) showed that a short period (4 h) of therapeutic sub-hypothermia partially rescued SGZ NSCs from apoptosis and increased the proliferation of SGZ neural precursor cells. Therefore, care should be taken in the selection of appropriate temperature and time parameters for therapeutic hypothermia in neonates following HIBD, as short periods may have a positive effect on endogenous neurogenesis, while longer periods may have the opposite effect. Currently, the clearest neuroprotective mechanism of action of therapeutic hypothermia is that it inhibits the classical complement pathway following HIBD, thereby reducing neurological damage from neuroinflammation (57).

Neural stem cells therapy

Stem cell-based treatments for HIBD have shown promising therapeutic efficacy in preclinical studies (17). Endogenous NSCs have the self-repair ability after brain injury but it is usually insufficient and needs time to proliferate and migrate to the lesion area. Therefore, transplantation of exogenous NSCs is probably a more efficient way to improve brain restoration after injury. Some studies point out that NSCs transplantation significantly reduces lesion volume in the acute phase and prevents neuron loss in the chronic phase after HIBD (58, 59). Therefore, NSCs transplantation therapy may be one of the most promising therapeutic measures for neurologic deficits induced by HIBD.

Exosomes therapy

Exosomes are endosomal origin membrane-enclosed small vesicles that contain various molecular constituents including proteins, lipids, mRNAs and microRNAs (71). Many studies have shown that exosomes play a crucial role in neurogenesis and are even of potential significance in treating some neurological diseases (72). A recent study (60) has pointed out that astrocyte-derived exosomes could carry miR-17-5p to protect neonatal rats from HIBD *via* regulating endogenous neurogenesis.

TABLE 1 Therapeutic approaches to promote endogenous neurogenesis and its mechanisms. HIBD, Hypoxic-ischemic brain damage; NSCs, Neural stem cells; EE, Enriched environment; PFT- α , Pifithrin- α ; BDNF, Brain-derived neurotrophic factor; VEGF, Vascular endothelial growth factor.

Therapeutic measures to promote endogenous neurogenesis	Mechanisms associated with neurogenesis	Study	
Therapeutic hypothermia	Short-term, has a positive effect on endogenous neurogenesis after neonatal HIBD by inhibiting the classical complement pathway, weakening neuroinflammation and thus promoting neurogenesis	(55–57)	
Neural stem cells therapy	NSCs transplantation significantly reduces lesion volume in the acute phase and prevents neuron loss in the chronic phase after HIBD	(58, 59)	
Exosomes therapy	Astrocyte-derived exosomes could carry miR-17-5p to protect neonatal rats from HIBD <i>via</i> regulating endogenous neurogenesis.	(60)	
Hyperbaric oxygen therapy	Promotes NSCs proliferation through the VEGF/ERK signaling pathway	(61)	
EE intervention	An intervention that promotes neurogenesis and functional recovery after ischemic brain injury and contributes to neuroprotection by upregulating expression of HIF-1 α in brain tissue	(62, 63)	
Medications	Drug name		
Anti-apoptotic drugs	PFT- α and Z-DEVD-fmk	Improve survival of endogenous NSCs after HIBD by inhibiting apoptosis-related signaling pathways, thereby promoting the process of endogenous neurogenesis	(64, 65)
	Atorvastatin	Promotes proliferation, differentiation and survival of NSCs by activating the PI3K/AKT and ERK pathways	(66)
Anti-inflammatory drugs	Minocycline	Alleviates depression-like symptoms by rescuing decrease in neurogenesis in dorsal hippocampus <i>via</i> blocking microglia activation	(67)
Endogenous growth factor analogues	BDNF and its analogues GSB-106 and GSB-214	Upregulate the PI3K/Akt and ERK pathways to promote endogenous neurogenesis after brain injury and improve neurological function	(68, 69)
	Epidermal growth factor, fibroblast growth factor	Promote proliferation and survival of NSCs after HIBD, promoting endogenous neurogenesis	(70)

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy, reported to have neuroprotective effects in multiple neurological disorders, is now being evaluated as a novel Adjuvant therapy to clinical management of neonatal HIBD (73). This technique restores the blood-brain barrier *via* cerebral vasoconstriction, decreasing cerebral blood flow and reducing cerebral hematoma, and simultaneously increasing oxygen supply to ischemic tissues (74). A meta-analysis study (75) pointed out that Hyperbaric oxygen therapy significantly improved the total efficiency of treatment for neonatal HIE patients and reduced the risk of sequelae, however, the underlying mechanism is not clear. One study (76) showed that the likelihood of neurological dysfunctions is lower in a HIBD neonatal rat model undergoing hyperbaric oxygen treatment, compared with controls, suggesting that this therapy may improve prognosis *via* neuroprotective effects. Thus, hyperbaric oxygen therapy may also improve prognoses in children with HIBD by promoting endogenous neurogenesis. One paper (61) reported that hyperbaric oxygen promotes NSCs proliferation *via* the VEGF/ERK signaling pathway after traumatic brain injury, implying that it might improve prognosis following HIBD by promoting endogenous neurogenesis.

Enriched environment intervention

Enriched environment (EE) encompasses both social interaction and the surrounding environment, based on the principle of maximizing opportunities for multisensory stimulation, voluntary physical activity, and social stimulation. EE is an intensive intervention (62) that can promote neurogenesis and functional recovery after cerebral ischemic injury, and is involved in neurological protection by upregulating HIF-1 α expression in brain tissue (63). Such research (77) has used a combination of EE stimulation and G-CSF in a neonatal rat HIBD model, showing that rats in an intervention group had significantly better adaptive, fine motor, and gross motor developmental indicators compared with the control group. These studies suggest that EE interventions may promote endogenous neurogenesis, leading to long-term improvements in neurological deficits among children with HIBD.

Anti-apoptotic drugs

High expression of the pro-apoptotic protein p53 in NSCs leads to disruption of endogenous neurogenesis after neonatal HIBD (78). Accordingly, anti-apoptotic drugs can maintain endogenous NSCs survival. The p53 pathway inhibitor pifithrin- α (PFT- α) (64) and the pro-apoptotic protein caspase-3 inhibitor Z-DEVD-fmk (65) significantly improve

endogenous NSCs survival after neonatal HIBD, thus promoting endogenous post-injury neurogenesis in the brain. Ample evidence (79) shows that PI3K/Akt and ERK play important roles in the process of endogenous neurogenesis as key anti-apoptotic signaling pathways, and that drugs activating these pathways promote endogenous neurogenesis by maintaining NSCs survival. For example, the anti-apoptotic drug atorvastatin (66) promotes proliferation, differentiation, and survival of NSCs by activating the PI3K/AKT and ERK pathways. Accordingly, drugs that act on anti-apoptotic pathways are expected to be clinically targeted for the treatment of neurological dysfunction after neonatal HIBD.

Anti-inflammatory drugs

Neuroinflammation has been demonstrated to inhibit neurogenesis and the presence of various inflammatory components, such as immune cells, cytokines, or chemokines, plays a role in regulating the survival, proliferation, and maturation of NSCs (80). It has been reported some anti-inflammatory drugs like minocycline (67) could alleviate depression-like symptoms by rescuing a decrease in neurogenesis in the dorsal hippocampus *via* blocking microglia activation, which may also apply to neonatal HIBD, because neuroinflammation is also one of the important injuries mechanisms of neonatal HIBD (81).

Endogenous growth factor analogues

Numerous growth factors can increase the proliferation of endogenous NSCs under a variety of conditions, thus promoting the endogenous neurogenesis process. For example, BDNF and its analogues GSB-106 and GSB-214 can upregulate the PI3K/Akt and ERK pathways to promote endogenous neurogenesis after brain injury and improve neurological function (68, 69). Other growth factors like epidermal growth factor, fibroblast growth factor, and VEGF can also promote NSCs proliferation and survival post-HIBD, thus promoting endogenous neurogenesis (70).

Conclusion

Currently, HIBD remains the leading cause of neonatal death and long-term neurological dysfunction. There is no effective treatment for the neurological sequelae caused by HIBD, neurogenesis is a promising therapeutic target for preventing HIBD-induced neurological sequelae in neonates. All of the treatments discussed above may improve the prognosis of neonatal HIBD through the target of neurogenesis. Thus, the search for optimized combined

neuroprotective treatments is urgent. Moving forward, the physiological processes of endogenous neurogenesis, their molecular pathways, and the intervention mechanisms of novel technologies should be investigated in greater depth. In these ways, the most appropriate treatments and technologies can be identified to alleviate the sequelae of neurological damage in children with HIBD, with a goal of also alleviating a heavy burden on their families and society.

Author contributions

AC and XC wrote and edited the article. JD searched for data. XZ reviewed and edited the article. All authors contributed to the article and approved the submitted version.

Funding

National Natural Science Foundation of China (82001166 and 82171186).

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Acknowledgments

The author would like to thank all the authors for their contributions to this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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