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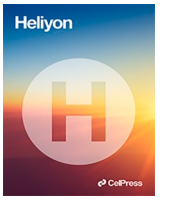

Review article

Mechanistic advances of hyperoxia-induced immature brain injury

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ABSTRACT

The impact of hyperoxia-induced brain injury in preterm infants is being increasingly investigated. However, the parameters and protocols used to study this condition in animal models lack consistency. Research is further hampered by the fact that hyperoxia exerts both direct and indirect effects on oligodendrocytes and neurons, with the precise underlying mechanisms remaining unclear. In this article, we aim to provide a comprehensive overview of the conditions used to induce hyperoxia in animal models of immature brain injury. We discuss what is known regarding the mechanisms underlying hyperoxia-induced immature brain injury, focusing on the effects on oligodendrocytes and neurons, and briefly describe therapies that may counteract the effects of hyperoxia. We also identify further studies required to fully elucidate the effects of hyperoxia on the immature brain as well as discuss the leading therapeutic options.

1. Introduction

Preterm births account for over 10 % of all births globally, affecting 15 million babies, of whom 1.1 million die; this represents 36 % of all neonatal deaths [1]. In recent decades, advances in perinatal medicine, obstetrics, and neonatal intensive care have increased survival rates of extremely preterm infants. However, 25%–50 % of severely preterm neonates struggle with memory, learning, executive function, voice development, and intelligence quotient [2–4]. Preterm birth affects individuals, their families, and wider society, and can lead to social and economic issues [5–7]. Studies have shown that encephalopathy of prematurity is associated with hyperoxia [8,9]. Therefore, oxygen is a crucial consideration in the care and treatment of premature neonates. Fetal brain development occurs under a low-oxygen environment, with a typical uterine PaO2 of 3.2 kPa (25 mmHg), or 70 % arterial oxygen saturation. Premature neonates are exposed to elevated oxygen levels following delivery [10]. Furthermore, extremely premature infants require additional oxygen during resuscitation and hypoxemia correction because of inadequate lung development, worsening the brain injury caused by excessive oxygen exposure. There is increasing interest in hyperoxia-induced brain damage, the pathogenesis of which has been shown to involve oligodendrocytes and neurons; however, the underlying mechanisms remain unknown. Therefore, this study examined the pathophysiological pathways involved in hyperoxia-induced immature brain injury, with a focus on oligodendrocytes and neurons.

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2. Experimental models

Suitable animal models are essential for mechanistic studies. Small animal models are cost-effective and appropriate for studying brain development, as rat and human brains develop similarly [11]. A previous study showed that postnatal days 2–10 (P2–P10) represent a period of rapid brain development in rodents [12]. P2–P5 in rodents is comparable to 23–32 weeks of gestation in humans [13]. Animal models of hyperoxia allow the simultaneous study of pulmonary and brain injuries [14], with most researchers inducing hyperoxia using 80 % oxygen. Concentrations of 85 % or higher have been used to study bronchopulmonary dysplasia (BPD) with brain injury. The majority of hyperoxia models initiate exposure between P0 and P10, and continued the exposure for between 2 h and 7 days. For the study of BPD with brain injury, the period of hyperoxic exposure can be up to 14 days (Table 1). Sex differences in adverse neurological outcomes have been identified in clinical studies and experimentally [15–19], with females having a superior prognosis to males [20]. A study by Donna et al. showed that stronger regulation of estrogen receptor alpha in female cells allowed them to better cope with oxidative stress [19]. However, owing to a lack of many studies confirming these findings and the difficulty of accurately screening newborn rodents, male-only rodent models of hyperoxia-induced brain injury are rarely adopted. Hyperoxia models must account for differences in sex, species, and genetic sensitivity to ensure their replicability and reliability [21].

Although rodent models have many advantages, such as short experiment times, low costs, large litter sizes, and low variability,

Table 1
Hyperoxia-induced brain injury animal model.

Years	O_2 (%)	HO onset	Duration	Species	Outcome	Ref
2003	≥80	P7	24 h	Wistar rat	Neuron injury	[22]
2004	40–80	P7	2 h-3d	synRAS &wt mice	Neuron injury	[23]
2005	80	P6	2–48 h	C57BL/6 $^{IRAK-4[-/-]}$ mice	Neuron injury	[24]
2005	> 95	P5	7 d	Sprague-Dawley	Neuronal plasticity injury	[25]
2006	80	P0	6 d	Sprague-Dawley	Microvascular degeneration, diminished brain mass	[26]
2006	80	P6	24 h	Wistar rat	Oligodendrocyte apoptosis	[27]
2008	80	P3, P6, P10	24 h	Wistar rat	Oligodendrocyte death	[28]
2008	80	P6	24 h	Wistar rat	Brain injury	[29]
2009	80	P6	2–48 h	Wistar rat	Brain injury	[30]
2010	80	P6	2–48 h	Wistar rat	Brain injury	[31]
2012	80	P3	24 h	Wistar rat	White matter injury	[32]
2012	80	P6	48 h	C57B/6J mice	White matter injury	[33]
2012	80	P6	12、48 h	Wistar rat	Brain injury	[34]
2012	95	P0	7 d	C57BL/6$^{(hEC-SOD)}$	Brain injury	[35]
2013	80	P6	48 h	C57B/L6	Periventricular white matter injury	[36]
2013	85	P2	12 d	C57BL/6 mice	Neurodevelopmental impairment	[37]
2014	80	P0	7 d	Sprague–Dawley	White matter injury	[38]
2014	80	P6	6–48 h	Wistar rat	Neuronal damage	[39]
2014	80	P6	24 h	Wistar rat	White matter injury	[40]
2015	80	P6	24 h	Wistar rat	Oligodendroglia development arrest	[41]
2015	80	P6	24 h	Wistar rat	Brain injury	[42]
2016	80	P6	24 h	Wistar rat	Brain injury	[43]
2016	80	P6	24 h	Wistar rat	White matter injury	[44]
2016	NA	P0	14 d	Sprague-Dawley	Brain injury	[45]
2017	80	P0	5 d	Sprague-Dawley	Hypomyelination and neuro-glial damage	[46]
2017	80	P0	5 d	NA	Brain injury	[47]
2017	80	P3	48 h	C57BL/6J	White matter injury	[48]
2017	80	P6	24–48 h	Wistar rat	Brain injury	[49]
2018	80	P6	24 h	Wistar rat	Cerebellar granule cell precursors and purkinje cells injury	[50]
2018	80	P6	24 h	SynRas mice	Ols apoptosis	[51]
2018	85	P0	1-14 d	Wistar rat	brain injury	[52]
2018	100	P0	4 d	Sftpc$^{(EC-SOD)}$ mice	Brain injury	[53]
2019	80	P0	7 d	C57BL/6J mice	Brain injury	[54]
2019	80	P1	14 d	Sprague-Dawley	Brain injury	[55]
2019	80	P6	24 h	Wistar rat	Cerebellar ols injury	[56]
2019	80	P6	24 h	Wistar rat	Ols apoptosis	[57]
2019	85	P1	10 d	C57BL/6J mice	Brain injury	[58]
2020	80	P3	48 h	Wistar rat	Hypomyelination	[59]
2020	80	P5	5 d	Wistar rat	Neuron apoptosis	[60]
2020	90	P0	7 d	C57B/6J mice	Brain injury	[61]
2021	80	P1	7 d	Sprague-Dawley	Brain injury	[62]
2021	85	P1	14 d	Sprague-Dawley	Brain injury	[63]
2022	80	P5	48 h	Mice	Interneuron density decreased	[64]
2022	80	P4	4 d	C57BL/6J	Hypomyelination	[65]
2022	85	P0	14 d	C57BL/6	Cerebrovascular function and neurogenesis impairments	[66]
2023	85	P1	7 d	Rats	Brain injury	[67]
2023	85	P1	14 d	GSDMD KO mice	Hippocampal brain injury	[68]
2023	95	NA	24 h	Sprague-Dawley	Brain injury	[69]

OLs: oligodendrocytes.

data from large animal models like nonhuman primates, pig, or sheep are urgently needed, especially for pathophysiological and translational studies [70]. Large animal models allow an enhanced simulation of hyperoxia-induced immature brain injury and monitoring of oxygen-related physiological indicators [71]. However, there have been few studies on hyperoxia-induced brain damage in large animal models.

The hyperoxic conditions used in cell studies are less varied than those of animal models, with most studies inducing hyperoxia with 80 % oxygen exposure continuously for 24 h. OLN-93 cells, a permanent oligodendroglia cell line, or primary oligodendrocyte precursor cells (OPCs) isolated from P0–P2 rat brain tissues are typically used (Table 2); few in vitro studies have examined neuronal cells.

The optimal onset and duration of hyperoxia in animal and cell culture models remain controversial. Both acute and chronic hyperoxia can damage neurons and oligodendrocytes (OLs) in the immature brain; however, the underlying mechanisms may differ. Animal models of chronic hyperoxia can be combined for simultaneous analyses of lung and brain injury to unravel potential interrelated pathways and screen for possible common therapeutic approaches.

3. Pathophysiology of hyperoxia-induced immature brain injury

3.1. Hyperoxia damages white matter in the immature brain

Several studies have demonstrated reduced myelin-related protein expression in the brains of animals exposed to hyperoxia. This decreased protein expression leads to myelin production issues and structural abnormalities, and resultant neurobehavioral problems [74–76]. Cranial magnetic resonance imaging in a rat model of hyperoxia showed that neonatal rats at P14 had increased average, axial, and radial brain diffusivity on diffusion tensor imaging, decreased fractional anisotropy, and delayed white matter development [32,36,44,51]. OLs, which contribute to the production of the myelin sheaths that encase neuronal axons and form white matter, are the main targets of hyperoxia-induced immature white matter injury (WMI). Therefore, we considered the effects of hyperoxia on OL death, proliferation, migration, and differentiation.

3.1.1. Hyperoxia-induced OL apoptosis

Apoptosis is the predominant mechanism by which OLs react to hyperoxia. Hyperoxia is believed to kill OPCs and immature OLs directly or indirectly, thereby reducing the number of mature OLs [27,28,32,44,51,56,77]. OL apoptosis is primarily caused by hyperoxia-induced oxidative damage and inflammation.

Hyperoxia causes oxidative stress by increasing reactive oxygen species (ROS) levels and decreasing antioxidant enzyme activity. The neonatal brain contains large amounts of unbound iron, which along with peroxides undergo Fenton reactions, generating ROS [78]. Normal ROS levels are required for cellular homeostasis [79]; hyperoxia-induced ROS production disturbs this balance. Excessive production of ROS, coupled with inadequate antioxidant activity, leads to oxidative stress, which causes DNA damage, mitochondrial membrane damage, and ultimately, apoptosis [80–82]. Moreover, the brains of P0–P7 neonatal rats contain OPCs and pre-OLs. These cells cannot scavenge ROS and their antioxidant systems are underdeveloped [83], rendering them more sensitive to oxidative stress and apoptosis, and ultimately leading to the development of WMI [84]. Fully differentiated mature OLs are more resilient to oxidative stress. Besides, antioxidant enzymes in the fetal brain increased during the third trimester. In particular, the expression levels of superoxide dismutase, catalase, and glutathione peroxidase increase by 150 % [85]. Previous studies have shown that superoxide dismutase 1 contributes to myelin formation [85,86], which is inhibited when superoxide dismutase 1 levels are decreased by hyperoxia [49]. It has also been observed that hyperoxia reduces glutathione peroxidase activity in living organisms, leading to decreased levels of glutathione and increased levels of oxidized glutathione in the immature brain. Consequently, free oxygen radicals accumulate in OPCs, promoting apoptosis [23,28,36]. These data emphasize that hyperoxia induces OL apoptosis, mainly through oxidative stress and inflammation. However, the mechanism by which excess oxygen crosses the blood-brain barrier and reaches the brain requires further investigation.

Table 2
Hyperoxia-Induced brain Injury cell culture model development.

Years	O_2 (%)	Duration	Cell	Outcome	Ref
2006	80	24–96 h	OLN-93	OPCs apoptosis	[27]
2008	80	0–24 h	OPCs	OPCs apoptosis	[28]
2012	80	24 h	OPCs and microglia	OPCs death	[32]
2014	80	24 h	OPCs	OPCs death	[40]
2015	80	?	Astrocytes	PDGFA reduction, and hypomyelination	[41]
2016	80	24 h	OPCs	OLs degeneration and maturation impaired	[44]
2016	80	24 h	OPCs	OPCs apoptosis	[72]
2019	80	24 h	OPCs, microglia and astrocytes	PDGFA improved OPCs proliferation and myelination	[56]
2020	80	24 h	OPCs	male-derived OPCs maturation impairment	[20]
2021	80	24 h	OPCs	male-derived OPCs maturation impairment	[19]
2021	80	48 h	OLN-93 and astrocytes	OPCs death	[73]

OPCs: Oligodendrocyte progenitor cells; PDGFA: Platelet-derived growth factor-A.

3.1.2. Hyperoxia inhibits OL proliferation

The effects of hyperoxia on OL proliferation have been extensively studied. Using a mouse model involving exposure to 80 % oxygen at P6–P7, Schmitz et al. reported a significant reduction in brain white matter $NG2^{+}Ki67^{+}$ OPCs [40,87]. Scheuer et al. made the same observation in cerebellar white matter [41]. Hyperoxia also inhibits the proliferation of neural stem cells and glial cells [66,

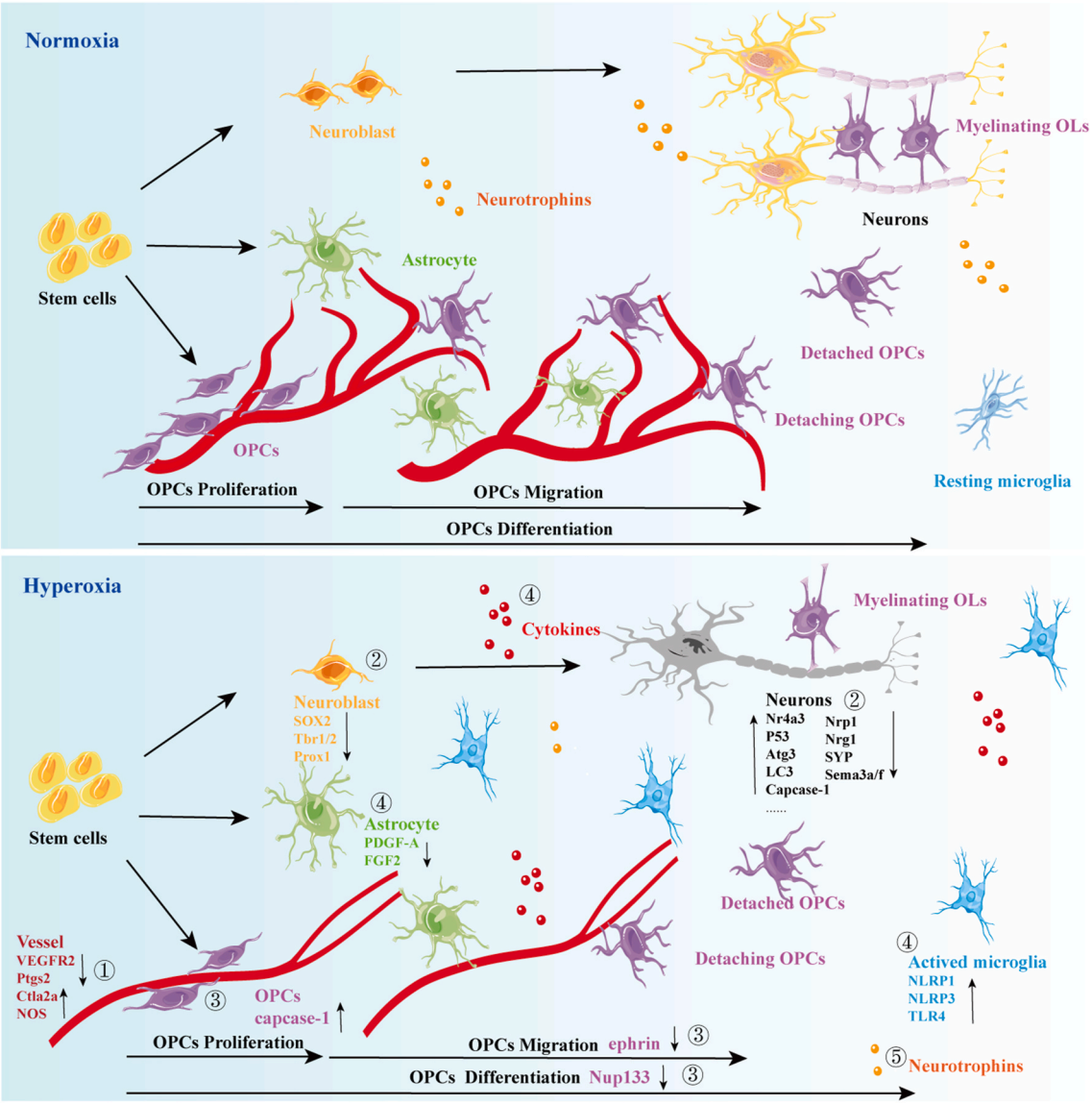

Fig. 1. Hyperoxia induces brain injury through the following mechanisms: ① decreased number and density of cerebral vessels. The expression of VEGF2 and Ptgs2 decrease, while the expression of Ctla2a and NOS increase; ②abnormal neural self-renewal, and neuronal death. Expression of autophagy and apoptosis markers increase, while expression of neuronal plasticity regulating factors (Nrp1, Nrg1, SYP, and Sema3a/f) and neuroblast transcriptional factors (SOX2, Tbr1/2, and Prox1) decrease; ③abnormal proliferation, migration, differentiation, and myelination of OPCs. Expression of apoptosis markers increase, while expression of the migration-related ephrin and the differentiation-related Nup133 decrease; ④increased microglia activation and inflammation. Expression of inflammasome components (NLRP1, NLPR3, and TLR4) and cytokines increase, while PDGF-A and FGF2 decrease in astrocytes; and ⑤decreased neurotrophins secretion. ↑: increased expression; ↓: decreased expression. Atg3: autophagy related 3; Ctla2a: T lymphocyte-associated protein 2 alpha precursor; FGF2: fibroblast growth factor 2; LC3: microtubule-associated protein 1A/1B-light chain 3; NLRP1: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein 1; NLRP3: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein 3; NOS: nitric oxide synthase; Nr4a3: nuclear receptor subfamily 4, group A, member 3; Nrg1: neuregulin 1; Nrp1: neuropilin-1; Nup133: nucleoporin 133; OLs: oligodendrocytes; OPCs: oligodendrocyte progenitor cells; PDGF-A: platelet derived growth factor-A; Prox1: prospero-related homeobox protein 1; Ptgs2: prostaglandin endoperoxide synthase 2; Sema3a/f: semaphorin 3a/f; SOX2: sex determining region Y box protein 2; SYP: synaptophysin; Tbr1/2: T-box brain protein 1/2; TLR4: Toll-like receptor 4; VEGF2: vascular endothelial growth factor receptor 2.

88,89]. Endesfelder et al. reported that hyperoxia decreases the expression of the transcription factors sex determining region Y box protein 2, T-box brain protein 1/2, and prospero-related homeobox protein 1 in OLs [90]. However, the exact mechanism through which hyperoxia inhibits OL proliferation remains unclear.

3.1.3. Hyperoxia inhibits OL migration

OPCs originate from differentiated neural stem cells in the ventral forebrain and migrate throughout the central nervous system on cerebrovascular scaffolds. After migration OPCs detach from cerebral arteries and differentiate into mature OLs [91]. Cerebrovascular endothelial cells regulate OPC migration and differentiation through Wnt signaling; therefore, cerebrovascular damage may result in WMI.

Hyperoxia prevents OPCs migration, thereby reducing the number of fully mature OLs [92]. A recent study found that hyperoxia reduced microvessel density and branching in the immature brain [66]. This effect persists throughout puberty in rats, causing neurobehavioral abnormalities [26,66]. Hyperoxia may inhibit OPC migration by stimulating microvascular nitric acid production. In the endothelial and perivascular cells of the immature brain, nitric oxide synthase and vascular endothelial growth factor receptor-2 are upregulated, reducing microvessel density [22,26]. Nitric oxide synthase inhibitors increase the expression of vascular endothelial growth factor receptor-2, eliminating cerebral vascular obstruction [26]. The poor autoregulatory capacity of the immature cerebrovascular system may also contribute to the effects of hyperoxia. Hyperoxia may directly influence mediators such as prostaglandin-endoperoxide synthase 2 (PTGS2) and cytotoxic T lymphocyte-associated protein 2 alpha (CTLA2α). PTGS2 dilates cerebral blood vessels and is produced and released in response to stimulation. In rat models, hyperoxia lowers the expression of *Ptgs2*, which is linked to cerebral vascular regulatory impairment, and decreases blood flow in the brain [93,94]. In addition, the expression of the antiangiogenic factor CTLA2α is upregulated in the brains of rats exposed to hyperoxia [26,66]. Ephrin receptor signaling, which is associated with OL migration, decreased significantly after 24 h of hyperoxia exposure, providing further evidence that hyperoxia inhibits OL migration [95].

Despite the many studies that have been conducted into this topic, little remains known about how hyperoxia affects the function of cerebrovascular cells and OL migration. Investigating OL migration is a potential approach for future studies on the etiology of hyperoxia-induced WMI.

3.1.4. Hyperoxia induces OL differentiation and maturation dysfunction

OL differentiation can be divided into four stages: OPCs, pre-OLs, immature OLs, and mature OLs. The differentiation of OPCs into mature OLs plays a crucial role in the generation of myelin sheaths around axons. Oxidative stress reduces the expression of genes that promote OPC differentiation (such as *Olig1*, *Olig2*, and *Sox10*) and increases the expression of differentiation-inhibitory genes (such as *Id2* and *Id4*), thereby hindering OL maturation [96]. A previous study showed that exposure to hyperoxia at P3–P5 increases the number of $NG2^{+}$ OPCs and decreases myelin basic protein production, suggesting that hyperoxia disrupts OL differentiation and maturation [48,97]. Notch signaling is also activated in the rat brain after hyperoxia, and a γ-secretase inhibitor has been shown to ameliorate the detrimental neurological effects of hyperoxia by interfering with Notch signaling [48,97]. Furthermore, nucleoporin 133 signal transduction has been shown to be important for hyperoxia-induced dysfunctional OL differentiation. The expression of nucleoporin 133 and its downstream target nuclei respiratory factor-1 in male-derived OPCs were downregulated by hyperoxia, resulting in the disruption of OL differentiation and maturation [19,73,98]. Carcinoembryonic antigen-related cell adhesion molecule 1 is a multifunctional protein that affects the proliferation and differentiation of numerous cells; its expression is regulated by hyperoxia, leading to reduced myelin production [99]. Interestingly, Brehmer et al. [32] hypothesized that hyperoxia induces OL apoptosis and that lipopolysaccharide is responsible for the disruption of OL differentiation.

Axonal lesions reducing the myelin sheath have been observed in rat brains after hyperoxia. Loss of axon-oligodendrocyte integrity caused by hyperoxia can cause permanent WMI [36]. Although mature OLs are resistant to oxidative stress, it remains unclear whether hyperoxia directly causes myelin damage via other mechanisms. The pathogenesis of hyperoxia-induced immature WMI is complex (Fig. 1). Owing to the lack of uniformity in the initiation and duration of hyperoxia in rodent models, stages of OL development may vary among studies. Furthermore, the use of diverse markers and experimental procedures across studies can lead to the identification of disparate mechanisms. Several pathways may be involved in the pathophysiology of hyperoxia-induced brain injury.

3.1.5. Hyperoxia affects OLs through microglia and astrocytes

Microglia and astrocytes contribute to OL differentiation and myelination [84,100]. Microglia can also promote myelin production and regeneration in response to demyelination, mostly through the secretion of growth factors [101]. Notably, microglial overactivation may reduce the number of OPCs and slow OL differentiation and maturation [102]. Many studies have shown that hyperoxia activates microglia by upregulating ionized calcium binding adapter molecule 1 protein and releasing interleukin (IL)-1β in the immature brain [40,44]. Minocycline prevents hyperoxia-induced microglial activation, reduces OL death, and promotes OPC proliferation and maturation [40].

Astrocytes provide essential lipids for myelin formation [103]. Gap junctions between astrocytes and OLs aid in myelin synthesis. Astrocytes become activated and neurotoxic under hyperoxic conditions, enhancing OPC proliferation, but inhibiting OL maturation, resulting in OL death [91,104,105]. Hyperoxia decreases the levels of astrocyte-associated growth factors such as fibroblast growth factor-2 and platelet-derived growth factor A in the immature brain [28]. Minocycline increased the hyperoxia-induced expression of platelet-derived growth factor A in astrocytes, mitigating the detrimental effects on OLs [56]. Furthermore, hyperoxia elevates the expression levels of inflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-6, IL-10, and IL-18 in the brain [24,30–32,49,77,106,107], which can affect OL survival, differentiation, and maturation [108]. Nevertheless, hyperoxia is not thought to destroy the

blood-brain barrier, and peripheral immune cells cannot therefore induce immature brain injury [44].

Overall, the studies described above show that abnormalities in OL survival, proliferation, migration, and differentiation are responsible for hyperoxia-induced WMI. The main mechanisms include oxidative stress, inflammation, and cerebrovascular abnormalities. More studies are needed to confirm the effects on OL migration and differentiation and to explore the mechanisms underlying hyperoxia-induced WMI, using male animals and cells when necessary. Moreover, other glial cells are also directly or indirectly involved in the pathophysiology of hyperoxia-induced WMI; this involvement requires further study.

3.2. Hyperoxia damages immature brain gray matter

3.2.1. Hyperoxia induces neuron death

Hyperoxia damages both immature white and gray matter. Research on gray matter injury has mostly focused on neurons in the gray matter. Both white and gray matter injuries can result in neurobehavioral alterations [24,51]. Despite variations in hyperoxia models, acute and chronic hyperoxia have been shown to be associated with increased neuronal death in diverse regions of the immature brain. The primary characteristic of acute hyperoxia is a decrease in the number of progenitor cells, immature neurons, and mature neurons. In contrast, chronic hyperoxia is characterized by a decrease in the volume of the hippocampus and cerebellum [37,39]. Hyperoxia-induced neuronal death primarily involves autophagy, pyroptosis, and apoptosis. A previous investigation revealed that the autophagy-related proteins autophagy related (ATG)3, ATG5, ATG12, BECLIN-1, microtubule-associated protein 1A/1B-light chain (LC)3, LC3A-II, and LC3B-II were upregulated in the brains of newborn rats at P6. After 24 h of hyperoxia, these proteins are downregulated, suggesting the occurrence of neuronal autophagy [109]. The protein gasdermin D is pivotal in pyroptosis. Naga et al. [68] found that knocking out gasdermin D reduced hyperoxia-induced cell death, suggesting that this protein is involved in the growth, development, and differentiation of neurons in the neonatal mouse hippocampus. However, few studies have investigated the relationship between autophagy and pyroptosis in immature brain injury. Whether hyperoxia can cause death in other ways requires further investigation.

Hyperoxia-induced neuronal apoptosis is primarily mediated by oxidative stress and inflammation. Several studies have shown that increased ROS levels following hyperoxia can directly trigger neuronal apoptosis by modulating sirtuin 1, p53, and other pathways [62,80–82]. Furthermore, reactive nitrogen is a significant factor in neuronal apoptosis [22]. Disruption of GABAergic neuron homeostasis is also caused by oxidative stress, which leads to neuronal apoptosis [110]. Hyperoxia upregulates the expression of inflammatory mediators, including nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein (NLRP)1 and NLRP3, in the immature brain [24,30–32,49,61,77]. Micili et al. demonstrated that hyperoxia increased NLRP3, caspase-1, and IL-1β levels in mouse brain [61]. Another study showed that caspase-1 inhibition reduced NLRP1 activation and neuron apoptosis [58]. The levels of caspase-1 and its downstream effectors, namely IL-1β, IL-18, and IL-18 receptor α, are notably increased in the immature brain. In addition, recombinant human IL-18 binding protein effectively mitigated neuronal apoptosis induced by hyperoxia [24]. It has also been suggested that TNF-α, IL-6, and IL-10 play a role in hyperoxia-induced neuronal apoptosis [24,30–32,49,77,106,107]. Hyperoxia triggers an inflammatory response via Toll-like receptor 4, knockout of which can prevent hyperoxia-induced neuronal apoptosis and cognitive impairment [111].

Neurotrophins include nerve and glial cell-line-derived factors that contribute to the survival, migration, and development of neurons. Hyperoxia reduces the expression of neurotrophic factors, glial cell line-derived neurotrophic factors, and associated signaling in the rodent brain, resulting in neuronal apoptosis [29,31,112,113]. Impaired interactions between OLs and neurons following hyperoxia can also lead to abnormal neurobehavioral functions [64].

To date, three pathways of neuronal death have been reported to be involved in hyperoxia-induced brain injury: autophagy, pyroptosis, and apoptosis. However, the relationships among the different pathways in immature brain injury remain unclear.

3.2.2. Hyperoxia affects neurogenesis

Two well established mechanisms contribute to the effect of hyperoxia on gray matter: neuronal death and disordered neurogenesis [64,66,90,114–116]. Endesfelder et al. found that the number of apoptotic cells in the cerebral cortex, hippocampus, and central gray matter increased after 24 or 48 h of exposure to 80 % oxygen, and the expression of transcription factors associated with immature, progenitor, and mature neurons decreased [39]. Subsequent studies have verified these results and additionally demonstrated a reduction in the expression of neural plasticity regulators such as neuropilin-1, neuregulin 1, synaptophysin, and semaphorin 3a/f [66,116,117]. Furthermore, Fedorova et al. [118] observed that hyperoxia reduces neuronal proliferation and upregulates the expression of nuclear receptor subfamily 4 group A member 3 in the subventricular zone of mice. These studies demonstrate the association between hyperoxia and disordered neurogenesis, and show the numerous factors involved. Whether hyperoxia exerts different effects on different brain zones and neuron types requires further research, as does the mechanism by which hyperoxia regulates transcription factors that affect neurogenesis.

3.3. Organ cross-talk in hyperoxia-induced immature brain injury

3.3.1. Lung-brain axis

Hyperoxia affects several other organs in addition to the brain. Preterm infants with BPD typically exhibit poor neurodevelopmental outcomes. Immature brain injury is observed in animal models of BPD. Therefore, most studies have focused on lung and brain interactions in hyperoxia. A study by Kim et al. revealed a positive correlation between limited alveolarization and inadequate myelination, as well as increased neuronal death, in an animal model of BPD and brain injury [45]. Increased proinflammatory

cytokine levels and decreased vascular endothelial growth factor expression in lung tissues were also found, and were associated with reduced brain weight, supporting the hypothesis that lung injury may aggravate adverse neurodevelopmental outcomes [45]. A recent study found that alveolar type II epithelial cells in hyperoxia-injured lungs released exosomes, which could enter the circulation, cross the blood-brain barrier, and cause brain injury [63]. Boris et al. identified the reduced bioavailability of circulating insulin-like growth factor-1 as a possible link between lung and brain developmental disruptions [119]. Activation of hypoxia-inducible factor 1-alpha, p53 signaling pathways, and the NLRP1 inflammasome may cause neuronal apoptosis though the lung–brain axis under hyperoxic conditions [58,120]. These studies suggest that extracellular vesicles migrating through the circulation may induce inflammation during hyperoxia-induced brain injury. However, Lithopoulos et al. observed that the arterial oxygen saturation levels in mice exposed to hyperoxia remained within the normal range, and therefore speculated that hyperoxia affects the lungs and brain independently [66]. Overall, it remains unclear whether immature brain injury is a direct result of hyperoxia or a consequence of lung injury mediated by the lung-brain axis. Further research is needed on the role of the lung–brain axis in hyperoxia-induced brain injury.

3.3.2. Gut–lung–brain axis

Metabolic processes play an important role in hyperoxia-associated neonatal diseases [121], and the involvement of the gut microbiome in these metabolic processes is receiving increasing attention. Functional metagenomic and metabolomic analyses of hyperoxia-induced gut dysbiosis have shown that hyperoxia leads to gut dysbiosis by eliminating beneficial oxygen-intolerant bacteria, suppresses unsaturated fatty acid metabolism in the gut, and inhibits the hypoxia-inducible factor 1 and glucagon signaling pathways in the serum [122]. Wang et al. showed that an imbalance of gut microbiota affects brain development and function in hyperoxia via the gut-brain axis [123]. Furthermore, Ahn et al. observed that the relative abundance of Proteobacteria increased in the brain, lungs, and gut of neonatal rats, but that these changes were substantially inhibited by stem cell transplantation [124]. A potential role for IL-6 in the regulation of the gut-lung-brain axis was also suggested by this study [124]. Cytokines and metabolites may therefore be vital mediators of the gut–lung–brain axis in hyperoxia-induced brain injury. The gut-lung-brain axis is depicted in Fig. 2. Despite the limited number of studies performed in this area to date, the gut-lung-brain axis is an important future treatment target for neonatal diseases. The relationship between other glial cells and the gut-lung-brain axis needs to be explored in future studies, as does the involvement of other organs, such as the heart, in hyperoxia. The interactions between these organs may be a promising research topic.

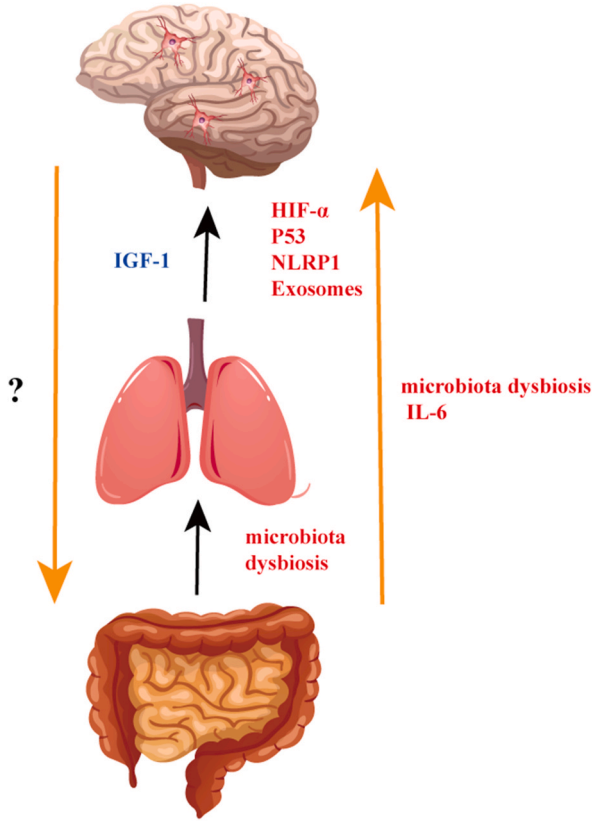

Fig. 2. Potential mediators of the gut-lung-brain axis in hyperoxia-induced brain injury. Blue indicates decreased expression; red indicates increased expression; ? indicates unknown. HIF: hypoxia-inducible factor; IGF-1: insulin-like growth factor 1; IL-6: interleukin 6; NLRP1: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein 1.

3.4. Therapeutic approaches for hyperoxia-induced immature brain injury

The damage to the immature brain caused by hyperoxia is well recognized and strategies have been adopted to avoid inducing hyperoxia in clinical practice. However, some premature infants require hyperoxic treatment. Therefore, it is necessary to identify drugs that can safely and effectively treat hyperoxia-induced brain injury in newborns. Currently, no such therapy is available. Here, we summarize the current therapeutic approaches for hyperoxia-induced immature brain injury, which involve the use of antioxidants, anti-inflammatory drugs, hormones, and mesenchymal stem cells (MSCs) transplantation.

3.4.1. Antioxidants and anti-inflammatory drugs

Various drugs, such as caffeine, nitric oxide, dextromethorphan, minocycline, donepezil, galantamine, and fingolimod, are neuroprotective in hyperoxia-induced brain injury through anti-inflammatory, antioxidant, and antiapoptotic effects.

Caffeine, a nonspecific adenosine receptor antagonist, is widely used in neonatal care [125]. In animal models of hyperoxia-induced brain injury, caffeine has been shown to reduce oxidative stress markers, promote antioxidative responses, downregulate chemokine and inflammatory cytokine expression, reduce expression of apoptotic molecules, and inhibit extracellular matrix degeneration [49]. However the clinically optimal dose and timing of caffeine administration remains controversial [125].

Nitric oxide plays a vital role in pulmonary vascularization, airway branching, and neuronal transmission [126,127]. It is a key mediator of the vascular endothelial growth factor pathway, and angiogenesis may be involved in the reduced vulnerability of the immature brain to injury following treatment with inhaled nitric oxide (iNO) [128]. iNO promotes angiogenesis and maturation in the immature brains of rats [128]. Moreover, iNO also exhibits neuroprotective effects in hyperoxia-induced immature brains through the early upregulation of brain-derived neurotrophic factor, reducing inflammation and OL death, and therefore increasing the density of mature OLs and myelination in the white matter of immature brains, which has been associated with improved learning ability [38]. However, iNO is thought to act on the lungs rather than directly on the brain. Therefore, the effect of iNO on the lung–brain axis seems to be a plausible explanation for its protective effects. Further experimental and clinical studies are required to establish the optimal dose and timing of iNO administration.

Dextromethorphan is a high-affinity sigma-1 receptor agonist, low-affinity N-methyl-*d*-aspartate receptor antagonist, and voltage-gated calcium channel antagonist, with additional anti-inflammatory and antioxidative properties [129]. Dextromethorphan has the capacity to increase cell viability and reduce hyperoxia-induced OL death in vitro and in vivo [130]. Minocycline is a widely used tetracycline antibiotic recently shown to have neuroprotective properties in animal models of diverse brain injuries. It protects against hyperoxia-induced WMI through direct protection of OLs and by microglial inhibition [40]. Donepezil, an acetylcholinesterase inhibitor, significantly reduces the hyperoxia-triggered activity of acetylcholinesterase, neural cell death, and upregulation of proinflammatory cytokines, attenuating the detrimental effects of hyperoxia in the immature brain [131]. Recently, galantamine, another acetylcholinesterase inhibitor, was found to inhibit hyperoxia-induced proliferation of microglia and astrocytes, proinflammatory cytokine production, and nuclear factor κB activation [132]. Moreover, fingolimod, a sphingosine-1-phosphate receptor, has been found to exert protective effects in different neural cell types by reducing inflammation and oxidative stress following neonatal hyperoxia. However, dexamethasone [133], lycopene [134], ketamine [135] and coenzyme Q10 [136] have been shown to offer no protection against neonatal rat brain injury induced by hypoxia.

Despite increasing knowledge of the pathophysiology of hyperoxia-induced brain injury, therapeutic options remain limited. Many drugs with protective effects against nervous system diseases, such as Alzheimer's disease and multiple sclerosis, have been proven effective in animal models of hyperoxia-induced brain injury. Therefore, known drugs with neuroprotective effects may represent potential future treatments.

3.4.2. Hormones

Endogenous hormones such as erythropoietin (EPO) and estradiol (E2) have been shown to have neuroprotective effects in hyperoxia-induced brain injury. EPO and its receptors are expressed by many cell types, including neurons, OLs, microglia, and astrocytes. Several studies have demonstrated the protective effects of both single and multiple EPO treatments on hyperoxia-induced brain injury [30,31,43,59]. In an animal model of hyperoxia-induced brain injury, EPO significantly reversed the reduction in neuronal plasticity [43], reduced oxidative stress and inflammation [30], limited stressor-inducible changes and cholinergic functions [31], and promoted OL maturation [59]. In addition, multiple animal and clinical in vitro and in vivo studies have shown the promise of EPO for the treatment of neurodegenerative diseases [137]. However, EPO treatment carries the risk of adverse effects on the hematopoietic system [137]. The clinical usefulness of EPO therefore remains to be determined, and may depend on the development of novel EPO analogs with more specific actions and fewer side effects.

E2, a form of the estrogen hormone, has neuroprotective properties in hyperoxia induced in vitro. E2 protects OPCs from hyperoxia-induced apoptosis by downregulating paired immunoglobulin-like receptor B [72] and preventing their migration [95], thereby reducing microglial activation and oxidative stress [19]. These properties result from the activation of E2 receptors and crosstalk with intracellular signaling pathways [138]. However, other studies have found no protective effects of E2 in mouse C8-D1A astrocytes exposed to hyperoxia [139]. This could be explained by the fact that high levels of fetal zone steroids circulate until term in preterm infants [139], meaning that preterm neonates have a specific hormonal milieu. This milieu, and the effect of gestational hormone supplementation on the immature brain must be explored in more detail [140].

3.4.3. MSCs

MSCs differentiate into tissue-specific cells under specific conditions. Thus far, MSCs have shown neuroprotective properties in

experimental animal models of brain injury [141]. Young et al. transplanted MSCs intratracheally at P5 into Sprague-Dawley rats exposed to hyperoxic conditions for 14 days [45] and found that MSCs simultaneously attenuated hyperoxic lung and brain injuries, attenuating the reduction in brain weight and myelin basic protein through anti-inflammatory effects [45]. Another study suggested that MSCs attenuate hyperoxia-induced dysbiosis in the lungs, brain, and gut primarily through antioxidative and anti-inflammatory effects [124]. As limited studies have been conducted, the underlying mechanisms remain unclear, and further studies are required to confirm these effects and identify the potential molecular mechanisms involved. Moreover, research should attempt to identify a safer route of MSC administration, such as transnasal transplantation.

4. Conclusion

Hyperoxia-induced immature brain injury is a major issue in preterm births. Animal models of hyperoxia-induced brain injury lack consistency, and there is ongoing controversy regarding the optimal onset and duration of hyperoxia. Hyperoxia-induced neurological impairment mostly manifests as damage to white and gray matter in the immature brain. However, the precise underlying mechanisms remain unclear. Immature brain injury resulting from hyperoxia may involve various processes, including oxidative stress, inflammation, and cerebrovascular abnormalities. Moreover, investigation of interorgan communication is a potential avenue for future research. Finally, although pharmaceutical and stem cell therapies appear promising strategies to limit hyperoxia-induced brain injury, their therapeutic value and optimal treatment regimens have not yet been confirmed in clinical settings. Therefore, clinical and preclinical research, including in large animal models, is required.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

CRediT authorship contribution statement

Yue Song: Writing – review & editing, Writing – original draft, Conceptualization. **Changqiang Yang:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

.The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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