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Oxidative Stress Diseases Unique to the Perinatal Period: A Window into the Developing Innate Immune Response

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Abstract

The innate immune system has evolved to play an integral role in the normally developing lung and brain. However, in response to oxidative stress, innate immunity, mediated by specific cellular and molecular programs and signaling, contributes to pathology in these same organ systems. Despite opposing drivers of oxidative stress, namely hyperoxia in neonatal lung injury and hypoxia/ischemia in neonatal brain injury, many of the same players such as toll-like receptors, NF κ B, and MAPK cascades play similar roles to damage tissue. In this review, we consider recent insights into the innate immune response to oxidative stress in both neonatal and adult models to better understand hyperoxic lung injury and hypoxic-ischemic brain injury across development and aging. These insights support the development of targeted immunotherapeutic strategies to address the challenge of harnessing the innate immune system in oxidative stress diseases of the neonate.

Graphical abstract

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Oxidative Stress: Injury Provides a Window into the Innate Immune Response

It could be argued that birth represents the moment in life at which a human being encounters the highest risk of injury secondary to oxidative stress. Throughout gestation, normal development proceeds in an oxygen tension that would kill most adult humans within a matter of minutes.¹ With birth, the environment instantly changes to one rich in oxygen and its associated toxicities. Furthermore, a risk for interruption of normal blood and oxygen delivery occurs with the transition away from placental support for gas exchange. Important observations made during this transition provide insight on oxygen toxicity, the innate immune response to oxidative stress, and how these responses are unique to the perinatal period.

Clinically, two diseases directly related to “oxidative stress” and exclusively encountered in the perinatal period exemplify these lessons – bronchopulmonary dysplasia (BPD) and hypoxic ischemic encephalopathy (HIE). Bronchopulmonary dysplasia is the most common morbidity complicating preterm birth and affects 10,000–15,000 infants per year in the United States alone.² Those born at the earliest gestation ages (<28 wks) are at the highest risk of developing BPD, and due to increased survival of these babies, the incidence of BPD is increasing.³ Babies at the highest risk of developing BPD are born in the late canalicular/early sacular stage of lung development, often resulting in poor gas exchange and hypoxemia.⁴ It is clear that supplemental oxygen delivered to the premature lung to overcome this hypoxemia contributes to the pathogenesis of BPD,⁵ and simply the cumulative oxygen exposure over the first two weeks of life predicts the development of this chronic disease.⁶

HIE often results from peripartum hypoxic and/or ischemic events and has been estimated to account for one in five neonatal deaths worldwide, leading to 717,000 deaths in 2010.⁷ Clinically, encephalopathy is characterized by disturbed neurological function shortly after birth, evidenced by decreased level of consciousness, depressed tone and reflexes, possibility of seizures, and often with impaired respiratory effort.⁸ Survivors of moderate to severe HIE are at risk for long term motor, behavioral and cognitive impairments.⁹ Whereas hyperoxia contributes to the pathogenesis of BPD in preterm infants, HIE results from decreased oxygen and metabolic substrates as a result of ischemia, and is classically defined as occurring in term (>37 weeks gestation) and near-term infants (36–37 weeks gestation). Therefore, while preterm infants (<36 week gestation) are certainly at risk for hypoxic brain injury, this review will focus on HIE-related brain injury in term and near-term infants.

Thus, these “oxygen radical diseases” of the neonate period provide a unique opportunity to study a unique aspect of perinatal immunology.¹⁰ The ultimate goal remains understanding how an innate immune response to oxidative stress unique to the perinatal period protects against, and potentially contributes to, these disease states. Through this effort, we may be able to apply what has been learned in other disease states and develop therapeutic strategies. In this review, we will use clinical and pre-clinical studies of BPD and HIE to demonstrate an emerging body of evidence that support the extraordinary presence of perinatal innate immune response to oxidative stress.

The response to oxidative stress varies across development and aging – lessons from hyperoxic lung injury

Pulmonary injury induced by breathing high percentages of inspired oxygen was first described nearly 250 years ago.¹¹ Experiments over the first part of the last century revealed that younger animals were relatively “resistant” to the toxic effects of oxygen when compared to their adult counterparts. This was true for turtles,¹² rats,¹³ fruit flies,¹⁴ and cats.¹⁵ In 1957, it was noted that neonatal rats were resistant to oxygen toxicity.¹³ This observation was made during studies into relationship between oxygen and retrolental fibroplasia (now known as retinopathy of prematurity). The investigators were attempting to expose the newborn rat to hyperoxia to determine the effect on the immature retinal vessels, however, the studies could not be completed due to the pulmonary toxicity noted in the nursing dams. Exposed to oxygen at the same time, neonatal and adult rats exhibited very different susceptibility to injury. After struggling with this for “several months,” the investigators devised a creative solution and completed their studies. From there, the unique resistance of neonatal animals to oxygen toxicity was demonstrated in various species,¹⁶ including mice.¹⁷ And while neonatal animals are resistant to mortality secondary to oxygen exposure, multiple studies have demonstrated that lung injury does occur and that normal lung development is disrupted, resulting in a “BPD phenotype.”¹⁸

In 1954, Gerschman and colleagues proposed that similar to radiation poisoning, oxygen toxicity resulted from direct injury to tissues from excess generation of oxidizing free radicals.¹⁹ Further work demonstrated that during hyperoxia, oxygen free radicals are produced by the electron transport chain in the mitochondria and by membrane-bound NADPH oxidase.²⁰ In the adult lung exposed to hyperoxia, injury from increased free radical production manifests as endothelial and alveolar cell destruction, pulmonary edema, and death.²¹ In the neonatal lung, arrested alveolar development leads to long-term pulmonary dysfunction.^{18, 22}

Given the mechanism of injury, interest grew in defining the role of a protective anti-oxidant response.²³ With these studies, differences in hyperoxia-induced antioxidant enzyme expression was noted between neonatal and adult animals.^{16, 24, 25} These findings suggested the presence of a developmentally-regulated, protective and programmed response to hyperoxia. Consequently, the signaling mechanisms linking hyperoxia to this response became an area of intense study. In this way, nature has provided a convenient framework to study the mechanisms underlying hyperoxia-induced lung injury. How could it be that the

same insult, given to a host different only in developmental stage, results in remarkably different phenotypes? Answering these questions necessitates study of the sensing and signaling pathways induced by hyperoxia. Work done in this area has implicated key differences between the neonate and adult innate immune response. By understanding these signaling mechanisms, and differences that exist between the neonate and adult, could reveal potential therapeutic targets meant to enhance the neonatal protective response and/or attenuate the damaging adult response.

Responding to Hyperoxia: What the Transcriptional Response Tells Us About Signaling and Sensing

For the purposes of this review, we will work backwards from the nucleus to the cell surface. With regards to developmental differences in hyperoxia-induced lung injury, more is known about the transcription factors involved. Perhaps not surprisingly, many of these transcription factors are central regulators of the innate immune response. Multiple signaling pathways have been interrogated in the setting of hyperoxia, many of which overlap with innate immune signaling. To provide a comprehensive review of every transcription factor and signaling pathway involved in the response to hyperoxia goes beyond the scope of this work. Instead, we will focus on the transcription factor NF κ B, and MAPK signaling as examples of developmentally regulated differences in the response to hyperoxia. We will conclude with a brief review of what is known regarding how hyperoxia triggers the innate immune response.

Redox sensitive transcription factors: different roles at different developmental stages

Multiple redox sensitive transcription factors have been implicated in the pulmonary response to oxygen including activator protein 1 (AP-1), nuclear factor, erythroid 2 related factor 2 (Nrf2) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF κ B).^{26, 27} Hyperoxia induced Nrf2 activity is protective both neonatal and adult animals.^{28, 29} In contrast, previous studies have demonstrated that maturational differences in hyperoxia-induced pulmonary activation of AP1 and NF κ B.^{30, 31} The transcription factor NF κ B is a key component of the innate immune system has been termed the “master regulator of the inflammatory response,” and one could hypothesize that targeting its activity in the perinatal lung could be beneficial. Certainly, inhibiting NF κ B activity has been actively pursued as a way to prevent injury associated with inflammation.^{32–34} In an elegant set of experiments, Dennery and colleagues showed us that neonatal mice demonstrate unique pulmonary hyperoxia-induced NF κ B signaling kinetics and downstream target gene expression.³⁵ Specifically, hyperoxia-induced NF κ B activation is protective, and stronger in intensity and longer in duration in the neonatal compared to adult lung. Importantly, when NF κ B activity is attenuated in the neonatal lung, their relative protection from injury disappears. In culture, hyperoxia-induced NF κ B activation occurs in macrophages, epithelial cells, endothelial cells, cultured perinatal lung epithelium, and developing mouse lung mesenchyme in cultured lung explants.^{26, 36, 37} Hyperoxia induces NF κ B activation in fetal rat lung fibroblast via a unique signal pathway not active in similarly exposed adult cells.³⁸ Highlighting its unique role in the developing lung, *complete NF κ B inhibition* disrupts

normal lung development.^{39, 40} Clearly, NFκB plays a unique role in the perinatal period that must be separately considered before manipulating its activity.

Signaling

How hyperoxia signals changes in transcription has long been a subject of debate. It is possible that observed transcriptional changes are secondary to programmed signaling, or dysregulation of cellular signaling pathways, or a combination of both. The implications are important: if the response is programmed, and either injurious or protective, therapies would aim to enhance or attenuate that response. If the signaling is dysregulated, therapies would aim to restore homeostatic cellular signaling mechanisms. The targets that ROS could affect to dysregulate normal cell signaling are nearly infinite, and a discussion here goes beyond the purpose of this review. We will focus instead on redox sensitive signaling pathways known to affect the response to hyperoxia.

Developmental differences in hyperoxia-induced pulmonary MAPK signaling

The role of two mitogen-activated protein kinase (MAPK) cascades, extracellular signal-regulated kinase (ERK) 1/2 and c-Jun N-terminal kinase (JNK) have been well studied in pathogenesis of hyperoxia-induced lung injury.⁴¹ The ERK 1/2 MAPK cascade lies upstream of multiple key transcription factors.⁴² Following exposure to oxidant stress, ERK signaling is generally considered to be “pro-survival”^{43–45} and occurs in multiple cell types including fibroblasts, smooth muscle, endothelial and epithelial cells in response to hyperoxia.^{46–57} Interestingly, even cells in culture demonstrate developmental differences in hyperoxia-induced ERK activation. For example, protective ERK activation occurs in adult, but not fetal type II alveolar epithelial cells exposed to hyperoxia.^{49, 52, 53, 57} Hyperoxia-induced ERK activation occurs in both rat and human fetal lung fibroblasts.^{48, 50} In human cells, this signaling is arguably detrimental as it results in increased production of collagen, potentially increasing the risk of abnormal lung development.^{48, 50} In smooth muscle airway cells, toll-like receptor induced ERK signaling is developmentally regulated.⁴⁶ These developmental differences are important given the central role ERK/MAPK signaling in normal lung development.⁵⁸

It is important to note that these *in vitro* findings may not accurately predict *in vivo* signaling. Hyperoxia-induced ERK signaling occurs in both neonatal and adult rodents.^{55, 59–63} Some have demonstrated that hyperoxia-induced ERK signaling does not occur in neonatal lung,⁶⁴ and only occurs in the adult lung with the addition of mechanical ventilation.⁶⁵ The effect of ERK blockade on hyperoxia-induced lung injury has been inconsistent,^{59, 60} but appears to benefit the adult.⁵⁵ Taken together, we can conclude that hyperoxia-induced ERK activation is developmentally regulated, and conclusions drawn from these and future investigations must be placed in the correct context.

The c-Jun NH₂-terminal kinases (JNKs) signal in response to hyperoxia and act through the transcription factors AP-1, Jun and Fos.⁴³ Hyperoxia-induced JNK activation has been demonstrated in both adult⁶¹ and neonatal⁶⁰ animals, and in cells isolated from adult⁶⁶ and fetal/neonatal^{48, 49, 67} animals. Attenuation of hyperoxia-induced JNK signaling improves survival of fetal type II epithelial,⁶⁷ and adult pulmonary epithelial^{54, 66} cells. *In vivo*,

inhibition of JNK protects the neonatal lung from oxygen toxicity^{60, 67} potentially through attenuation of TGF- β 1 signaling.^{68–70} In direct contrast to this finding in neonatal mice, absence of JNK signaling increases susceptibility to hyperoxia in adults.⁷¹ Of note, TGF-beta1 does not increase in the adult lung exposed to hyperoxia.⁷² The results of these studies emphasize that consideration of the developmental stage is critical when choosing therapeutic targets to attenuate lung injury.

Sensing: TLR, DAMPs, and more

The current paradigm suggests that exposure to hyperoxia results in ROS that overcome antioxidant defenses resulting in cellular dysfunction and death.^{11, 26, 73} This proposed mechanism implies that the lung injury is inevitable following exposure to hyperoxia. Another guiding dogma is that hyperoxia is a byproduct of modern medicine never before encountered, thus robbing evolution of the opportunity to orchestrate a well-executed response. Whether gradual changes in atmospheric oxygen,⁷⁴ or the “relative hyperoxia” encountered with birth^{1, 75} have provided these protections is unknown. That being said, a growing body of literature suggests that hyperoxia induces an active innate immune response, thus opening up therapeutic targets to prevent lung injury.

Charles Janeway hypothesized the presence of innate immune receptors in 1989,⁷⁶ and Nobel Prize winning work uncovered the presence of Toll-like receptors.⁷⁷ Since that time, our understanding of how these pattern-recognition receptors (PRR) allow our immune system to recognize pathogen-associated molecular patterns (PAMPs) has evolved greatly.⁷⁷ It has since been recognized that in damage-associated molecular patterns (DAMPs) also stimulate the innate immune response.⁷³ DAMPs include a diverse set of ligands including fibronectin, heat shock proteins, HMGB1, and surfactant proteins A and D that can signal through TLRs.⁷⁸ Our understanding of the role of TLR in mediating injury following ischemia-reperfusion is increasing.⁷⁹ However, relatively little is known about how hyperoxia and reactive oxygen species interface with the innate immune response through TLR signaling.

Many DAMPs have been implicated in the pathogenesis of lung injury following exposure to hyperoxia. Pulmonary fibronectin levels increase in both adult^{80–82} and neonatal mice^{83–85} following exposure to hyperoxia. HMGB1, has been implicated in the pathogenesis of hyperoxia-induced lung injury in both neonatal⁸⁶ and adult⁸⁷ mice. Adult SP-D deficient mice are resistant to hyperoxia,⁸⁸ although SPD overexpression is protective.⁸⁹ Adult HSP70^{-/-} mice exhibit profound sensitivity to hyperoxia.⁹⁰ Similar to DAMPs, multiple TLRs have been implicated. Adult TLR3-deficient mice are protected from lung injury induced by hyperoxia.⁹¹ TLR4 signaling has been implicated in both the pathogenesis, and protection from, hyperoxia-induced lung injury in adult mice.^{92–94} Likely, cell-type dependent differences exist that determine whether TLR4 signaling is protective or detrimental.⁹⁵ We are unaware of studies done in neonatal mice with absent or attenuated TLR3/4 signaling. However, treatments that attenuate TLR4 expression (Vit. D) decrease pulmonary injury in neonatal rats.^{96, 97} Whether this observation is solely dependent on TLR4 expression is unknown. Furthermore, while multiple individual TLRs and DAMPs

demonstrate a role in the pathogenesis of hyperoxia induced lung injury, linking specific ligands to specific receptors remains to be done.

Developmental considerations must be accounted for when investigating the specific ligands responsible for initiating innate immune signaling via the TLRs in the oxygen exposed lung. Multiple studies have shown that TLR signaling is unique in the perinatal period. TLR expression by neonatal and adult monocytes and granulocytes is similar.^{98–100} This observation may not hold true for other cell types, in the preterm population, or over lung organogenesis.^{98, 101–103} Perhaps more important than the expression pattern of the receptors is the ability of the receptors to signal a response.¹⁰⁴ Early studies demonstrated an impaired neonatal response to TLR 1/2, TLR2/6, TLR4 and TLR7 agonists, while the response to a TLR7/8 agonist was fully intact.⁹⁹ Interestingly, following birth the TLR3, TLR7 and TLR9 response rapidly reaches adult levels, whereas the TLR4 response takes longer to develop.^{105–108} Furthermore, the induction of some pro-inflammatory cytokines are at adult levels following TLR8 or TLR9 activation.^{106, 109–111} In fact, neonatal blood dendritic cells respond to TLR7 and TLR9 stimulation at levels equal to or higher than similarly exposed adult cells.¹¹² Of note, the investigators are actively working to exploit the robust neonatal response to TLR7/8 agonists to develop vaccine adjuvants.^{113–115} Yet, important questions remain unanswered. Will these observed differences between neonatal and adult TLR signaling *in vitro* be found in the lung *in vivo*? Does hyperoxia signal DAMP-mediated TLR signaling in the lung? How do developmental differences in TLR expression and signaling affect neonatal and adult lung injury? Will understanding these differences reveal new therapeutic targets to prevent injury? It is likely that these developmental differences in TLR signaling will dictate age-specific therapeutics to prevent hyperoxia-induced lung injury.

The response to oxidative stress varies across development and aging – lessons from Hypoxic/ischemic brain injury

Injury to the developing brain is a major contributor to morbidity and mortality in preterm and term infants. As with BPD, the pathophysiology of neonatal brain injury is complex and multifactorial. As described above, oxygen exposure contributes to neonatal lung injury. In contrast, neonatal brain injury is largely due to ischemia and decreased oxygen, with generation of reactive oxygen species linking the pathogenesis of both disease states. In general, the mechanisms leading to ischemic brain injury are believed to be similar in the developing brain and in adults and has been reviewed in depth elsewhere.^{116–118} However, there are some differences, likely owing in part to the emerging role of innate inflammation in shaping synaptic communication and neuronal proliferation.

The BLOOD BRAIN BARRIER AND IMMUNE ACCESS

Historically, the mature central nervous system was considered “immunologically privileged” due to the blood brain barrier and its prevention of non-specific leakage of molecules and cells from the blood into the brain. In contrast, in the neonatal period the blood brain barrier (BBB) was considered immature and leaky. However, we now know that neither of these paradigms is true. It is now apparent that immune responses from infiltrating

leukocytes, cytokines and chemokines play important roles in both neuroprotection and hypoxic/ischemic damage in both adult and developing brains.^{116, 119–121} Further, there is now evidence that the tight junctions that are essential for an intact BBB are formed and functional early in embryonic development,¹²² possibly as early as E15 in mouse embryos.¹²³ Despite this, capillaries within the rat cortex do not have an adult-like appearance until postnatal day (PND) 14–21,¹²⁴ suggesting that the structural and molecular organization of the BBB evolves over early development. Interestingly, it has been demonstrated that IgG accumulations following intrastriatal injections of IL-1 β or TNF- α are higher in 21 day old rats compared to 2-hour old pups, implicating that the BBB in neonatal pups may be more resistant to inflammatory stress than in juveniles.¹²⁵ However, in response to hypoxia-ischemia (HI), there may be higher permeability to IgG in PND7 rats compared to PND30.¹²⁵ Further, in response to experimental stroke, the BBB may be much more permeable in adult rats compared to PND7.¹²⁵ Therefore, what was once thought to be a powerful defense against inflammatory response is now considered a key player in pathological inflammatory response, likely in an age related manner.

As mentioned in previous sections, oxidative stress and inflammation are often interconnected. In the neonatal brain, oxidative stress can initiate an inflammatory response and, in turn, the inflammatory response generates ROS. It has been observed that the developing brain may be further at risk for ROS-mediated injury due to imbalanced brain antioxidant defense mechanisms, high concentrations of unsaturated fatty acids, high rates of oxygen consumption and low concentrations of antioxidants.¹¹⁶ Oxidative stress contributes to BBB breakdown by several mechanisms including damage to the cellular components of the BBB (proteins, lipids and DNA), modulation of tight junctions, activation of matrix metalloproteins and cytoskeletal reorganization.^{126, 127} Further, the injurious role of oxidative stress in neonatal brain injury is supported by the protection that is conferred by enhancing antioxidant metabolism through overexpression of important ROS-utilizing enzymes glutathione peroxidase or modulation of the ROS scavenger superoxide dismutase.¹²⁸ The inflammatory response that follows oxidative stress is well-documented following ischemic injury in adult brains¹²⁰ and our understanding of the inflammatory response in the developing brain has expanded greatly over the past two decades and the responses may be different. For example, genetic deletion of inflammatory mediators such as NADPH oxidase, IL-1 α or IL-1 β does not show the same neuroprotection in neonates as it does in adults.¹²⁷ Unfortunately, trials using antioxidant compounds failed to improve outcome in adult stroke,¹²⁹ though there is hope that the anti-inflammatory properties of melatonin may prove protective following neonatal ischemic brain injury.¹³⁰ Further, targeting downstream mediators of oxidative stress such as inhibition of poly(ADP ribose) polymerase-1 or transient receptor potential melastatin-2 channels, have shown to be promising in adult mouse trials,¹³¹ but their role in developing brain injury are yet to be known.

INNATE IMMUNITY AND SIGNALING IN HYPOXIC-ISCHEMIC BRAIN PATHOLOGY

The immune response is integral in normal development of the CNS,^{119, 132} highlighting the complex influence it has on shaping cognitive ability as well as the developing brain's response to injury. For example, TNF α signaling has been shown to be involved in the regulation of neuronal progenitor proliferation and differentiation,¹³³ but, as mentioned

above, may affect BBB integrity.¹²⁵ However, the exact role of TNF α in neonatal injury is not fully understood. In addition, microglia play a critical role in synaptic pruning via complement signaling¹³⁴ and mediate vasculogenesis¹³⁵ throughout brain development. In response to ischemic injury, however, the role of microglia after ischemia appears to be age dependent. In adults, microglia have long been thought of as toxic, evidenced by inhibition of microglia conferring neuroprotection.¹²⁰ In neonatal rats however, depletion of microglia worsened parenchymal injury after stroke¹³⁶ suggesting a beneficial role for these resident phagocytes in the developing brain. Further, the alteration of microglial phenotypes after neonatal stroke¹³⁷ may play a role in these age-related differences. Neutrophils are another immune component that seem to act differently in neonates compared to adults after ischemia. While circulating neutrophils appear to contribute to HI injury in the newborn period owing to reduced injury in neutrophil depleted pups,¹³⁸ neutrophils do not transmigrate into the neonatal brain following ischemia within the first 42 hours in contrast to stroke in adult animal models¹³⁹. This does not appear to be due to an intrinsic inability of neutrophils to transmigrate, but rather it is due to decreased ability of neutrophils to adhere to P-selectin compared to the adult brain after ischemia.¹²⁵ Finally, while peripheral monocytes infiltrate the BBB after stroke in adult models, the transmigration of circulating monocytes across the BBB is relatively low,¹⁴⁰ further defining the role of resident microglia described above. Whether expression of specific selectins, cytokines and/or chemokines account for the relative lack of infiltration of innate lymphocytes after neonatal ischemia remains unknown.¹²⁷

In the developing brain, several mediators of innate immunity play a dual role in physiology and pathology. TLRs 1–9 mRNA expression has been detected in developing mouse brain^{141, 142}. During brain maturation, TLR3 activation impairs neural progenitor cell proliferation¹⁴³ and inhibition of TLR-3 in fetal life alters brain development through IL-6 signaling.¹⁴⁴ Regarding the contribution to injury, TLR-1, -2, and -7 are upregulated 24h after and TLR-2, -3, -6, -7, and -9 are upregulated 72h¹⁴² after hypoxic-ischemic injury, whereas TLR-5 is downregulated¹⁴¹ in the first 24h. While it is unclear if there is a role for increased expression of TLR-1 and -7, reports have suggested reduced infarct volume in TLR-2 KO mice.¹⁴¹ Despite no change in expression,^{141, 142} activation of TLR3 after ischemia, possibly via RNA release from necrotic cells,¹⁴⁵ sensitizes the neonatal brain to subsequent HI injury via enhanced pro-inflammatory cytokine and chemokine expression and altered microglia phenotype by reducing the anti-inflammatory phenotype of microglia (M2).¹⁴⁶ At the same time, there is an increase in TLR ligands. For example, studies have revealed that there may be gender specific increases in TRIF and CX3CR1 signaling following HI injury in mice¹⁴². Additionally, HMGB1 increases after hypoxia-ischemia¹⁴⁵. Together, the upregulation of TLRs and their ligands (DAMPs and PAMPs) after hypoxic-ischemia signify the role of the innate immune system in the injury, likely through modulation of downstream pro-inflammatory intracellular pathways such as NF κ B, MAPK, and AP-1.¹¹⁶ While most of what is known about these pathways comes from adult ischemia models, the role of NF κ B in neonatal injury has become better delineated in recent years. While NF κ B may provide endogenous neuroprotection in the late phase of injury¹⁴⁷, targeted inhibition of NF κ B after neonatal stroke provides neuroprotection¹⁴⁸ and improved outcome¹⁴⁹ via inhibiting apoptosis. Given the multiple roles of many of these inflammatory

mechanisms in developmental regulation, neuroprotection, and injury, studies targeting inflammation should heed attention to timing of inflammatory damage and whether anti-inflammatory agents have adverse affect on brain development.

Conclusions

Both BPD and HIE are oxygen radical diseases unique to the perinatal period. An extensive amount of work has been done in an attempt to understand the mechanisms linking exposure to oxidative stress and pathogenesis of disease. Through this work, developmentally-regulated contributions of the innate immune response have been uncovered. Despite opposing drivers for oxygen radical generation (hyperoxia vs. hypoxia), many of these responses are similar in these two pathologies. Further work may ultimately reveal opportunities to either enhance a protective response or attenuate damaging pro-inflammatory signaling unique to the perinatal period.

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