

The Infancy of the Brain and Hyperoxia

Abstract

In spite of significant advances in obstetrics and neonatal concentrated care, preterm newborn children often experience the ill effects of neurological impairments in later life. Due to the immaturity of endogenous radical scavenging systems, preterm and full-term infants are typically vulnerable to damage from reactive oxygen species. It is common knowledge that elevated oxygen levels experienced during the crucial stage of maturation have the potential to profoundly influence the processes of development. It is known that supra physiological oxygen concentrations used in the care of critically ill infants or for resuscitation have negative effects on the developing lung and retina, which contributes to the pathophysiology of neonatal diseases like broncho pulmonary dysplasia and prematurity retinopathy. In addition, research conducted in the past ten years suggests that hyperoxia also causes the death of neuronal and glial cells, which contributes to the damage to the white and grey matter found in premature infants. Hyperoxia can alter developmental processes during the crucial stage of brain maturation, disrupting neural plasticity and myelination. Therefore, protective and/or regenerative strategies are highly warranted in situations requiring oxygen supplementation in addition to the development of appropriate monitoring systems. In this section, we provide an overview of the pathophysiology of oxygen exposure on the developing central nervous system and its impact on neonatal brain injury, as well as a summary of the clinical and experimental evidence and potential therapeutic strategies.

Keywords: Preterm • Newborn • Endogenous radical scavenging system • Physiological oxygen level • Broncho pulmonary dysplasia • Hyperoxia

Introduction

The survival rates of very preterm and critically ill full-term infants have significantly improved thanks to significant advancements in obstetrics and neonatal intensive care. Perinatal mortality has diminished by 25% over the course of the past 10 years and has expanded the enduring populace. However, despite all efforts, perinatal brain injury remains a significant contributor to child mortality and disability. Early brain development can be impacted by preterm birth, resulting in long-term individual, family, and socioeconomic effects. The level of rashly conceived newborn children has wrinkled in industrialized nations during the last decades, and represents 5.5-11.4% of all live births. Due to the rising prevalence of infertility treatments, multiple pregnancies, and older mothers, this number is likely to rise further. Over the past two decades, intact long-term survival of premature infants has almost become the norm. The Very Low Birth Weight (VLBW) population, defined as having a birth weight of less than 1,500 g, has grown thanks to advances in neonatal respiratory care. The immediate and long-term effects of prematurity have become the primary focus of clinical efforts as a result of an increase in the survival rate. Unfortunately, a significant number of patients continue to have motor and cognitive function-affecting neurologic deficits. Periventricular leukomalacia affects approximately 10% of those who survive very preterm birth and later exhibit motor deficits characteristic of cerebral palsy [1, 2].

Progression of brain development

The mammalian brain's development is a dynamic process that involves structural and functional maturation processes. Neuronal cell development and proliferation, migration, glial cell proliferation, axonal and dendritic outgrowth, synaptogenesis, and the myelination of axons are all

Eva Parker*

Department of Neuroscience, Aix-Marseille University

*Author for correspondence:
prker@amu.ac.eu

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features of brain evolution. Neuronal migration processes typically complete at the edge of viability in extremely preterm infants (around 24 weeks of gestation), but glial cell maturation, outgrowth, and connectivity formation continue. Metabolic factors like mitochondrial development, cerebral vascular density and blood flow, the maturation of glucose utilisation systems, and cytochrome oxidase activity are crucial to the formation of neural electric activity [3].

During physiological mental health, at first framed exaggerated neurons are erased by physiological coherent apoptosis. During a perinatal affront, unintentional activation of the very much refined apoptotic cell passing machinery may happen. Two distinct signaling pathways are used to carry out apoptosis. The intrinsic pathway is triggered by cellular stress or DNA damage, whereas the extrinsic pathway involves extra-cellular signaling via cell death surface receptors (such as Fas and TNF-). At the mitochondrial level, both pathways have the potential to converge. The release of pro-apoptotic factors (i.e., apoptosis-inducing factor [AIF] and cytochrome c) in the cytosol, which activates death mechanisms including the formation of the active apoptosome (apoptosis protease-activating factor-1 [Apaf-1]), causes the mitochondrial inner membrane potential to decrease and induce permeability upon a strong harmful trigger. Several intrinsic factors, including members of the Bcl-2 family, influence these mechanisms. The activation of caspases and the leakage of mitochondrial membranes with the release of cytochrome c into the cytoplasm are two outcomes of the formation of free radicals during altered oxygen tension. Depending on the sort of affront, caspase-1 and caspase-3 are initiated. The majority of apoptotic factors, such as caspases, are highly expressed in the developing brain, making the organism more vulnerable to harmful activation. In addition, it appears that caspases play important non-apoptotic roles in a variety of cellular processes, including synaptic plasticity, dendritic development, learning, and memory [4, 5].

Oxygen in association with brain injury

The evolution and respiration of cells and organisms are significantly influenced by the fluctuating oxygen levels in the environment. The clinical and exploratory insights of the previous ten years have explored how untimely openness to a lot of oxygen in the neonatal period may upset mind development. There is increasing

evidence that hyperoxia damages the developing brain. Encephalopathy of prematurity with cystic or diffuse periventricular leukomalacia may occur in preterm infants who are exposed to supra physiological oxygen levels for an extended period of time or in a fluctuating manner in comparison to intrauterine conditions. In full-term newborn children experiencing birth asphyxia revival with high oxygen fixations fundamentally expands mortality and dreariness. Apoptosis, autophagy, alterations in the expression of neurotrophins and growth factors, oxidative stress, inflammation, and alterations in genes related to synaptic plasticity are all linked to hyperoxia-induced subtle neuro degeneration in rodents. In addition, transient hypo myelination may result in white matter microstructural changes that last for a long time [6].

Impact of hypoxia on neuronal plasticity

In addition to diffuse WMI, most preterm birth survivors experience a decrease in cortical gray matter volume. The hindering impact of neonatal hyperoxia on neuronal endurance and separation has been portrayed already. From birth until P5, rodents are exposed to oxygen, which increases neuronal apoptosis and causes density loss in various parts of the developing rat brain. In addition, hyperoxia administered for 24–48 hours on P6 appears to reduce both the total number of progenitors and immature and mature neurons as well as their proliferation. After prolonged hyperoxia exposure from P2 to P14, the hippocampal and cerebellar volumes of 14-week-old mice are measured using MRI volumetry. To capability appropriately, the CNS needs to create adequate formation of neuronal availability. The ability of synapses to alter the strength or efficacy of transmission, known as synaptic plasticity, is essential for the transmission of impulses and, as a result, of numerous neuronal processes. In addition, it was demonstrated that 24-hour hyperoxia in 6-day-old rats induced acute, subacute, and persistent reductions in the expression of genes involved in synaptic plasticity regulation. As a result, hyperoxia appears to affect the rodent's neuronal connectivity as well as the survival and differentiation of neuronal cells. Impaired neuronal networks, along with WMI, may be to blame for changes in long-term cognitive development [7].

Impact of hypoxia on changing brain proteomics

Acute (P7) and long-term (P14 and P35)

changes in the brain proteome of mice exposed to high oxygen levels for 12 hours on P6 have been studied in order to identify intracellular pathways involved in a pathological modulation of maturation processes. Showed that high oxygen levels had an immediate effect on brain protein changes. These suggest that there is a problem with vesicle trafficking (such as synapsin and pacsin), cell growth and differentiation (such as hnRNP and EF1), neuronal migration, and axonal arborisation (such as TUC-2/4, GAP43, and doublecortin). Late protein changes on P35 suggest that the organization of the cytoskeleton, intracellular transport, synaptic function, and energy metabolism have been disrupted for a long time or continuously [8].

Treatment Strategy

By using brain active substances

Neonatal hyperoxic brain injury has seen the testing of a number of other medications used to treat CNS disorders. Sedative, anxiolytic, analgesic, and anesthetic properties can be found in dexmedetomidine, a selective agonist of 2 receptors. It has been extensively discussed for its neuroprotective effects. After 24 hours of hyperoxia, the application of dexmedetomidine significantly reduced hyperoxia-induced neurodegeneration and IL-1 mRNA and protein levels in 6-day-old Wistar rat pups. Dexmedetomidine treatment also normalizes the reduced-to-oxidized glutathione ratio and decreases lipid peroxidation. More research is needed to determine if this compound protects against other experimental brain injury models. Caffeine is a substance that is frequently used in neonatal care to prevent apnea and stimulate the respiratory system. Intriguingly, large, multi-center, placebo-controlled studies with caffeine use have shown a decrease in cerebral palsy and neurodevelopmental impairment. In neonatal creature. A model of persistent hypoxia, caffeine has been displayed to enhance hypomyelination as well as ventriculomegaly. At 24–48 h of hyperoxia exposure, the administration of 10 mg/kg caffeine to 6-day-old rodents prevented neuronal progenitor cell loss and reduced apoptosis. Since caffeine is now protected to utilize under the watchful eye of youngsters, further examinations are anticipated to confirm these impacts [9].

Stem cell therapy

Stem cells are undifferentiated cells that can, under certain conditions, differentiate into tissue-

specific cell lines. These cells can be neuronal, mesenchymal, or haematopoietic, depending on where they came from. In experimental animal brain injury models, Mesenchymal Stem Cells (MSCs) appear to have relevant neuroprotective properties. On P5, MSCs (5 10⁵ cells) were injected intravenously into newborn Sprague-Dawley rats that had been exposed to hypoxia for 14 days. Hyperoxia induced apoptotic cells in the dentate gyrus and hypomyelination were significantly reduced in the MSC-treated pups. Since trial data is restricted to one publication and the hidden components are hazy at this point, we anticipate further examinations for affirmation of the noticed impacts and recognizable proof of the possible molecular systems included [10].

Conclusion

Hyperoxia contributes to the pathogenesis of injury in the preterm and full-term brains by causing oxidative stress. From current exploratory evidence, it very well might be conjectured that oxygen causes cell demise and significantly adjusts maturational cycles. Numerous cell types, including neurons, oligodendrocytes, astrocytes, and macroglia cells, are impacted. Animal behavioral studies have shown effects like motor hyperactivity and cognitive impairment that are similar to those seen in school-aged for-ever preterm infants. In addition, the characteristic MRI images of prematurely born infants at term resemble the images of hyperoxia exposed rodents with reduced hippocampal size and white matter abnormalities. Therapeutic efforts to establish adequate monitoring systems and define the ideal oxygen saturation are highly warranted. Additionally, it is extremely difficult for current experimental research to develop adjunctive therapies in situations where oxygen supplementation cannot be avoided.

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