Therapy for Neonatal Hyperoxia-induced Lung Injury

Therapy with hyperoxia is often needed to treat newborns with respiratory disorders. Supplemental oxygen administered to newborn infants with respiratory failure can increase oxidant stress and lead to lung injury. Lung injury often resolves with fibrosis, which is prominent in larger infants after prolonged exposure to oxygen and mechanical ventilation. Prolonged exposure of neonatal rats to hyperoxia resulted in decreased alveolar septation, increased terminal air space size, and increased lung fibrosis, which is very similar to human bronchopulmonary dysplasia (BPD). It is originally manifested with mucosal metaplasia of the airways, emphysema, and widespread interstitial fibrosis. Improved medical care, including antenatal steroids, surfactant therapy, and better ventilator strategies and nutritional support, has allowed survival of the most premature infants and has significantly altered the pathology of BPD from severe lung injury to the new BPD. The new BPD is characterized by impaired alveolar formation and vascular development. Despite the recent improvements in preventing respiratory distress syndrome in preterm infants, BPD remains a major cause of morbidity and mortality during the first year of life and many infants have significant respiratory problems throughout childhood, including increased airway reactivity and development of obstructive airway disease throughout childhood. More than 30% of preterm infants born before the gestational age of 30 weeks develop BPD. Currently no effective therapy is clinically available to prevent long-term pulmonary sequelae of BPD. Thus, it is important to explore new strategies for the prevention and treatment of BPD.

In this issue of Pediatrics and Neonatology, Ozdemir et al used resveratrol, a natural phytoalexin present in grapes, peanuts, and mulberries, to treat hyperoxia-induced lung injury in newborn rats. Resveratrol has antioxidant and anti-inflammatory activities and has been shown to reduce lung injury in sepsis and bleomycin-induced lung injury. They found that resveratrol significantly reduced the fibrosis score, nitric oxide and tumor necrosis factor-α levels, and increased the glutathione and superoxide dismutase levels in the hyperoxia group.

Supraphysiological concentrations of oxygen generate excessive amounts of reactive oxygen species, which can activate signaling pathways to induce downstream targets. The signaling pathway seems to play an important role in hyperoxic cell death. Extracellular signal-regulated kinase 1/2, a mitogen-activated protein kinase subfamily member, plays a crucial role in hyperoxia-induced lung injury. Once oxidative stress damages lung cells, the injured and dead cells are replaced through an increased proliferation and differentiation of fibroblasts. Excessive cell growth and proliferation, collagen overproduction, and pulmonary fibrosis may result if these courses are not modified. Ozdemir et al’s study showed that oxidative stress and nitric oxide contributed to the pathogenesis of hyperoxia-induced lung injury and that resveratrol prevents hyperoxic lung injury. The pathogenesis of BPD is multifactorial, and researchers consider that pulmonary oxygen toxicity plays a central role in the lung injury process. These findings further confirm that pulmonary inflammation and oxygen toxicity play crucial roles in the lung injury process, which leads to the development of BPD.

The alveolar stage of lung development in the rodent begins on postnatal Day 4, and saccular division is completed by postnatal Day 14. The newborn rat is particularly appropriate for studies of neonatal oxygen injury because the developmental stage of the rodent lung at birth overlaps with that of the human preterm neonate at 24–28 weeks’ gestation. The limitations of animal models of hyperoxic lung injury are the oxygen concentrations used that exceed the level of oxygen supplementation currently applied to the preterm infants and the lack of the fluctuations in oxygen concentrations that are clinically used in preterm infants. However, animal models are essential for the study of novel strategies to prevent and treat hyperoxic lung injury. Future studies are need to further refine and modify the current animal models to better mimic the human condition. BPD in very preterm human neonates involves prenatal insults, e.g., intrauterine growth restriction and infections. Therefore, the
creation of a perinatal double-hit animal model of BPD could be critical to mimic closely the pathogenesis in human preterm neonates as a basis for research on recovery of normal lung growth.

Conflicts of interest

The author declares no conflicts of interest.

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References