Oxidative Stress and Potential Renal Damage in Neonates

Oxygen therapy is common practice in the care of neonates, especially in preterm neonates. High oxygen concentrations can lead to oxidative stress and disturb the balance between reactive oxygen species (ROS) and antioxidant defenses. ROS cause direct injury to proteins, lipids, and amino acids through multiple pathways, and they lead to cell damage and death. Preterm neonates are particularly vulnerable to oxidative stress as they have low concentrations of antioxidants. These unsatisfied detoxifying mechanisms include inadequate inducible antioxidant enzymes, glutathione stores, and nutritional antioxidants. The lung is the primary target organ prone to damage by ROS, and this has been intensively studied. Other extrapulmonary effects of hyperoxia have also been demonstrated in the brain and retina. Therefore, common complications of prematurity such as bronchopulmonary dysplasia, retinopathy of prematurity, and periventricular leukomalacia are all strongly linked to oxidative stress.

Nephrogenesis (the development of nephrons) is usually completed at about 34–36 weeks' gestation. Therefore, preterm neonates are often born at a time when nephrogenesis is still ongoing. In children and adults born preterm, increasing frequency of reduced kidney size, impaired renal function, and hypertension indicate that renal development may be impaired after birth. The causes of impaired renal development following preterm birth are still unknown; however, recent studies showed oxidative stress may play a role in this mechanism. Oxidative stress is associated with proximal tubule injury in kidneys of human neonates. Early life exposure to hyperoxia in rats leads to hypertension and a 25% reduction in nephron number in adulthood. Hyperoxia also creates mild increases in renal tubular necrosis, dilatation, regeneration and interstitial inflammation. There are different results concerning the effects of neonatal hyperoxia on nephrogenesis. Exposure to 65% oxygen during the early postnatal period in a neonatal mouse model did not cause immediate changes in renal structure. There were significant glomerular enlargements in early adulthood, but no overt long-term deleterious effects on glomerular structure in middle age. Another neonatal rat model showed that 80% hyperoxia exposure resulted in a significant reduction in both nephrogenic zone width and glomerular diameter, but it did not affect the nephron number. These early maldevelopment findings suggest the potential for accelerated nephron loss in adulthood.

Oxidative stress is also implicated as an important molecular mechanism in the initiation and progression of fibrosis in a variety of organs. In addition to pulmonary and liver fibrosis, oxidative stress also plays a role in kidney fibrosis. ROS increases extracellular matrix (ECM) deposition in tubular epithelial cells, tubular interstitium, and mesangial cells. Kidney fibrosis is a common pathway of progressive renal disease leading to impaired renal function regardless of the underlying pathology. Transforming growth factor β1 (TGF-β1) has been shown to be the key inducer of ECM accumulation and decreasing degradation. TGF-β1 is one of the most potent profibrogenic cytokines evident in nearly all fibrotic diseases. TGF-β1 stimulates ROS production; however, oxidative stress can activate latent TGF-β1, and a vicious profibrogenic circle progresses. One neonatal rat model showed activation of TGF-β1 in hyperoxia induced lung injury. Connective tissue growth factor (CTGF) is a downstream mediator of TGF-β1. Current studies showed that CTGF played a role in fibroblast proliferation and ECM synthesis. The CTGF gene is regulated by TGF-β1 at the level of transcription, and the effects of TGF-β1 on fibroblasts are partially mediated by CTGF. Expression of CTGF has been demonstrated in human renal fibrosis, and it is possibly involved in glomerulosclerosis and tubulointerstitial fibrosis. In the study of Jiang et al., CTGF was found to play a role in neonatal rat kidney fibrosis induced by hyperoxia. Jiang et al also found that hyperoxia caused renal damage in neonatal rats as shown by a higher number of tubular injuries, larger glomeruli, and higher collagen content. These findings suggest that silencing CTGF gene expression or inactivating
CTGF biological activity may be a potential therapeutic approach to kidney fibrosis. Hyperoxia induced oxidative stress in multiple organ systems. In neonates and preterm newborns, oxidative stress arises following oxygen therapy and inadequate detoxifying mechanisms of neonates. Common complications of prematurity in lung, brain, and retina are strongly linked to oxidative stress. Recent studies also elucidate the role of oxidative stress in neonatal renal damage. Further studies that focus on the therapy of antioxidants are necessary to target the oxidative stress and reduce organ damage.

Conflicts of interest

The author declares no conflict of interest.

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References