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Neonatal hyperoxia: effects on nephrogenesis and the key role of klotho as an antioxidant factor

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Category of study: Opinions
Brenner et al. (1) hypothesized that susceptibility to hypertension and kidney injury in adulthood could be related to congenital or programmed reduction in glomerular number. At roughly the same time, Barker and coworkers (2) observed relations among low birth weight and adult disease, such as cardiovascular injury.

With these two hypotheses raised, the nephrology community started to give particular attention to the fact that premature birth or low birth weight could lead to a low glomerular endowment, leading to increased susceptibility to kidney disease in adulthood.(3) Disorders of the glomerular endowment are particularly complex. Since human renal development occurs only in the intrauterine phase, any inadequacy in glomerular number is permanent in adulthood.(4)

The occurrence of preterm birth is still high in a large number of countries worldwide. Recently, it has been demonstrated that preterm birth affects 1 of every 10 infants born in the United States.(5) Furthermore, one million of those children die secondary to problems related to premature birth. Prematurity is the largest cause of death in the first month of life and is responsible for over ~75% of pediatric deaths in the neonatal stage.(6)

In terms of kidney development, Sutherland and coworkers analyzed autopsy from 28 kidneys from preterm neonates, and demonstrated kidney maturation impairment after preterm birth.(7) Renal development accelerated after preterm birth, with a high number of glomerular generations and a reduction of the neogenic zone in the kidneys of preterm neonates. Of major concern, in contrast with gestational controls, preterm kidneys presented glomeruli structural abnormalities and a significantly larger cross-sectional area of the renal corpuscle, suggestive of renal hyperfiltration. These findings indicate that the preterm kidney may have fewer functional nephrons and increased susceptibility to impaired renal function in both the early postnatal period and adulthood.

In addition to premature birth, which is an aggravating factor per se, infants are often treated with supplemental oxygen, exposing neonates at the time of birth to abrupt and premature high-oxygen levels in contrast to the intrauterine low-oxygen environment. Relative hypoxia is a physiological trigger of the expression of vascular endothelial growth factor (VEGF) in the avascular mesenchyme leading to the induction
of vascular proliferation and differentiation during renal morphogenesis.\(^{(8)}\) Thus, it would be expected that alterations in oxygen levels might have effects on renal development.

In fact, despite the literature being still limited, studies show that the effects of neonatal hyperoxia (HO) increase oxidative stress and adversely affect glomerular and tubular development. This is confirmed by enlarged renal corpuscles, renal tubular necrosis, and interstitial inflammation during the perinatal period\(^{(9)}\). These detrimental effects may extend into adulthood, presenting as hypertension.

Ali et al.\(^{(10)}\) demonstrated in animal models of HO-induced kidney injury that hyperoxia during postnatal kidney development was accompanied by a substantial reduction of renal klotho expression in adulthood. Klotho plays an essential role in oxidative stress, inflammatory process, and cell apoptosis. Klotho downregulation was associated with marked injury from tubular and glomerular damage, characterized mainly by glomerular hypertrophy, which may be a consequence of hyperfiltration by the remainder nephrons. The authors showed that treatment with klotho increased renal intrinsic antioxidant capacity, characterized by increased expression of catalase and manganese superoxide dismutase (MnSOD), two crucial enzymes in the oxidative injury process.

Klotho not only has antioxidant actions, but also plays an important role in VEGF-mediated effects, such as vascular morphogenesis and maintenance of endothelial function. The effects of klotho in the morphogenesis include the induction of vascular growth factors by the bone marrow, and the promotion of the 3-dimensional arrangement of endothelial cells, fibroblasts, and extracellular matrix to form new vessels.\(^{(11)}\)

It has been reported that the Klotho has a crosstalk with the VEGF receptor and transient receptor potential canonical 1 to regulate VEGF-mediated calcium entry and the hyperactivity of calcium-dependent proteases, thus maintaining endothelial quiescence.\(^{(12)}\) Klotho deficiency provokes a constant input in intracellular calcium, leading to vascular hyperpermeability accompanied by endothelial apoptosis or loss of endothelial integrity.

The significance of VEGF during kidney development has been well established. Knockout mice of a single VEGF allele die \textit{in utero} between day 10-11 due to lack of vasculogenesis and angiogenesis, which is the first stage of the formation of the vascular network\(^{(13)}\). The key role of VEGF is mediated through two tyrosine kinase
receptors VEGFR-1 and VEGFR-2, both are highly expressed on endothelial cells, and genetic deletion these receptors also leads to embryonic lethality due to compromised blood vessel maturation (14).

In parallel, the angiopoietins (Angpts) are widely expressed in the foetal kidney showing a crucial role in renal vascular maturation. Angpt-1 and -2 are the natural ligands of the Tie-2 receptor, which is a tyrosine kinase receptor crucially implicated in endothelial cell quiescence, proliferation and maturation during nephrogenesis (15). The role of Angpts during vascular morphogenesis is supported by studies that showed that Angpt-2- deficient mice have disrupts kidney vessel patterning, such as alterations of peritubular capillaries which surround the cortical parts of the proximal and distal tubule (16).

Ali and coworkers’ findings on the role of klotho on kidney development open up a new horizon for the possible mechanisms contributing to disorders in preterm neonatal kidney exposed to hyperoxia. It will be exciting to explore whether among the molecular pathways influenced by klotho, the vascular growth factors, such as VEGF and VEGF receptors, angiopoietins and tyrosine kinase receptors can influence kidney development, and whether this pathway can be targeted to prevent and treat the deleterious effects of hyperoxia in premature newborns (Figure 1).

Taken together, these results pave the way for the development of novel therapeutic renoprotective strategies and point to the possible exogenous Klotho administration in premature infants with oxidative stress-associated renal injury.

References

Figure 1. The exposure to hyperoxia (HO) during the period of active nephrogenesis contributes to renal dysmorphogenesis. Renal morphogenesis is tightly regulated by the balance between angiogenic factors and antioxidants. The HO lead to oxidative stress causing a reduction in klotho expression, which can lead to a vicious cycle with a highly oxidative environment. The klotho suppression may lead to an imbalance of vascular growth factors, such as VEGF and Angpts. Besides, HO can directly inhibit VEGF expression. Treatment with klotho can prevent renal disturbances, through its antioxidant actions and acting directly on vascular growth factors. Abbreviations: VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Angpts, angiopoietinas; Tie-2, tyrosine-protein kinase that acts as cell-surface receptor for Angpts.