Perinatal Origins of Adult Disease - Role of the Kidney Development

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성인 질병의 주산기 기원에 대한 신장 발달의 역할

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〈Abstract〉

In recent years, there has been an increase in research designed to delineate the underlying causes of perinatal programming. Starting with epidemiological observations that birth weight was inversely associated with cardiovascular disease, a variety of studies both in humans and in experimental models have begun to demonstrate how the perinatal milieu can subtly alter vasculogenesis and nephrogenesis. Additionally, rates of prenatal and postnatal growth each appear to contribute to future vascular, renal and metabolic function. Nephrogenesis is affected by changes in maternal nutrition and health, and recent data more specifically linking these changes with renal function and hypertension are presented. Additionally, renal functional changes in later life may be influenced by changes in renal tubular transporters noted early when maternal nutrition is compromised. Various hormonal systems affected by maternal nutrition in utero may effect subsequent changes in renal function via subtle alterations in renal function and structure initiated during nephrogenesis. The purpose of this lecture is to discuss recent reports that have begun to elucidate factors that initiate perinatal programming as it affects renal disease and cardiovascular disease in later life.

Introduction

The concept that events in the perinatal period have far-reaching effects is increasingly accepted. An enlarging body of data strongly suggests that restricted or altered maternal nutrition, or exposure to certain medications and substances, might not cause major malformation yet can result in a tendency to hypertension, cardiovascular events, proteinuria and altered renal function in adult life for the exposed offspring.

Barker and colleagues[1, 2] were the first to examine large cohorts of middle-aged persons for whom birth weight was recorded and, thus, available. They observed that birth weight was inversely correlated with blood pressure and the frequency of cardiovascular events in adult life. In recent years, a number of studies have provided data that begin to define hypotheses as to how perinatal programming, as this phenomenon is called, takes place. A number of factors affected by perinatal events within the circulation, the kidneys and other organs have been proposed as being involved in the pathogenesis.

The first World Congress on Fetal Origins of Adult Disease took place in February 2001 and the second took place in Brighton, UK, in June 2003. The summary from the most recent meeting points out that increasing numbers of researchers and clinicians alike are recognizing the potential importance of the concept that springs from perinatal programming–that much adult disease may originate from events that happen in utero.

Role of Nephron Number

The concept that the number of nephrons may be associated both with blood pressure and renal function arose a number of years age[3, 4]. There are now both experimental data and some limited clinical data showing that perinatal programming is intimately intertwined with the number of nephrons that form.

Rodriguez[5] examined renal samples from autopsies in 56 extremely-low-birth-weight infants who had succumbed in infancy. These infants weighed 1,000 g or less at birth, and their renal tissue was compared with autopsy samples from 19 full-term infants. The researchers also divided each group into those who had had renal failure during their brief lives and those who had not. Radial glomerular counts were utilized to estimate glomerulogenesis. The preterm infants who had survived longer showed glomerular size compensation and had evidence of hypertrophy. Rodriguez[5] surmised that in this very-high-risk group of preterm infants in whom glomerulogenesis is still occurring, renal development is at risk, and conclude that it is important to obtain long-term data. This same group[5] has attempted to address the long-term follow-up of 20 extremely-low-birth-weight infants who had renal failure in the newborn period; 11 (55%) also had aortic thrombi during this time period. The children, ranging in age from 3.2 to 18.5 years, were examined as part of their usual care, and the report is based on retrospective data. In follow-up, nine of the 20 had a decrease in renal function, and important risk factors for progression appeared to include a high urine protein/creatinine ratio (i.e. above 0.6) at 1 year of age, a serum creatinine level above 0.6 mg/dL and a higher body mass index (above the 85th percentile). While this study was also retrospective, it points out not only the issue of perinatal growth, but also that of growth thereafter. Babies of extremely low birth weight, who receive the necessary evil of nephrotoxins for their survival, would appear to be at higher risk than full-term infants who are small for gestational age.

Na et al[6] performed a retrospective review of 56 children with nephrotic syndrome. Among 56 patients having nephrotic syndrome, 8 had IUGR, and 48 were AGA. The 24-hour urinary protein level in children with IUGR was significantly higher than that in children who were AGA. There was a statistically significant difference in the incidence of steroid resistance and in the time to remission between the children with IUGR and those being AGA. Also, there was a significant difference in the incidences of treatment with cytotoxic agents and complications such as hypertension. This report indicates that IUGR predicts an unfavorable progression of nephrotic syndrome.

Keller et al.[7] performed morphometry in persons who had died in accidents, and linked the histological findings with the presence or absence of hypertension during life. They observed that glomerular number was reduced in hypertensive persons who had died accidentally in comparison with glomerular number in those who had not had hypertension.

Role of Retinoids

Retinoids are important in renal development, and in-utero vitamin A depletion is recognized as causing renal anomalies[8]. Renal development depends on epithelial-mesenchymal interactions; much evidence suggests that retinoids modulate nephrogenesis in a dose-dependent manner in vivo and in vitro. Retinoic acid has a number of effects, including regulation of the c-ret proto-oncogene.

Role of Steroids

Dexamethasone and other steroids may affect nephrogenesis. Studies published in recent years have expanded the observations that glucocorticoids influence nephrogenesis. There may be specific time-frames in which the foetus is vulnerable to alterations in the levels of ambient glucocorticoids. Ortiz (9) studied a rat model in which dexamethasone (0.2 mg/kg/day) was administered to pregnant rats on specific days (days 13-14, 15-16, or 17-18, etc.) during gestation. They observed that administration of dexamethasone during days 17-18 of gestation led to a 17% decrease in nephron number in the offspring, and to elevation in blood pressure in adult life. However, while offspring whose mothers had received dexamethasone at days 13-14 and 15-16 also had hypertension as adults, no change in their nephron number was observed.

Role of Renin-Angiotension System

The renin-angiotensin system plays a major role in normal renal development. Woods[10] reported that a low-protein diet led to a decrease in renal renin messenger RNA and a decrease in angiotensin II and plasma renin activity in the neonatal kidney. When mature, the offspring subject to such a maternal diet had fewer nephrons and higher blood pressure.

Sahajpal and Ashton[11] examined glomerular number in rats that had been born to mothers who had been on either a normal diet or a low-protein diet throughout gestation. Rats were studied at age 4 weeks, at which point renal function was apparently normal, and equal in the control offspring and the low-protein offspring. However, after a dose of an angiotensin-converting enzyme inhibitor (enalapril, 5 mg/kg) or angiotensin II infusion (30 ng/min/kg) the low-protein offspring had an exaggerated decrease in glomerular filtration rate. Angiotensin II type 1 receptors were increased by 24% in the offspring of mothers that had received a low-protein diet during gestation.

The renin-angiotensin system plays an important role in renal growth and development. Exposure of the neonate to angiotensin converting enzyme (ACE) inhibitors increases mortality and results in growth retardation and abnormal renal development. We have demonstrated that ACE inhibition in the developing kidney reduces the renal expression of growth factors, which may account for renal growth impairment[12].

Role of Iron

Lewis[13] performed long-term studies in offspring of iron-restricted mothers. The maternal diet contained only trace amounts of iron in the restricted group (3 mg/kg/day) relative to the control diet (150 mg/kg/day). At 3 months of age, offspring of iron-restricted mothers had elevated blood pressure. The phenotype of these offspring appeared similar to that observed in the rat model of maternal protein restriction. Looking at offspring at 3 months, the glucose tolerance appeared better in the animals with protein-restricted mothers than in the offspring of controls.

Conclusion

Importantly, multiple molecules are involved in nephrogenesis. Identifying, among those factors critical to nephrogenesis, those that might be influenced by maternal nutrition and exposures will be important in defining the mechanisms of perinatal programming.

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