Hypertension Research (2024) 47:2942–2944
https://doi.org/10.1038/s41440-024-01812-6

COMMENT

Fetal origins of adult hypertension and renal injury: an epigenetic memory matter?

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Keywords DOHaD · Hypertension · Kidney · Epigenetic

Received: 20 June 2024 / Accepted: 3 July 2024 / Published online: 13 August 2024

The developmental origins of health and disease (DOHaD) is a concept that environmental exposures during an early life (particularly the in-utero period) can develop chronic disease in adulthood, notably non-communicable diseases such as obesity, cardiovascular disease, hypertension, type 2 diabetes, neuropsychiatric disease, and chronic kidney disease [1]. This hypothesis was first noted through the Dutch famine birth cohort study, following a historical disaster in 1944-1945, in which men with famine exposure in their early life (the first half of pregnancy) exhibited a significantly higher rate of obesity [2]. Subsequently, Barker et al. have shown that not only obesity but also cardiovascular disease and other lifestyle-related diseases can originate in impaired intrauterine growth and development [3, 4], thus the concept being referred to as Barker's hypothesis.

In parallel with such epidemiologic observations, a number of animal studies have shown that malnutrition and environmental influences during an early developmental stage can determine disease risk in later life [4]. The underlying mechanisms seem multifactorial and multilayered: undernutrition of the fetuses causing resultant intrauterine growth retardation and tuning of gene expressions ("programming") by developmental plasticity, the alterations of blood distribution and energy expenditure toward "thrifty" phenotype through short-term metabolic and cardiovascular changes, and chronic endocrine/metabolic alterations leading to structural changes and long-term effects in a tissue- and gene-specific manner [4]. Accumulating evidence has shown that the mechanisms include epigenetic and transcriptional modulations, cellular stresses, metabolic adaptations, alterations to the microbiome, and social determinants [1, 5]. Some of these mechanisms (i.e., epigenetic) act promptly at the time of the perinatal insult, whereas other mechanisms (e.g., endoplasmic reticulum stress) may play a role to influence metabolic changes postpartum during catch-up growth. Among them, epigenetic modulation seems most important [1, 5]. This includes DNA methylation, post-transcriptional histone modification, and microRNA-mediated repression [1], potentially giving rise to multiple metabolic alterations and creating disease phenotypes in later life. Offsprings with intrauterine growth retardation resulting from maternal malnutrition and/or placental insufficiency exhibit various degrees of global or tissue-directed epigenetic modifications [1]. In fact, such epigenetic modulation could be relevant to adverse metabolic phenotype in humans of prenatal famine exposure [6].

Developmental programming is also important in terms of risk of kidney disease and hypertension [7, 8]. Adverse events experienced in utero can affect development of fetal kidney, eventually reducing total nephron number. Low birthweight and prematurity are the most consistent clinical surrogates for a low nephron number, associated with increased risk of hypertension and chronic kidney disease in adulthood [7]. An animal model of maternal low-protein diet showed that prenatal programming could cause hypertension and renal injury in later life, together with an altered renin-angiotensin axis and a deficit in total nephron number [8]. Molecular and cellular mechanisms how low-protein diet leads to hypertension and renal injury in the offspring, however, have not been precisely investigated.

In the current issue of *Hypertension Research*, Shimizu *et al*. reported that fetal malnutrition by maternal low-protein diet resulted in offspring hypertension and renal

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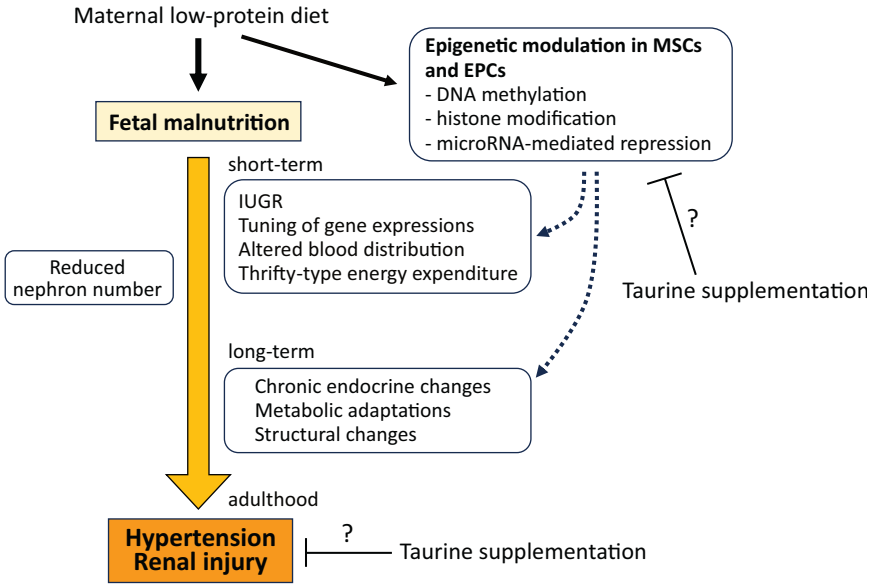

Fig. 1 A hypothetical view of mechanistic link between fetal malnutrition, epigenetic modulation, and hypertension and renal injury in adulthood, and a possible role of taurine in this scheme. Dashed lines mean less solid pathways. Taurine supplementation could ameliorate dysfunction of EPCs and may prevent hypertension, but its roles for epigenetic modulation and renal injury remain undefined. MSCs mesenchymal stem cells, EPCs endothelial progenitor cells, IUGR intrauterine growth retardation

injury in adulthood, in conjunction with abnormal epigenetic modulation in renal mesenchymal stem cells [9]. Maternal low-protein diet also induced a reduced number of label-retaining cells (progenitor cells in the kidney during tubular regeneration) and endothelial progenitor cells in the offspring [9]. These findings first highlighted the notion that abnormal epigenetic modifications can accumulate as a "memory" in mesenchymal stem cells and progenitor cells during development and growth. Another important finding of the present study is that taurine supplementation to the malnourished mother can ameliorate such alterations in the offspring and prevent hypertension in adulthood [9]. The study may give a clue for proposing the importance of taurine supplementation upon maternal undernutrition to prevent adverse outcomes and potential disease risk of the offspring in later life. Taurine, a naturally occurring amino sulfonic acid synthesized by the liver in adults, is a principal constituent in breast milk and postulated to be an important nutrient in neonatal development [10]. Taurine has been reported as a key substance in maternal protein restriction and fetal malnutrition, being implicated in the development of brain [11] and pancreatic islets [12].

The present study gives an interesting suggestion on the mechanistic link between fetal malnutrition, epigenetic modulation, and reversal by taurine (Fig. 1). However, it is not known how and how much specific epigenetic modulation could occur in mesenchymal stem and progenitor cells, and how taurine could reverse these alterations in this model. Also, the difference between protein restriction and caloric (carbohydrate) restriction is not clear at present [1]. Further investigations are no doubt necessary to answer these important questions and to explore novel therapeutic strategies preventing hypertension and other adverse consequences related to DOHaD.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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