Review

Intrauterine undernutrition—renal and vascular origin of hypertension

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Abstract

Objective: A large number of clinical and experimental studies supports the hypothesis that intrauterine undernutrition is an important determinant of hypertension, coronary heart disease and non-insulin-dependent diabetes in the adult offspring. In this review, the renal and vascular repercussions of maternal undernutrition are emphasized, and the physiopathologic mechanisms discussed. The origin of hypertension is detailed based upon the findings of kidney functional parameters and endothelium function studies. A working model linking hypertension to intrauterine undernutrition is proposed.

Keywords: Hypertension; Renal function; Nitric oxide; Endothelial function; Low birth weight

1. Introduction

Undernutrition is still an important public health problem in underdeveloped countries. Maternal undernutrition can affect several physiological functions of the newborn [1]. In addition, correlation between fetal growth restriction in humans and susceptibility to a number of adult chronic diseases, including coronary heart disease, stroke and hypertension have been identified [1,2]. The “fetal programming” hypothesis proposes that these cardiovascular and related disorders derive from fetal adaptations in utero to maternal undernutrition that permanently alters growth characteristics, and postnatal metabolism and physiology [2].

The mechanisms underlying the programming of hypertension by maternal undernutrition are likely to be multifactorial and complex. However, a role for the kidney and the endothelium in the maintenance of raised blood pressure has been reported.

2. Impairment of renal development in intrauterine undernutrition: clinical studies

Evidence from human studies suggests that the kidney may play a key role in the association of maternal undernutrition and the intrauterine programming of hypertension. Renal structure, and specifically nephron number, is a major determinant of blood pressure and renal function [3]. Characteristically, in human populations, the high incidence of hypertension is associated with a decrease in number of nephrons. In fact, an inverse relationship between total nephron number and the risk of developing arterial hypertension has been proposed by Brenner et al. [4,5]. In the African American population, where a high prevalence of hypertension and progressive renal disease was demonstrated, autopsy findings showed smaller kidneys that could be related with lower nephron number [6]. In addition, Keller et al. [7] showed that middle-aged white patients with
primary hypertension had a significant reduction in the number of nephrons per kidney than matched normotensive controls, suggesting a close relationship between number of glomeruli and blood pressure levels.

It has been long recognized that maternal nutritional status is a fundamental point in determining an adequate organogenesis; it is not unexpected that less than optimal diets during pregnancy could interfere in the total nephron number. Therefore, the influences of intrauterine undernutrition on nephrogenesis may underlie the programming of hypertension [8]. This hypothesis receives support from human observations. In fact, Hinchliffe et al. [9] showed that intrauterine growth retardation caused a profound decrease in the number of nephrons but not in the nephron volume of kidneys analyzed within a year of birth. Konje et al. [10] demonstrated that slowly growing fetuses have disproportionately small kidneys. In Australian aborigines, a population in which renal failure is several times higher than in the Australian Caucasian population, an ultrasound study showed that in 174 children aged between 5 and 18 years, birth weight was related to kidney volume; individuals of lower weight at birth appeared to have thinner kidneys of normal length, suggesting decreased nephron number [11]. In addition, Bergstrom et al. [12] demonstrated that conditions in utero, reflected by low birth weight, might affect the risk of renal cell cancer in adulthood.

These observations indicated that the kidney during its period of development can be influenced quite dramatically by alterations in the intrauterine environment that lead to impairment of nephrogenesis and development of hypertension in adult life.

3. Impairment of renal development in intrauterine undernutrition: experimental studies

Several evidences derived from animal studies indicate that changes in fetal environment may affect renal development. This hypothesis receives support from observations that the protein malnutrition, for some part of pregnancy, has been found to reduce nephron number and cause hypertension in the adult offspring. In fact, Merlet-Benichou et al. [13] described a reduction in nephron number in offspring of rats submitted to substantial protein restriction in utero. Franco et al. [14] found in both male and female SHR submitted to intrauterine undernutrition reduced glomeruli number. Woods [15] showed that 50% restriction of protein intake during pregnancy produces offspring with a reduced number of glomeruli, glomerular enlargement and hypertension in adulthood. In addition, Langley-Evans et al. [16] demonstrated that prenatal exposure to a maternal low protein diet in mild-late gestation in the rat induces an impairment of nephrogenesis and hypertension in adult life. Nwagwu et al. [17] have shown that low protein diet in utero induced increased blood urea, urinary output and urinary albumin excretion in resulting offspring.

In our previous work, we have demonstrated that when pregnant rats were subjected to 50% food restriction during the first, second half or throughout pregnancy, the renal function of the offspring was impaired 3 months after birth. Morphometric evaluation showed that the number of glomeruli was significantly decreased both in newborn and adult offspring, irrespective of the period in which restriction was imposed. Glomerular diameter showed a significant increase in every studied group, which characterized a compensatory hypertrophy in the remaining nephrons [18,19]. These findings led us to raise the hypothesis that intrauterine undernutrition could be the determinant of the early appearance of glomerulosclerosis in adult life. In fact, in a subsequent study when renal function studies were performed in 18-month-old intrauterine undernourished rats, a significant decrease in glomerular filtration rate (GFR) and renal plasma flow (RPF) levels was observed when compared to normal controls at the same age. The GFR values were very similar in 3-month-old intrauterine undernourished rats and in control animals, which means that the age related decline in GFR was manifested earlier in young adults because of a significant decrease in the number of glomeruli. Increased blood pressure levels were observed from 8 weeks on while proteinuria began to increase later, in 9-month-old animals. Histological evaluation of kidney sections showed a markedly increase in glomerulosclerosis and tubulointerstitial lesions in 18-month-old intrauterine undernourished rats. Immunohistochemical studies revealed that an accelerated process of glomerulosclerosis took place in those rats, with high expression levels of fibronectin, desmin and D-actin in both glomeruli and Bowman’s capsule as well as in interstitial areas [20]. These findings led us to conclude that the age-induced renal changes could be accelerated in this model of intrauterine undernutrition, with renal structural changes occurring early in life.

Collectively, these studies suggest that intrauterine environment may permanently modify the structure of the kidney, however, that it is not merely a reduced nephron number that is responsible for the hypertension, but compensatory maladaptive changes that occur intrarenally when nephrogenesis is compromised.

4. Mechanisms of impaired renal development in intrauterine undernutrition

4.1. Role of the fetal exposure to maternal glucocorticoids

Fetal exposure to an excess of glucocorticoid appears to be a critical first step in the programming of hypertension [21]. In the fetal period, adverse effects of glucocorticoids upon the structural development of the kidney are inferred. In fact, Celsi et al. [22] have recently demonstrated that the treatment of pregnant rats with dexamethasone (synthetic glucocorticoid) inhibits renal growth in their offspring, culminating in a lower nephron number and in develop-
ment of hypertension. In studies in which dexamethasone treatment was given to pregnant sheep for 2 days only early in gestation (days 26–28 of a total gestation period of ~150 days), the adult sheep had increased blood pressure from 4 months after birth until severe years of age. The nephron number was significantly reduced by 40% from that in age-matched control animals [23]. These data are consistent with a critical period for programming of adult hypertension being close to the start of nephrogenesis. Therefore it is possible that impaired renal development observed in intrauterine undernourished animals could be consequent of fetal exposure to an excess of glucocorticoid. The mechanism by which glucocorticoids exert this effect is, however, unknown.

4.2. Role of the renin–angiotensin system

It is well established that the renin–angiotensin system (RAS) plays an important role in the normal morphological development of the kidney [24]. Thus, changes in this system programmed in utero may be responsible for the renal alterations observed in animals submitted to intrauterine undernutrition. In fact, Ingelfinger et al. [25] observed that maternal protein restriction suppresses renal renin gene expression in newborn offspring. Sherman and Langley-Evans [26] demonstrated that rats exposed to low protein diet in utero when treated with captopril for a period preceding the development of hypertension (postnatal weeks 2–4), hypertension does not develop at eight weeks. This length of treatment would be sufficient to inhibit the intrarenal angiotensin system, but was too late in rat renal development to be able to affect nephrogenesis. It might, however, protect these young rats from developing hypertension by reducing renal sodium-retaining capacity. In addition, Woods et al. [27] showed that renal renin and tissue angiotensin II mRNA levels were significantly reduced in newborn submitted to low protein diet in utero, suggesting that intrauterine undernutrition promoted suppression the newborn intrarenal RAS and this could affect nephrogenesis, resulting in a lower total number of nephrons.

4.3. Role of the upregulation of the sodium transport and altered gene expression in nephron

In kidneys from the offspring of rats given a low protein diet during pregnancy, an increased expression of several genes has been detected, including those encoding sodium transporters. Manning and Vehaskari [28] suggested that inappropriate sodium retention and expansion of extracellular volume could be involved in hypertension observed in rats submitted to intrauterine undernutrition. In a subsequent study, Manning et al. [29] demonstrated that some tubular sodium-related transporters as bumetanide-sensitive Na–K–2Cl co-transporter (BSC1) and thiazide-sensitive Na–Cl co-transporter (TSC) were increased at different ages, suggesting that transcriptional upregulation of Na\textsuperscript{+} transport could originate hypertension in this model. It thus appears that, when nephrogenesis is compromised, the nephrons have an increased capacity to retain salt and water. This is likely to contribute to the development of hypertension.

4.4. Conclusions

There is strong evidence from both clinical and experimental studies that the kidney can be influenced by alterations in the intrauterine environment. In kidneys from rats submitted to intrauterine undernutrition, a reduction in total nephron number has been detected. It thus appears that, when nephrogenesis is compromised, alteration in renal function and glomerulosclerosis are observed. This is likely to contribute to the development of hypertension in adult life (Fig. 1).

5. Endothelial dysfunction in intrauterine undernutrition

The vascular diseases that have been linked to intrauterine undernutrition are characterized by endothelial dysfunction, with loss of the modulatory role of the endothelium may be a critical and initiating factor in the development of these pathogenesis, including hypertension [30]. Endothelial cells actively regulate basal vascular tone and vascular reactivity in physiological and pathological conditions, by responding to mechanical forces and neurohumoral mediators with the release of a variety of relaxing (endothelium-derived relaxing factor, EDRFs) and contracting (endothelium-derived constricting factor, EDCFs) factors [31].
activity of the endothelium extends, however, far beyond the control of vascular tone and reactivity, and the release of vasodilating mediators clearly reflects only one aspect of the homeostatic and protective role of the endothelium. Nevertheless, endothelium-dependent vasodilation is generally used as a reproducible and accessible parameter to probe endothelial function in different pathophysiological conditions [32].

6. Impaired endothelium-dependent relaxation: clinical studies

Human studies have demonstrated considerably association between low birth weight and endothelial dysfunction. Leeson et al. [33] used a noninvasive method to evaluate endothelium-dependent dilatation in the brachial artery, and reported significant, graded and positive association of low birth weight with impaired endothelial function in 9- to 11-year-old children. This study was performed in the absence of clinical complications and cardiovascular risk factors. In addition, Goodfellow et al. [34] and Leeson et al. [35] reported the same correlation between impaired endothelium-dependent relaxation and low birth weight in young adult, suggesting that the impact of prenatal growth on vascular disease does not operate through modification of acquired risk factors.

These observations suggest that intrauterine environment may be important in the cardiovascular system regulation. The relation between birth weight and vascular function may result from programming of the vascular wall by fetal nutrition or environment, or it may be a marker for a genetic association between early growth and endothelial function.

7. Impaired endothelium-dependent relaxation: experimental studies

Impaired responses to different endothelium-dependent agonists have been consistently demonstrated in different vascular beds of intrauterine undernourished rats. Holemans et al. [36] demonstrated that maternal undernutrition during pregnancy caused abnormal response to acetylcholine and bradykinin in mesenteric arteries from resulting offspring. In another study, Ozaki et al. [37] found in skeletal circulation of the fetal rat submitted to intrauterine undernutrition reduced endothelium-dependent response. Franco et al. have shown that intrauterine undernutrition induced decreased endothelium-dependent vasodilation in vivo in the mesenteric circulation [38] and in aortic rings [39] of the Wistar adult offspring. In addition, the same authors demonstrated that severe restriction of all dietary constituents during pregnancy aggravates the already existing endothelial dysfunction in aortic rings isolated from spontaneously hypertensive rats offspring [14]. In contrast, other investigators have not found attenuated responses to acetylcholine in femoral arteries isolated from intrauterine undernourished rats [40]. The discrepancies may be related to differences in the feeding protocol used since the consequences of malnutrition depend on several factors, including the severity and duration of nutritional deficiencies. The type of circulation, the size of the vessel and the conditions of the study may be another source of disparity. Furthermore, endothelial cells from different vascular beds exhibit metabolic and structural differences and may be affected differentially by intrauterine undernutrition.

8. Mechanisms of impaired endothelium-dependent vasodilation in intrauterine undernutrition

The study of the mechanisms involved in the alterations of endothelium-dependent responses is important for better understanding the pathways whereby intrauterine undernutrition leads to endothelium dysfunction and consequently to the development of hypertension and other cardiovascular diseases. Considering that nitric oxide (NO) is the most important agonist involved in this alteration, the intrauterine undernutrition could be promoted by the following.

8.1. Decreased responsiveness of the smooth muscle to NO—role of cGMP

Whereas some of the earlier reports showed enhanced endothelium-independent vasodilatation [36,40], preserved responses to sodium nitroprusside have been repeatedly demonstrated in different vascular beds isolated from intrauterine undernourished rats [14,38,39]. On the other hand, recent studies have shown that the response to nitroprusside was reduced in the rats submitted to low protein diet in utero [41–43]. In one of these studies, significant attenuation of cGMP levels and soluble guanylate cyclase (sGC) expression in resistance cerebral microvessels from intrauterine undernourished rats was found [42]. These findings suggest that abnormalities in the cGMP pathways may be involved in the abnormal endothelium-dependent and -independent relaxation observed in these animals.

8.2. Reduction in NO synthesis

Reduced activity of nitric oxide synthase (NOS), measured by conversion of $^3$H-arginine to $^3$H-citrulline, has been described in aortic isolated from intrauterine undernourished rats [39]. In addition, in the same animals, decrease in gene expression for endothelial nitric oxide synthase (eNOS) was observed [39]. Furthermore, Alves et al. [44] demonstrated that the urinary excretion of NOx (NO$_2^+$NO$_3^-$) was significantly decreased in intrauterine undernourished rats, suggesting that intrauterine undernutrition can promote alteration in endothelial function, in part, by decrease in NO synthesis.
8.3. Substrate availability

Although the supply of L-arginine is not rate-limiting factor for NO synthesis in normal circumstances, reduced availability or impaired transport or metabolism of L-arginine could be a mechanism of endothelial dysfunction in intrauterine undernourished rats. Alves et al. [44] demonstrated that supplementation with L-arginine corrected the high blood pressure levels and improved relaxation to acetylcholine in mesenteric arteriolar bed isolated from intrauterine undernourished rats. Paradoxically, this was associated with a decrease in NOS activity [39], suggesting that L-arginine treatment might improve relaxation in rats submitted to intrauterine undernutrition via alternative NO-independent pathways by scavenging superoxide anion or enhancing cGMP levels.

8.4. Decrease in NO bioavailability—role of superoxide anion

The biological NO activity may be modified by reactive oxygen species (ROS), such as superoxide anion. An increase in superoxide concentration putatively leads to the scavenging of NO and to the cellular damage associated with endothelial dysfunction [30]. Franco et al. [38] demonstrated that treatment of arterioles from the restricted rats with SOD and MnTMPyP (a cell-permeable metalloporphyrin SOD mimetic) corrected the decreased endothelium-dependent relaxation induced by intrauterine undernutrition, suggesting a role for superoxide anion in the impaired endothelial function observed in these animals. These authors also demonstrated that intrauterine undernutrition markedly attenuated the superoxide dismutase (SOD) activity and increased superoxide anion concentrations [38]. Confirming these findings, the treatment of intrauterine undernourished rats with both vitamins C and E promoted reduction in the blood pressure levels, and the antihypertensive effects of these antioxidants vitamins were accompanied by improved endothelium-dependent vasodilation and decreased superoxide anion concentration [45]. In addition, we have found that NADPH oxidase inhibition attenuated superoxide anion generation and ameliorated vascular function in rats submitted to intrauterine undernutrition. Although it is not clear which mechanisms are responsible for the increase in NADPH oxidase activity, a decrease in superoxide anion generation after losartan treatment associated with an increased production of ANG II was observed, suggesting a role of ANG II-mediated superoxide production via activation of NADPH oxidase [46].

8.5. Conclusions

A broad spectrum of evidences suggests that intrauterine undernutrition promotes alterations in NO pathways. Decrease in NO synthesis associated with increased superoxide anion concentration play an important role in endothelium dysfunction observed in resulting offspring (Fig. 2).

9. Gender difference in intrauterine undernutrition

9.1. Blood pressure

There are conflicting findings in the literature about the effect of the intrauterine undernutrition on the development of hypertension in males and females. Kwong et al. [47] demonstrated increased blood pressure levels only in male offspring of rats subjected to intrauterine undernutrition. These authors suggested that male preimplantation embryos have higher capacity to respond to the maternal environment and may, as a consequence, exhibit heightened sensitivity to specific programming influences. Woodall et al. [48] considered male and female offspring together as no gender differences were apparent in offspring of control or restricted diet groups. Ozaki et al. [40] demonstrated that maternal undernutrition during pregnancy causes gender-related hypotension in the resulting offspring, although Franco et al. [39] detected higher blood pressure in both male and female offspring from undernourished dams than in their respective controls. Therefore, the effects of severe nutrient restriction during pregnancy in Wistar rats are gender-independent, but the severity depends on the sex of the animals. The severity of the hypertension is greater in males than in females similarly to that found in other models of hypertension. The gender dichotomy in the manifestation of the severity of the hypertension would seem to be unrelated to the initiating causative mechanism of the hypertensive disorder. Methodological differences could explain the contradictory results. In the various studies, the composition of the diets varied not only in the protein content but also in the fat, carbohydrate and salt contents. Thus, changes in dietary composition may contribute to differences in the consequences of
the fetal undernutrition on the developing cardiovascular system in male and female rats.

9.2. Vascular reactivity

There are few studies that evaluated gender difference in the vascular reactivity in intrauterine undernourished rats. Although decreased acetylcholine-induced relaxation was observed in both male and female offspring, the abnormalities are more pronounced in males than in females [14,36,39,40].

The mechanisms involved in endothelial dysfunction observed in female offspring have not been routinely evaluated. A recent study has revealed that NOS activity, but not gene expression for eNOS, was reduced in female animals [39,40], suggesting that the vasoprotective role of the estrogen on the vascular responses has been lost in females submitted to intrauterine undernutrition.

9.3. Conclusions

There is little information that is not controversial concerning the effects of intrauterine undernutrition on gender differences in development of hypertension and endothelial function. However, some studies have demonstrated that alterations in blood pressure or vascular reactivity are more severe in male than in female rats. In addition, the mechanism(s) involved in endothelial dysfunction observed in female offspring could be a direct response to decreased estrogen levels.

9.4. Future perspectives

The present communication reviews the studies on the deleterious effects of intrauterine undernutrition in kidney and vascular endothelium. These data support the view that intrauterine undernutrition constitutes an important model of hypertension in the young offspring, reinforcing the importance of both educational and nutritional programs during pregnancy in undeveloped countries.

References