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Prenatally programmed hypertension: role of maternal diabetes

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Abstract

Epidemiological and experimental studies have led to the hypothesis of the fetal origin of adult diseases, suggesting that some adult diseases might be determined before birth by altered fetal development. Maternal diabetes subjects the fetus to an adverse environment that has been demonstrated to result in metabolic, cardiovascular and renal impairment in the offspring. The growing amount of obesity in young females in developed and some developing countries should contribute to increasing the incidence of diabetes among pregnant women. In this review, we discuss how renal and extrarenal mechanisms participate in the genesis of hypertension induced by a diabetic status during fetal development.

Key words: Hypertension; Maternal diabetes; Renal impairment; Sodium retention

Introduction

Increased blood pressure is the leading risk factor for heart disease, stroke and renal diseases. One of six people worldwide is estimated to be hypertensive, and it is expected that this number will increase to 1.5 billion by 2025 (1). In Brazil, the prevalence of hypertension is estimated to be between 5 and 30% depending on the area screened (2). The majority of the cases of hypertension are designated as essential or primary, with causes that are not defined (3). Increased evidence from both epidemiologic and experimental studies (4,5) has shown that alterations in the maternal environment can affect embryonic and fetal life, predisposing an individual to cardiovascular, metabolic and endocrine diseases in adult life. This concept has been known as prenatal programming or the Barker hypothesis (6,7).

In this review, we consider experimental results from studies performed mostly on rats and mice (8-11) to discuss how renal and extrarenal mechanisms participate in the genesis of hypertension induced by a diabetic status during fetal development.

Maternal diet

The relationship between prenatal insult, reduced nephron number and the development of hypertension was reported by Brenner et al. (12), who also suggested that food restriction could impair nephron formation, resulting in inappropriate sodium retention (12,13). Confirming this hypothesis, studies utilizing animal models were performed in which dams were subjected to a 50% restriction of food intake (14-16) or a low-protein diet during pregnancy (17,18). These studies provided evidence that the reduction in nephron number was associated with an increase in blood pressure in adult offspring (14-18). The mechanism responsible for the reduction in nephron formation is not completely known. Langley-Evans and McMullen (19) suggested that the maternal diet can have an impact on cell proliferation and differentiation, reducing the cell number or changing the balance of cell types within tissues, leading to a subsequent alteration of physiological function. Woods et al. (20) reported that dietary protein restriction during pregnancy caused suppression of the intrarenal renin-angiotensin system in the offspring, a system that is essential for the normal development of the embryo. The exposure to glucocorticoids during fetal development, which affects tissue development and function, may also contribute to these changes considering that dams subjected to a low-protein diet during pregnancy had reduced activity and expression of 11β-hydroxysteroid dehydrogenase, the enzyme responsible for protecting the embryo from maternal corticoids (21).

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Maternal diabetes mellitus

Nevertheless, the relationship concerning the prenatal insult due to maternal diabetes is still a matter of debate. Amri et al. (22) showed a decreased nephron number in the offspring of streptozotocin (STZ)-treated rat dams with induced diabetes at the beginning of pregnancy. In others studies, Rocha et al. (8) and Magaton et al. (9) examined the effect of diabetes mellitus induced in rats before mating, on the blood pressure and renal function of the adult offspring and observed development of hypertension without a reduction in nephron numbers. In the studies by our group (8-10,23), diabetes induction took place before pregnancy, preventing the effect of STZ on the development of the fetus. Moreover, in the studies by Amri et al. (22), the nephron count was performed using glomerular isolation. We used a methodology in which glomerular number is counted in 40 fields of kidney slides and glomerular diameter and area are calculated using a computer program. With another experimental protocol by Tran et al. (11), diabetes was induced in Hoxb7-Tg mice (transgenic mice in which a green fluorescent protein (GFP) is expressed in the ureteric bud under the control of the Hoxb7 promoter) on the 13th day of pregnancy. It was found that kidneys from neonate offspring of diabetic mothers had smaller glomeruli with a relative reduction in nephron number and with nephron collapse. Furthermore, the timing of the prenatal insult can affect kidney development in various ways. Ortiz et al. (24) treated rats with dexamethasone at different periods during pregnancy and did not observe reduction of glomerular number in all groups, suggesting that there are specific periods of gestation during which dexamethasone interferes with nephron formation.

Glucocorticoids during pregnancy

During pregnancy, glucocorticoids are used to accelerate fetal pulmonary maturation and to prevent respiratory distress syndrome (25). However, this treatment may have adverse effects on the developing fetus (26,27). In animal models, the administration of dexamethasone during pregnancy affected kidney development and caused hypertension (24,27,28). However, Ortiz et al. (24) observed that the offspring of dams treated with dexamethasone on the 13th and 14th days of pregnancy developed hypertension without a reduction in glomerular number, demonstrating that other factors besides the reduction in nephron number can be related to hypertension in prenatal insult models.

Renal sodium excretion

Renal sodium excretion is another important factor contributing to the onset of hypertension. Rocco (29) studied the sodium excretion of diabetic offspring with and without sodium overload and observed that, under normal conditions,

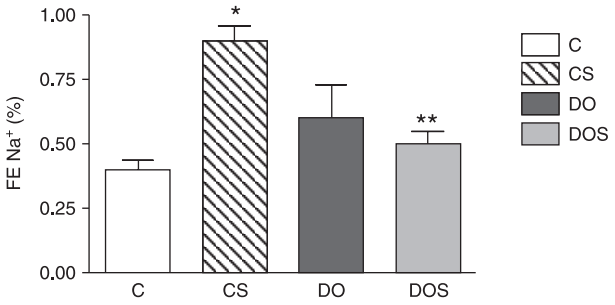

Figure 1. Fractional excretion of sodium (FE Na^+) in rats submitted to sodium overload (CS and DOS) or without sodium overload (C and DO). Data are reported as means ± SEM. C = control; DO = diabetic offspring. *P < 0.05 compared to C; **P < 0.05 compared to CS (analysis of variance followed by the Bonferroni test). Reprinted, with permission, from Rocco (29).

the offspring of diabetic mothers (DO) presented values of sodium excretion similar to control. However, after sodium overload, DO were unable to increase sodium excretion, as did the control group (Figure 1), and their hypertensive status was aggravated. Nehiri et al. (30) also examined the sodium excretion of DO that received a high-sodium diet for three consecutive days and observed that their increase in sodium excretion was significantly delayed compared to control. Moreover, the study of the renal cortex of DO revealed increased expression of epithelial sodium channel (ENaC) and sodium/potassium ATPase (Na^+/K^+ ATPase) without a decrease in the sodium/hydrogen exchanger (NHE3) or other sodium transporters, suggesting that sodium retention was due to increased reabsorption at the distal segments of the nephron (30).

Renin-angiotensin system

An imbalance of the renin-angiotensin system can also cause sodium retention in prenatally programmed hypertensive rats. Wichi et al. (31) measured tissue angiotensin-converting enzyme (ACE) activity in the heart, kidneys, liver, and lungs of DO and observed that ACE activity was enhanced in their hearts, kidneys, and lungs. The positive correlation between hypertension and increased ACE activity was first suggested by Blumenfeld (32), who reported that ACE had an important role in the pathophysiology of hypertension in diabetics (33). More recently, Sharifi et al. (34) demonstrated increased ACE activity in the kidneys, heart, lungs, and aorta of hypertensive two-kidney, one-clip rats.

Magaton et al. (9) analyzed the concentration of angiotensin in renal tissue from adult DO. Angiotensin II (ANG II) and other peptides produced by the renin system, i.e., ANG III, ANG 1-7, and ANG IV, have been reported to influence blood pressure by changing the arteriolar resistance (35). Particular attention has been focused on ANG 1-7 due to

its action. Unlike ANG II, which causes vasoconstriction, proliferation and hypertrophy, ANG 1-7 has been shown to have opposite effects, promoting vasodilatation and antiproliferation (36). In a study by Magaton et al. (9), the concentration of ANG II in renal tissue was similar in the control and DO groups, but the concentration of ANG 1-7 was decreased in DO compared to control, a fact possibly indicating that changes in formation and/or degradation of ANG 1-7 had occurred. Corroborating these results, Chen et al. (37) recently observed that ACE2 gene expression was lower in the hypertensive DO than in control offspring. Considering that ACE2 is a protein involved in the formation of ANG 1-7 (38), its deficiency can be associated with reduced ANG 1-7 levels and development of hypertension in DO.

Nitric oxide system

Sodium retention in prenatally programmed hypertensive rats may also be the result of the imbalance of the nitric oxide (NO) system. In the kidney, NO has numerous important functions including the regulation of renal hemodynamics, maintenance of medullary perfusion, and modulation of tubuloglomerular feedback and tubular sodium reabsorption, resulting in a net effect of natriuresis and diuresis (39,40).

Cavanal et al. (10) measured NO production in aorta segments from DO and control rats using the fluorescent probe 4,5-diaminofluorescein diacetate (DAF-2) and observed that basal NO production was significantly depressed in DO compared to control. After stimulation with acetylcholine (Ach) or bradykinin (BK), NO production increased significantly in all groups, but the increase was of a greater magnitude in the controls than in DO rats. In the DO rats supplemented with L-arginine, NO production was significantly improved, suggesting that decreased substrate availability could contribute to the reduced NO production in this experimental model (Figure 2).

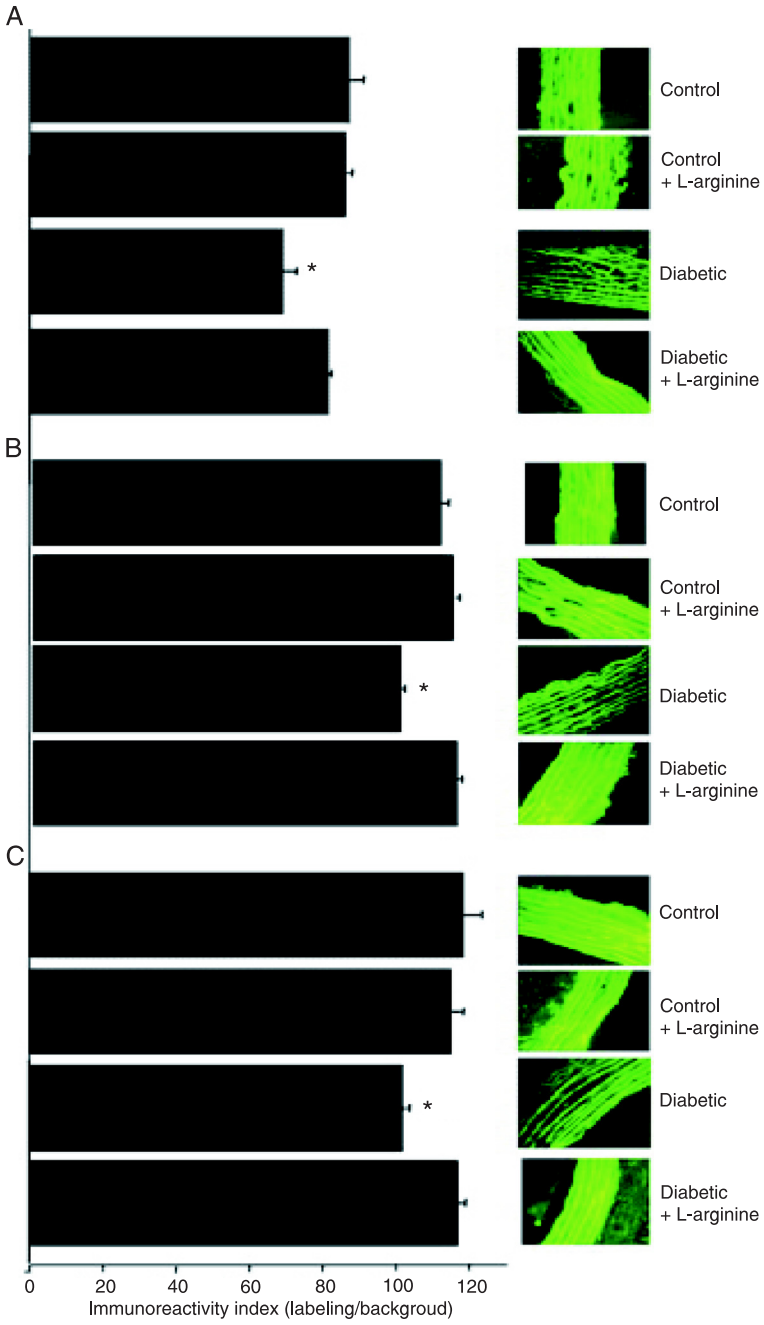

Figure 2. Quantification of DAF-2 fluorescence and representative high power photomicrographs of the aortic rings (magnification 400X). *A*, Under basal conditions; *B*, after stimulation with 0.1 mM acetylcholine, and *C*, after stimulation with 0.1 mM bradykinin. Data are reported as means ± SEM; *P < 0.05 *vs* control, control plus L-arginine (L-arg) or diabetic plus L-arg (analysis of variance followed by the Bonferroni test). Reprinted, with permission, from Cavanal et al. (10).

Under normal conditions, L-arginine levels in the plasma or in the vessels are above the metabolic requirements because they are in excess of the Km of NO synthase enzymes. In kidney disease, renal influx/production of L-arginine can be lower than normal, resulting in locally reduced production of NO. This could be valid in DO because an important decline in glomerular filtration rate was observed in several studies (8-10,23). Moreover, decreased renal ANG 1-7 content could also interfere with NO production, as suggested by Li et al. (41). The authors observed

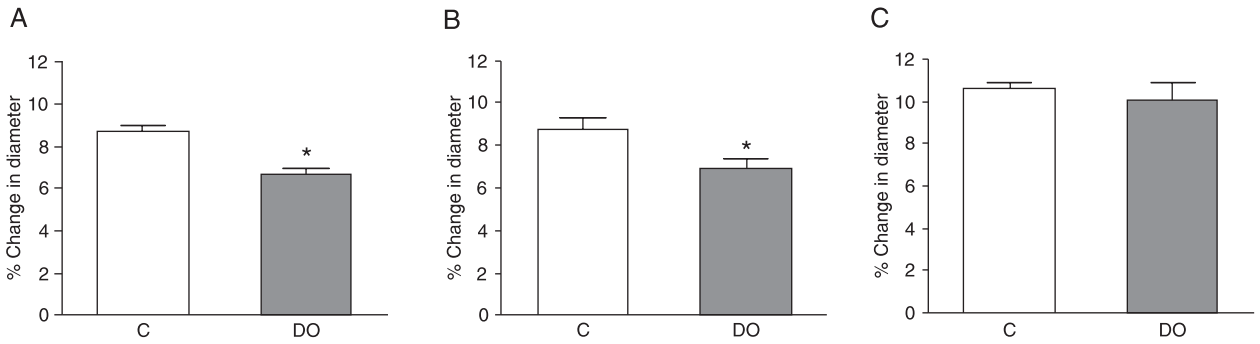

Figure 3. Changes on vascular diameter of the mesenteric arterial bed. Maternal diabetes caused an impaired response to endothelium-dependent agents. Bar graphs show the response of the mesenteric microvessels to *A*, acetylcholine (300 µg/mL); *B*, bradykinin (3.0 µg/mL) and *C*, sodium nitroprusside (1.0 mg/mL) in control (C, open bars, N = 6) and diabetic offspring (DO, filled bars, N = 9) groups. Data are reported as means ± SEM of percent change. *P < 0.05 compared to control (analysis of variance followed by the Bonferroni test). Reprinted, with permission, from Rocha et al. (8).

that the vasodilatory effect of ANG 1-7 in mouse aorta was completely abolished by pretreatment of the vessels with L-NAME and also in endothelium-denuded vessels, indicating that endothelial NO mediates the vasodilatory effect of ANG 1-7 in this model.

Disarrangement in the NO system could also contribute to the development of hypertension due to the vascular effects. To study this issue, the vascular reactivity of DO was evaluated in the mesenteric bed of 12-month-old rats (8). The vasodilatory effect of Ach and BK on norepinephrine-precontracted arteries was reduced in DO (Figure 3). However, the vasodilatory effect of nitroprusside was not impaired, suggesting that the occurrence of disturbances in NO production and/or sensitivity could be contributing to the hypertension observed in DO rats (8).

Metabolic abnormalities

In addition to the development of hypertension, offspring exposed to maternal diabetes during fetal life have been shown to present an increased risk for obesity and diabetes mellitus type 2 (42,43). Silverman et al. (44) evaluated offspring from women with pregestational diabetes mellitus (type 1 or type 2) or gestational diabetes and observed that the prevalence of impaired glucose tolerance was significantly increased in this group compared to control. Similar results were obtained by Pettitt et al. (45), who studied the effect of abnormal glucose tolerance on the offspring during pregnancy in Pima Indian women. The authors correlated the metabolic abnormalities existing in diabetic pregnancy to insulin resistance, obesity, and diabetes in the offspring (45). The mechanism by which maternal hyperglycemia increases the risk of metabolic disarrangement in the offspring is not fully understood. It is possible that the increased offer of glucose to the fetus could act as a stimulus to enhance insulin production and expose the fetus to hyperinsulinemia (43,44). The increase in fetal leptin production can also contribute to the metabolic disarrangement (46,47). Increased concentrations of hormones, such as insulin and leptin, at critical periods of development can work as "endogenous functional teratogens" (48). For example, offspring from hyperglycemic rats develop a "malprogramming" of hypothalamic neuropeptidergic neurons, causing an increase of orexigenic neuropeptide Y and Agouti-related protein, which could lead to hyperphagia and increased weight gain (49).

The insulin overproduction observed during the neonatal period can also be related to the development of cardiovascular disturbances during adult age (42,50,51). Besides the effect of insulin on carbohydrate metabolism, this hormone presents several actions, including the modification of lipid and protein metabolism, ion and amino acid transport, cell cycle and proliferation, cell differentiation, apoptosis, and NO synthesis (52-54). In addition, insulin and other hormones, such as ANG II and norepinephrine, can influence each other (55-57). ANG II impairs the insulin signaling pathway through the SOCS 3 protein. ANG II acting throughout the AT1 receptor decreases insulin-induced NO production due to ERK 1/2 and JNK activation (56). Moreover, ANG II via the AT1 receptor enhances NADPH oxidase activity, increasing reactive oxygen species (ROS) generation (58). Recently, Zhou et al. (59) showed that up-regulation of ANG II and oxidative stress were associated with endothelial dysfunction and insulin resistance in hypertensive Dahl salt-sensitive rats. ROS may affect vascular function: a) directly on endothelial cells and vascular smooth muscle cells, resulting in structural and functional damage; b) by scavenging or inactivating endothelium-relaxing factors, such as NO or prostacyclin, and c) by producing peroxynitrite, a potent constrictor and lipid-oxidizing radical (60,61). Taking into account the multiple relationships between hormones, intracellular messengers and vascular mediators,

the coexistence of hypertension and glucose intolerance is expected.

Conclusions

The exact mechanism involved in the onset of systemic hypertension in the offspring of diabetic mothers is not completely understood. However, the results discussed in this review suggest that several mechanisms may contribute to the development of systemic hypertension in this experimental model and reinforce the need for close monitoring of hyperglycemia during pregnancy to avoid permanent changes in offspring homeostasis.

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