Review

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# Mechanisms involved in developmental programming of hypertension and renal diseases. Gender differences

**Abstract**

**Background:** A substantial body of epidemiological and experimental evidence suggests that a poor fetal and neonatal environment may "program" susceptibility in the offspring to later development of cardiovascular, renal and metabolic diseases.

**Materials and methods:** This review focuses on current knowledge from the available literature regarding the mechanisms linking an adverse developmental environment with an increased risk for cardiovascular, renal and metabolic diseases in adult life. Moreover, this review highlights important sex-dependent differences in the adaptation to developmental insults.

**Results:** Developmental programming of several diseases is secondary to changes in different mechanisms inducing important alterations in the normal development of several organs that lead to significant changes in birth weight. The different diseases occurring as a consequence of an adverse environment during development are secondary to morphological and functional cardiovascular and renal changes, to epigenetic changes and to an activation of several hormonal and regulatory systems, such as angiotensin II, sympathetic activity, nitric oxide, COX2-derived metabolites, oxidative stress and inflammation. The important sex-dependent differences in the developmental programming of diseases seem to be partly secondary to the effects of sex hormones. Recent studies have shown that the progression of these diseases is accelerated during aging in both sexes.

**Conclusions:** The cardiovascular, renal and metabolic diseases during adult life that occur as a consequence of several insults during fetal and postnatal periods are secondary to multiple structural and functional changes. Future studies are needed in order to prevent the origin and reduce the incidence and consequences of developmental programmed diseases.

**Keywords:** developmental programming; hypertension; renal diseases; renin-angiotensin system; sex differences.

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## Introduction

Developmental programming has emerged as a major new concept related to lifelong health and performance of the offspring. A substantial body of epidemiological and experimental evidence suggests that a poor fetal and neonatal environment may "program" susceptibility in the offspring to later development of hypertension, as well as cardiovascular, renal, metabolic and endocrine diseases. The developmental origins hypothesis proposes that when an insult occurs at a critical period of development, the resulting adaptive responses may lead to permanent and long-term changes in organ growth, structure, function and metabolism. Fetal or perinatal responses may include loss of structural units such as nephrons, cardiomyocites or pancreatic β-cells within the developing organ system that probably confer individuals an immediate adaptive benefit for survival, but result in the programming of a reduced functional capacity of an organ system for life [1–3].

Epidemiological studies throughout the world have provided convincing support for the concept of developmental programming by showing a strong association between low or high birth weight and the subsequent risk of developing a range of pathologies as adults, including hypertension, cardiovascular and renal diseases, obesity, type 2 diabetes, immune dysfunction, and behavioral problems [4–6]. The relationship between adult disease and birth weight forms a U-shaped curve, demonstrating increased risk with both low [7, 8] and high birth weight [9, 10]. The low birth weight

is followed by an accelerated catch-up growth during infancy and childhood that has important consequences later in life because it may predispose to obesity and cardiovascular diseases in adulthood [11–13].

The current evidence showing that fetal and early postnatal life are critical developmental windows, emphasizes the importance of interventions designed to correct the developmental defects during these periods, because if the organ systems are indeed programmed, later interventions may be much less effective [14, 15]. In this regard, studies in animal models and humans showed that offspring whose mothers experience nutrient restriction only during early stages of pregnancy, still exhibit many of the phenotypes observed in offspring born from mothers that are undernourished for the whole pregnancy. These phenotypes include increased adiposity, poor growth, poor glucose tolerance, and dyslipidemia [16–18].

Moreover, many developmental programming studies have found that male and female offspring exhibit different phenotypes following insults in utero, as well as differences in the severity or the age-dependent development of cardiovascular and renal diseases. In this regard, studies performed in animals models of intrauterine growth restriction (IUGR) induced by placental insufficiency, protein-restricted diet and global-restricted diet have shown that male and female offspring are hypertensive early in life, but blood pressure (BP) may decrease transitorily to normal levels in females during adulthood [19–21]. Sex differences can be caused by differences in patterns (genetic, transcriptional and morphological), or in timing of development and can be influenced by steroid hormone exposure during intrauterine and postnatal life [22].

Numerous animal studies have been conducted to elucidate the mechanisms leading to developmental programming of arterial hypertension and renal dysfunction, and to identify potential therapeutic targets that can be used clinically to overcome their negative consequences. A large number of models in rats, mice, sheep, swine and guinea pigs have been used to perturb prenatal and/or postnatal development. The altered development has been elicited by global dietary restriction, low protein diets, micronutrient-restricted diets, high-fat diet, impaired placental perfusion, glucocorticoid exposure, gestational diabetes, chronic hypoxia, neonatal hyperoxia, and reductions of cyclooxygenase-2 (COX2) or renin-angiotensin system (RAS) activity [1, 3, 20, 23–28].

Although several mechanisms seem to be involved in the developmental programming of hypertension and renal disease, it has been proposed that the cardiovascular and renal diseases are partly secondary to a reduction in nephron number during renal development (Figure 1) [29–31]. It has been shown that various adverse events during fetal life or lactation period such as low protein intake, zinc and vitamin A deficiency, reduced placenta perfusion or administration of steroids induced significant reductions in body weight and nephron endowment [23, 32–34]. The loss of nephrons within the developing kidney would result in the programming of the organ's reduced functional capacity for adult life. The inverse relationship between nephron number and BP during adult age is supported by many clinical and experimental studies [30, 31, 35]. Studies performed in rats have shown that the BP increment during aging is significantly greater when there is a 37% decrease in nephron endowment than when this decrease is 17% [27, 28, 36, 37]. Based on the available clinical and experimental data it may be proposed that it is the reduction in nephron number during nephrogenesis, rather than a decrease in nephron number after nephrogenesis is completed, that predisposes the adult to renal and cardiovascular diseases. The increase in BP and the deterioration of renal function as a consequence of an altered renal nephrogenesis are sex-dependent and probably related to the degree that renal development is affected [27, 28, 30, 36, 38, 39].

The decrease in nephron endowment during renal development can be secondary to changes in several regulatory mechanisms, such as RAS or COX2 activity. In support of these possibilities it has been reported that the administration of steroids or a low protein intake to the pregnant mother, or the reduction in uterine perfusion, induces a decrease in RAS activity and nephron endowment (Figure 1) [30, 40, 41]. It is also known that

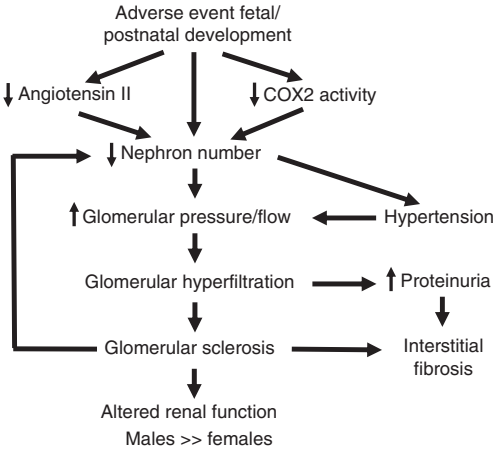


**Figure 1** Renal changes in response to an increase in blood pressure and a decrease in nephron number in developmental programming of hypertension. A greater activation of several mechanisms explains the greater alteration of renal function in males than in females. Different mechanisms are involved in the altered renal function sex-dependent adaptations.

the administration of a converting enzyme inhibitor (CEI) or an AT1 receptor antagonist (ARA) during renal development induces significant decreases in body weight and nephron endowment and, both, an important increment of BP and a deterioration of renal function [27, 30]. The importance of COX2 in renal development and fetal programming of hypertension has been demonstrated in studies showing that COX2 inhibition during nephrogenic period elicits a decrease in body weight and nephron number, the development of hypertension and a deterioration of renal function during adulthood [28, 42].

## Mechanisms of developmental programming of hypertension and renal diseases

These mechanisms include morphological and functional changes of the cardiovascular and renal systems, hormonal and metabolic alterations, epigenetic changes, the disruption of apoptotic and proliferative timing or cell pattern and the induction of oxidative stress and inflammation processes. In the next sections, evidence supporting the importance of these mechanisms – and demonstrating that there are important sex-dependent differences in the evolution of the developmental programming of hypertension and renal disease – will be summarized.

## Cardiovascular changes

Accumulating evidence demonstrates the existence of morphological and functional changes in the cardiovascular system in several models related with developmental programming of hypertension. However, the role of these changes has not been extensively examined and further studies are clearly needed to further define their importance. With respect to the heart, it has been shown that IUGR may alter patterns of cardiomyocyte hyperplasia, apoptosis and hypertrophy that modify the myocardial and vascular development during growth as well as cardiac function during adulthood [2, 43]. It has also been reported that hypoxia during pregnancy can alter fetal heart growth, resulting in cardiac structural abnormalities of offspring that persist at a adult age. These abnormalities involve ventricle septal defects, myocardial thinning, ventricle dilatation, reduction in cardiomyocyte proliferation, increased apoptosis of cardiomyocytes and increased percentage and size of differentiated binucleated cardiomyocytes. Subsequently, the increased cell death in the fetal heart may lead to cardiomyocytes hypertrophy and to an increase in the heart to body mass ratio [2, 44–48]. Moreover, studies performed in sheep have shown that placental insufficiency causes a delay in the differentiation of mononucleated to binucleated cardiomyocytes and an increase in cardiomyocytes size [49–51], which is associated with an increase in apoptosis and in the insulin-like growth factor (IGF)-1 and IGF-2 receptors gene expression [52, 53]. Conversely, the administration of glucocorticoid during fetal life decreased DNA content in the left ventricle [54], while adrenalectomized sheep fetuses exhibited greater cardiomyocyte proliferation [55].

Experimental evidence also shows that male and female offspring adapt differently to developmental stressors, with female offspring exhibiting a protected cardiovascular status. This sex-specific effect is consistent with findings in rats in which IUGR, as a result of either hypoxia or low protein diet, caused cardiac remodeling and impaired recovery to ischemia-reperfusion in adult male offspring, but had no effect on the female heart [47]. It has also been shown that female rats exposed to chronic prenatal hypoxia exhibited an improved contractility and increased coronary flow with respect to male rats [48, 56]. Moreover, human studies showed that IUGR children tend to keep their relatively smaller left cardiac structures in adulthood. These morphological alterations may lead to insufficient cardiac functioning for increasing metabolic demands in postnatal life. Subsequently, as in animal models, the heart may respond by growth and hypertrophic remodeling, that is a strong and independent risk factor of cardiovascular morbidity and mortality in adulthood [57–59].

Vascular structural and functional alterations have also been reported in several models of fetal programming associated with low birth weight. These studies have showed that protein and caloric restriction during gestation induces an intima-media thickness remodeling and changes in the composition of the extracellular matrix of aorta and mesenteric arteries [60–62]. Regarding endothelial function, impaired endothelium-dependent vasodilatation has been reported in aorta, carotid and mesenteric arteries in offspring of dams following moderate zinc deficiency, protein restriction, caloric restriction or hypoxia during pregnancy. In addition, male offspring with IUGR showed a more pronounced reduced vascular relaxation than female [21, 62, 63]. These functional alterations are associated with an increased production of reactive oxygen species (ROS), an increased AT1 expression, and a decrease of endothelial nitric oxide synthase (eNOS) and soluble guanylate cyclase expression [64–66]. The

decreased bioavailability of nitric oxide (NO) in conduit and resistance arteries would induce a decrease in arterial compliance and impair the vascular smooth muscle response to the increases in shear stress that occur as a consequence of the BP elevation.

## Renal changes

The renal changes occurring in developmental programming of hypertension are secondary not only to the BP increment but also to the adaptation to a decrease in nephron number. As already mentioned, this decrease in nephrons has been observed in most of the experimental models of fetal programming that have examined the number of nephrons using appropriate techniques [23, 32–34]. The reduction in nephron endowment is accompanied by a significant elevation in single nephron glomerular filtration rate (snGFR) that is already evident at a young age [27] and that probably occurs when trying to maintain total GFR within normal limits. The increase in snGFR would be secondary to an elevation in glomerular capillary pressure as a consequence of a reduction in afferent arteriolar resistance and an increase in postglomerular resistance. The greater snGFR in males than in females probably contributes to the greater proteinuria and greater renal damage found in males when there is an alteration in renal development (Figure 1) [37, 38]. The proteinuria would also be responsible of the greater renal damage in males because protein overload of proximal tubule cells activates intracellular signals that induce an increase of vasoactive, inflammatory mediators and growth factors [67, 68]. The sex-dependent differences in the deterioration of renal function have been reported using different models of developmental programming and are more evident as animals aged [30, 36, 37, 39, 69].

The decrease in preglomerular resistance in order to increase snGFR seems to be secondary to an increase of COX2-derived metabolites in both sexes, but this increase is significantly greater in males than in females during aging [37]. An increase of COX2 and NOS1 expression in the macula densa of males, but not females, would be accompanied by an enhanced production of prostaglandins (PGs) and NO (Figure 2). Consequently, these vasodilator molecules would induce a decrease of preglomerular vascular resistance in males. The increment in COX2 and neuronal NOS in the macula densa could be secondary to a greater oxidative stress and a greater RAS activity in male rats [36, 70]. An enhanced efferent arteriolar tone, secondary to a greater sensitivity to angiotensin II (Ang II) and a decrease in eNOS, could also be involved in the renal damage found in male animals with a reduced nephron endowment (Figure 2) [36].

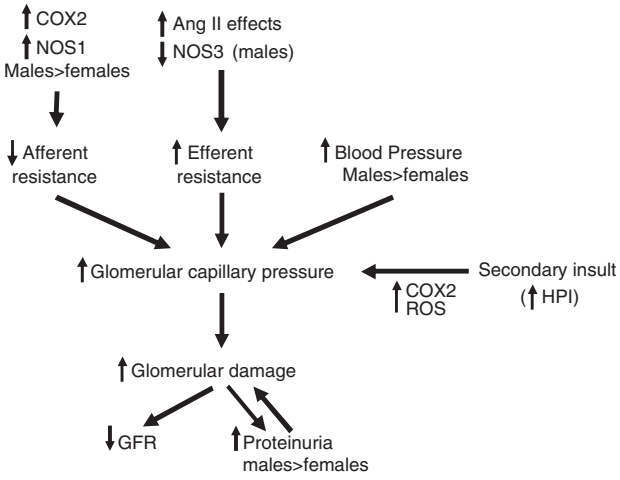


**Figure 2** Renal mechanisms leading to an increase in glomerular capillary pressure, glomerular damage and to a deterioration of renal function in developmental programming of hypertension. Ang II, Angiotensin II; COX2, cyclooxygenase-2; NOS, nitric oxide synthase; intake HPI, high protein; ROS, reactive oxygen species; GFR, glomerular filtration rate.

A dramatic sex-dependent difference in the evolution of the glomerular and tubulointerstitial damage during aging is found when nephron endowment is reduced during renal development. The accelerated progression of glomerulosclerosis (GS) in males is most probably secondary to a greater increment of glomerular capillary pressure because the changes in pre- and postglomerular resistance would allow the higher BP in males to be transmitted to glomerular capillaries, causing a progressive mechanical disruption of their integrity and accelerating underlying injury. As a consequence of the progressive sclerosis some glomeruli fail and non-functional and poorly functioning units emerge. Then, the remaining glomeruli need to hyperfilter and as a consequence of this, a vicious cycle of progressive renal injury occurs that would be responsible for the greater decrease of GFR and renal blood flow (RBF) in males than in females during aging (Figure 1). The greater tubulointerstitial damage in males may be partly secondary to the sex-dependent differences in GS and proteinuria [38]. The deterioration of the renal structure and renal function together with the higher BP in males most probably contributes to the greater mortality rate at adult ages in males than females with a reduced nephron endowment. Regulatory mechanisms such as Ang II, oxidative stress and gonadal steroids may be involved in the sex-dependent evolution of glomerular hypertrophy and renal damage during aging [36, 71].

Renal functional reserve is affected when there is a reduction in nephron endowment because the renal vasodilatory and excretory responses to increments in plasma aminoacids (AA) concentration are abolished [72]. This decrease in renal functional reserve is already observed with a small reduction in nephron number (17%) and most probably occurs because glomerular pressures and flows are at a level that can not increase more when submitted to a vasodilatory stimulus. Blockade of the renal hemodynamic response to an increment in plasma AA could also be secondary to an elevated GS index and greater glomerular volumes [27, 28] and to an alteration of the mechanisms involved in the regulation of this response [73, 74]. The decrease in renal functional reserve as a consequence of an altered renal development also reduces the renal ability to maintain sodium balance because the renal excretory response to an acute sodium load or to a prolonged increment in sodium intake are significantly blunted, leading to the development of a sodium-sensitive hypertension during aging (Figure 3) [38, 72]. Figure 4 shows that the pressure-natriuresis relationship is shifted to the right without changes in the slope at a young/adult age. However, the shift in the pressure-natriuresis relationship is also accompanied by a change in the slope at an adult/advanced age [38]. The decrease in the renal ability to maintain sodium balance could be secondary to an increased expression of Na-K-2Cl transporters in the ascending limb of the loop of Henle, an activation of renal sympathetic nerves and/or a greater activity of the RAS [36, 75–77].

The greater deterioration of renal function during aging in males than in females with an altered renal development is more evident when a secondary insult such as a prolonged increment in protein intake is elicited. It has been reported that a high protein intake (HPI) induces an increment in proteinuria in males but not in females at a young/adult age (Figure 2). However, at an old age, this HPI not only induces a greater increment of proteinuria in males than in females but also leads to a significant decrease (70%) of GFR only in males [37]. This accelerated aging-dependent deterioration of renal function in males, in response to a secondary insult such as a prolonged HPI, could be explained by an increase in COX2-derived metabolites and by a greater ROS production [36, 37]. This hypothesis is supported by studies showing that an enhanced production of ROS exacerbates the proinflammatory PGs actions [78]. Considering the increased popularity of HP diets used in efforts to lose weight, the results reported in our previous studies [37] may have important clinical implications. These results strongly suggest that a HP diet should be absolutely avoided in male patients that may have had an alteration in renal development, such as those treated with glucocorticoids to accelerate lung maturation or those with a low birth weight [30, 31, 39]. These results support the notion that stimuli that elicit even a moderate alteration in renal development will induce a significant increment in arterial BP and a deterioration of renal function that will be more important in males than in females during aging. These observations also emphasize

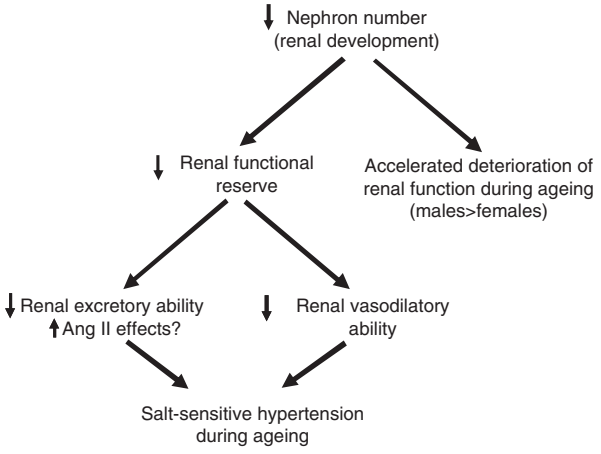


**Figure 3** The decrease in renal functional reserve secondary to a decrease in nephron number during development reduces the vasodilatory and excretory abilities of the kidney and leads to a sodium-sensitive hypertension during aging.

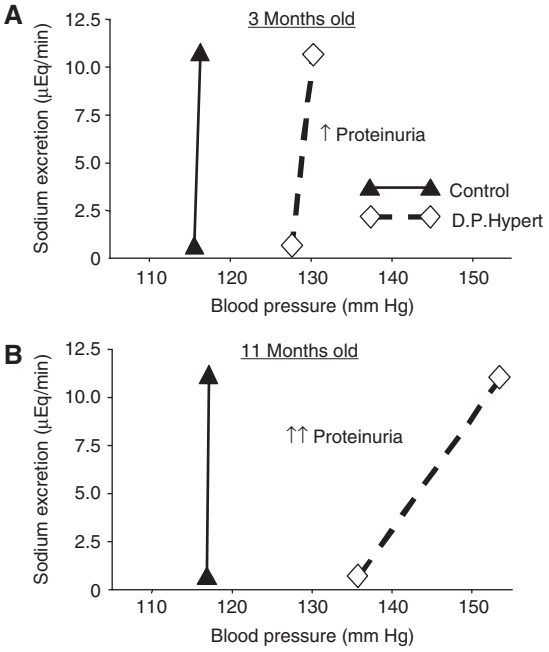


**Figure 4** Changes in pressure-natriuresis relationship in (A) young/adult (3 months) and (B) advanced- age(11 months) rats with developmental programming of hypertension (D.P. Hypert) secondary to a decrease of Ang II effects during renal development. Data obtained from reference [38].

the importance of not affecting the mechanisms involved in the regulation of renal development.

## Renin-angiotensin system

The involvement of RAS in the rise of BP and in the alterations of renal function has been demonstrated in most of the developmental programming models currently used [37, 38, 79–82]. This involvement has been reported in studies showing that BP decreases to normal levels when a CEI or an ARA is administered [37, 38, 79, 80], and showing that several components of the RAS are activated [79, 80, 82, 83]. An increase of Ang II effects seems to be involved in the development of a sodium-sensitive hypertension during aging in animals with developmental programming of hypertension [37, 38]. It has also been demonstrated that the greater increment of BP during aging in males than in females with a reduced nephron endowment is secondary to a greater activation of Ang II effects in males [38]. Several studies have examined whether the involvement of the RAS in developmental programming of hypertension is secondary to an enhanced renin activity and to changes in the expression and/or sensitivity of Ang II receptors in renal and extrarenal resistance vessels (Figure 5) [79, 80, 82, 84, 85]. Contradictory data with respect to the plasma renin activity (PRA) levels in animals with developmental programming of hypertension have been reported [82, 86]. These results may be explained by the multiplicity of models employed and the sex and age at which the studies were performed. However, most of the studies performed support the notion that the regulation of PRA is altered because the increased BP perse would be expected to reduce renin release [87] but PRA is within normal levels in most animals with developmental programming of hypertension. An increase in the sensitivity but not in the $AT_1$ receptor expression in extrarenal resistance vessels may also be involved in the BP elevation in these animals (Figure 5) [36, 85]. The sex-dependent differences in the hypertension may also be explained by different levels of $AT_2$ receptor expression in both sexes [84].

An increased renal sensitivity to Ang II has also been reported in animals with an adverse event during renal development because acute increments in Ang II lead to a renal vasoconstriction that is greater than that found in normotensive animals [36, 83, 85]. This enhanced renal hemodynamic sensitivity to Ang II occurs at a young age and is maintained at adult and advanced ages [36]. The increased sensitivity to Ang II cannot be explained by an increase in $AT_1$ receptors in the renal vasculature because

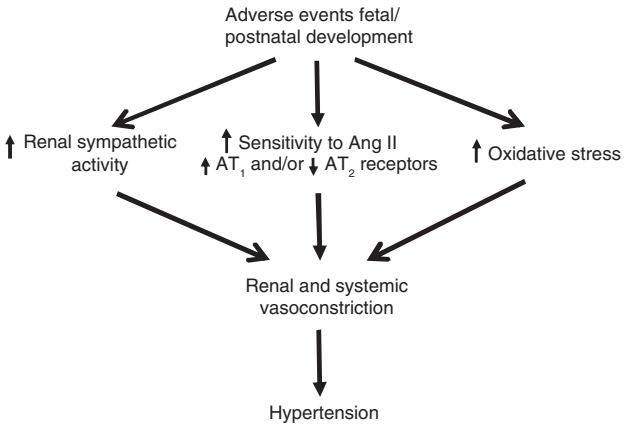


**Figure 5** Renal mechanisms linking an adverse environment during fetal and/or postnatal development with an increased risk for hypertension and renal disease.

the expression of these receptors seems to change at different ages, being elevated at a young age, normal at an adult age and decreased at an advanced age, when compared to the expression found in normotensive animals [36, 83, 85]. The greater hemodynamic sensitivity to Ang II could be secondary to an enhanced affinity and/or activity of glomerular $AT_1$ receptors to Ang II and/or to a fall in $AT_2$ receptors. In this regard, it has been reported that the $AT_2$ receptor expression is reduced and the ratio $AT_1/AT_2$ is enhanced in male rats with an altered renal development (Figure 5) [83].

$AT_1$ receptor sensitivity in renal vessels is similarly enhanced in both sexes of animals with developmental programming at adult and advances ages despite renal $AT_1$ receptor expression changes during aging and may be greater in males than in females at an advanced age [36, 85]. This sex-dependent difference in $AT_1$ receptor may contribute to the greater renal damage found in males as Ang II is a potent growth factor [88] and a gender-based difference in the function of the RAS has been proposed as a mechanism that explains why women progress more slowly than men to end stage renal disease [89]. The similar renal response to Ang II in both sexes could be considered as unexpected because several studies have proposed that the renal Ang II effects are modulated by sex hormones [90, 91]. These studies have shown that Ang II-induced vasoconstriction is modulated by estrogens [91] and that testosterone mediates the greater renal sensitivity to Ang II in young male rats submitted to a growth restriction during fetal development [90]. However, these studies did not compare the renal hemodynamic response to Ang II in both sexes. The absence in the renal vessels of a greater vasoconstrictor effect of Ang II in males has also been demonstrated in studies performed in humans [92,

93]. In fact, these studies showed that the renal vasoconstrictor effects of Ang II are greater in women than in men. A sex difference in the renal activation of signaling pathways downstream of the Ang II receptors could contribute to the observed renal response to Ang II [94].

## Oxidative stress and inflammation

Human and animal studies support the notion that oxidative stress and inflammation are connecting links between intrauterine insult and programming of cardiovascular and renal diseases in postnatal life. Epidemiological studies have reported elevated levels of lipid peroxidation in women with growth-restricted fetuses [95, 96] and in their hypertensive infants [97, 98]. In addition, it has been shown that maternal inflammatory stress may affect the placenta and influence expression of fetal genes related to inflammatory processes. The epigenetic changes resulting in stimulation of proinflammation activity may persist during adult life, enhancing the risk of atherosclerosis in IUGR subjects. In this regard, it has been described an association between maternal reactive protein C and atherosclerosis lesions in these subjects [99, 100].

The involvement of oxidative stress in the developmental programming of hypertension has been also demonstrated in numerous experimental studies. They have reported that hypertension and vascular dysfunction are associated to an elevated oxidative stress and that the administration of antioxidants induces a significant decrease in BP [23, 36, 101, 102]. The increase in oxidative stress seems to be related to an overactivity of Ang II (Figure 5) because the antioxidant-induced decrease in BP is prevented when hypertensive animals are pretreated with an ARA [36]. This interaction between Ang II and oxidative stress is supported by studies showing that oxidative stress mediates the vasoconstrictor effects of Ang II [103] and that the Ang II effect on oxidative stress is enhanced in adult sheep exposed to glucorticoids in utero [104]. It has also been shown that the hypertension and vascular dysfunction in adult offspring of mothers with low protein diets are related to the Ang II enhanced vascular superoxide anion production [105]. Vascular dysfunction in developmental programming is also associated to an increase in proinflammatory markers and a decrease in NO and PG. In this regard it has been reported that prenatal hypoxia increases myogenic response and decreases endothelium-dependent relaxation of mesenteric arteries in adult offspring by reducing vascular NO and vasodilator PG bioavailability [106, 107].

A significant increase of oxidative stress also occurs in other organs and tissues of animals with developmental programming of hypertension. Previous studies showed that adult offspring of mothers treated with glucocorticoids during pregnancy have an increased ROS production in the coronary circulation and in the cardiac tissue [108, 109]. It has also been demonstrated that maternal hypoxia increases oxidative and inflammatory stress in fetal hearts and that antioxidant treatment to mothers exposed to hypoxia prevents the increase of oxidative stress in the heart and liver of their offspring [110–112]. Moreover, an increase of oxidative stress in the kidney has been associated with the deterioration of renal function in different experimental models of developmental programming [23, 36, 113, 114]. In this regard, Tomat et al. demonstrated that the elevation in BP and the decreased renal function secondary to dietary zinc restriction during fetal life and lactation is accompanied by an activation of renal apoptosis and renal oxidative stress damage [23, 113]. The increase in renal oxidative stress in developmental programming is significantly greater in males than in females [36, 114] and probably contributes to the greater GS in males [27, 28].

## Sympathetic nervous system

Experimental and clinical studies have reported that sympathetic nervous system is also involved in developmental programmed hypertension. Human studies have shown an enhanced sympathetic activity response to psychological stress in subjects who were small for gestational age [115]. Experimental studies have proposed that the kidneys play an important role in the BP increment secondary to the sympathetic overactivity. They have demonstrated that renal norepinephrine content is elevated in adult offspring of mothers administered glucorticoids or having reduced uterine perfusion during pregnancy. Renal denervation in these rats induces a decrease of BP and in the renal sodium transporter abundance [75, 116]. It has also been reported that basal renal sympathetic activity is enhanced in these rats and that the hypertension and renal sympathetic activity are exacerbated by stress in animals models of developmental programming [117, 118, 119].

Several mechanisms may be involved in increasing sympathetic activity in developmental programming of hypertension. One possibility is that the sympathetic overactivity may be initiated by renal afferents as a consequence of renal dysfunction. In support of this possibility it has been shown that renal function and renal

structure are affected in animals with developmental programmed hypertension and that renal sympathetic afferents can be activated by minor injury [27, 30, 36, 37]. The change in renal afferents results in an increase in central sympathetic nerve activity and hypertension, which are prevented by renal denervation [76]. It is also possible that prenatal programming of sympathetic overactivity is secondary to an increase in adiposity and plasma leptin [116]. Finally, it has been proposed that RAS may also be involved in the enhanced renal sympathetic activity (Figure 5). This latter possibility is supported by studies showing that hypertension is associated to an enhanced $AT_1$ receptor expression in several areas of the brain and that the intracerebroventricular administration of an ARA induces a significant reduction in BP [120]. It has also been reported that the administration of a CEI prevents the exaggerated renal sympathetic and pressor responses to physical stress in rats with developmental programming of hypertension [121]. The involvement of Ang II in the effects of sympathetic overactivity in this hypertension is further supported by studies showing that stimulation of the $AT_1$ receptor on catecholaminergic cells is required for the full development of Ang II-dependent hypertension [122].

## Sex hormones

Sex-dependent differences in developmental programming of cardiovascular and renal diseases have been explained by the effects elicited by sex hormones and their interaction with other regulatory mechanisms. The importance of sex hormones was first suggested by studies showing that intrauterine growth-restricted male and female animals are hypertensive during the pre-pubertal age. However, after puberty, BP remains elevated in male animals and may decrease transitorily to normal levels in their female counterpart [20, 71, 116]. The involvement of sex hormones in BP regulation at adult life has also been reported in numerous studies performed in other models of experimental hypertension, such as spontaneously hypertensive and Dahl salt-sensitive rats [123].

To address gonadal hormones impact on BP, most investigators have examined BP changes in response to castration or ovariectomy in animals, with and without the simultaneous administration of testosterone or 17β-estradiol, respectively. Several studies have shown that hypertension can be induced in female growth-restricted offspring by removal of the ovarian hormones and that BP decreased again to normal levels when treated with estradiol [20, 124]. These studies proposed that estradiol has a protective effect against programmed BP increments in female offspring of mothers with reduced uterine perfusion or with a severe reduction in protein intake during pregnancy. Ojeda et al. [122] have also reported that testosterone is implicated in contributing to hypertension in adult males with IUGR because their hypertension is abolished when they are castrated and BP increased again to hypertensive levels after treatment with testosterone.

The importance of sex hormones in BP regulation seems to be related to their effects on other mechanisms such as RAS and oxidative stress. In this regard, it has been reported that testosterone may serve as a stimulus to enhance intrarenal angiotensinogen in adult male growth-restricted offspring, thus exacerbating the increase in BP in adulthood [21]. With respect to the cardio-renal protective effects of estradiol, it has been shown that it reduces renal inflammation and oxidative stress [125] and down-regulates renal AT1 receptors [126]. It has also been demonstrated that estradiol can reduce angiotensin converting enzyme (ACE) dependent pathway through which Ang II is synthesized, and increase ACE2-dependent pathway that generates Ang [1–7], which acts as a negative regulator of the vasoconstrictor effects of Ang II [127]. Therefore, it is clear that the regulation of the RAS by estrogen serves as a potential mechanism in mediating the sex-specific differences in BP induced by fetal insults.

## Growth related hormones and metabolic alterations

The decrease in body growth found in developmental programming of cardiovascular and renal diseases may be secondary to changes in several hormonal factors such as growth hormone (GH), IGFs, placental growth hormone (PGH) and insulin. Under normal conditions it has been shown that IGFs control growth independently of fetal GH secretion, while PGH is the prime regulator of maternal serum IGF-1 during pregnancy. The involvement of these hormones in developmental programming is suggested by studies showing that total as well as free PGH and IGFs are significantly lower in pregnancies with intrauterine growth retardation [127, 128]. Moreover, the levels of IGF-1 and insulin are reduced in the cord blood of IUGR neonates [129]. These hormonal systems can be affected by different intrauterine injuries and may play a role in the future occurrence of insulin resistance and hypertension. In this regard, it has been shown that iron or zinc deficiency may reduce the activity of hormones involved

in fetal and neonatal growth, like IGF-1 and its receptors [130, 131]. It has also been reported that prenatal dexamethasone exposure in female offspring weaned onto the high-fat diet potentiates hepatosteatosis and inhibits the GH axis function, because it induces a decrease of plasma IGF-I concentrations and in the hypothalamic GHRH mRNA [132]. The involvement of these changes in growth-related hormones is further supported by a study showing that pre-weaning GH treatment reverses hypertension and endothelial dysfunction in adult male offspring of mothers undernourished during pregnancy [133].

Insulin resistance seems to be one of the most important disorders linking fetal restricted growth with increased risk of obesity and metabolic diseases in adult life [134]. A previous study in adult male subjects born at term reported an inverse relationship between birthweight and insulin resistance [135]. Fetal undernutrition may also program metabolic disorders because it may reduce glucose uptake and increase gluconeogenesis in the liver, increase lipid peroxidation in the muscles and reduce insulin inhibition of lipolysis in adipose tissue [136]. Moreover, the enhanced risk of metabolic syndrome development in subjects born with IUGR has been associated with an increased cortisol release [137]. Finally, it has been proposed that an increase in adiposity is involved in the hypertension found in IUGR neonates. In support of this notion, it has been reported that adiposity seems to be a risk factor for increased BP [138], and programming of increased adiposity has been reported in models of maternal undernutrition [139] or with reduced uterine perfusion during pregnancy [116].

## Epigenetics changes

Epigenetic modifications could be involved in some of the structural and functional alterations in vessels, heart and kidneys that increase the predisposition to cardiovascular and renal diseases in developmental programming models. These epigenetic changes include DNA methylations, histone modifications and microRNAs. DNA methylation takes place on cytosinephosphate-guanine dinucleotide-rich regions that are generally found in promoter regions involved in regulating gene transcription. By this mechanism, gene transcription is silenced. Histones modifications, by methylation, acetylation, phosphorylation, biotinylation, ubiquitination and ADP-ribosylation, regulate gene expression by determining the access of transcription factors to DNA [140]. Finally, microRNAs, small single-strand RNA that do not encode proteins, regulate post-transcriptional expression level of genes involved in several processes such as apoptosis, cell growth and differentiation of vessels, heart and kidneys [141]. These epigenetic changes during gestation can alter the pattern of gene expression without changing DNA sequences and therefore give rise to different phenotypes [140].

The epigenetic changes can be secondary to a deficiency in some micronutrients such as choline, niacin, folic acid, vitamin B12, vitamin C, methionine, glutathione, zinc and selenium. These micronutrients seem to be essential for the epigenome because they are structural components of enzymes that modify DNA and histones (DNA methyltransferases, histone lysine methyltransferases, and histone deacetylases enzymes) [142]. The epigenetic changes secondary to a deficiency in these micronutrients may persist into adult life and increase the predisposition to cardiovascular and metabolic diseases. In this regard, it has been reported that an alteration in DNA methylation patterns during development leads to an increase in body weight, a higher percent body fat, an increased insulin resistance, and an elevated BP during adulthood [143]. It has also been shown that prenatal protein restriction in rodents induces alterations in hepatic glucocorticoid receptors and PPAR gene methylation, which are prevented by adding folic acid to the diet [144]. Folate supplementation also prevents the elevation of BP and the impaired endothelium-dependent vasodilatation elicited by undernutrition during fetal life [145]. The epigenetic changes may also explain why developmental insults in one generation can have consequences for later generations even in the absence of further insults. Experimentally, transmission to the next generation of a "programed" phenotype has been demonstrated for birth weight, metabolic dysfunction, elevated BP and vascular dysfunction [145, 146].

## Conclusion and expert opinion

This review summarizes the most important mechanisms linking an adverse environment during fetal and postnatal development with an increased risk for cardiovascular, renal and metabolic diseases. These mechanisms include renal morphological and functional changes associated to enhanced activity of RAS, COX-2 and sympathetic nervous system. Moreover, a decrease on NO production and bioavailability, an increase in apoptosis, oxidative stress and inflammation, alterations in growth related hormones, and epigenetic changes have also been described as

possible mechanisms leading to the cardiovascular and renal diseases in adulthood. Conversely, sexual dimorphism in the adult responses to an adverse environment during fetal and postnatal periods has been reported in numerous experimental models, with female offspring exhibiting a protected cardiovascular status. A role for sex hormones in modulating the RAS and oxidative stress is strongly suggested as a possible mechanism in mediating the sex-specific differences in BP increments induced by fetal and early postnatal insults. Recent studies have shown that the progression of the cardiovascular and renal diseases is accelerated during aging in both sexes.

It must be considered that the fetal and early postnatal insults that may lead to the development of cardiovascular, renal and metabolic diseases in adulthood may occur frequently throughout the world. Some examples of such insults are the exposure to a restriction of proteins or several micronutrients during fetal and postnatal development or to an excess of corticoids to accelerate lung development in preterm born babies.

Even though there is an extensive literature of fetal and neonatal programing of hypertension and renal diseases based on animal studies; more epidemiological research is needed to prove that the mechanisms previously described are also evidenced in humans. Consequently, new guidelines should be created to prevent or treat early alterations in important regulatory systems, like RAS, COX-2-derivated metabolites, NO, sympathetic nervous system, growth related factors, that can lead to cardiovascular, renal and metabolic diseases in adult life. Moreover, the notion of a personalized therapy has become an important issue to treat the later consequences of fetal insults. This new approach, based on prenatal and early postnatal history of individuals, requires robust methodologies to study genetic, epigenetic, morphological and functional alterations during early stages of life.

## Outlook

A great number of studies performed during the last decades have examined the involvement of some mechanisms in the development of cardiovascular, renal and metabolic diseases as a consequence of an adverse event during fetal and postnatal development. However, most of the experimental studies have been performed in male animals and at a young/adult age. New investigations are clearly needed to determine the mechanisms involved in the sex-dependent evolution of these diseases during aging. Future studies should also examine to what extent the cardiovascular, renal and metabolic diseases are transmitted to the next generations even in the absence of further insults. Finally, new investigations also need to determine potential therapies and preventive strategies that can be used clinically to overcome or diminish the cardiovascular and renal consequences of an adverse event during fetal and postnatal development.

## Highlights

- Epidemiological and experimental studies have shown that an adverse event during fetal periods leads to changes in birth weight and increases the predisposition to the development of cardiovascular, renal and metabolic diseases at an adult age.
- Male and female offspring exhibit different phenotypes following insults in utero, as well as differences in the severity of cardiovascular and renal diseases.
- It has been shown that IUGR may alter patterns of cardiomyocyte hyperplasia, apoptosis and hypertrophy, modifying the myocardial and vascular development during growth and cardiac function at an adult age.
- Several models of fetal programming have shown that IUGR induces vascular structural and functional alterations that are associated to an increased production of reactive oxygen species, an increased AT1 expression, and a reduced production or bioavailability of NO.
- The renal changes occurring in developmental programming of hypertension are secondary not only to the BP increment but also to the long-term adaptation to a decrease in nephron number. Changes in RAS and COX2 activity may be involved in the reduction of nephron endowment that occurs as a consequence of an adverse event during fetal and postnatal development.
- The decrease in renal functional reserve, as a consequence of the reduction in nephron endowment, increases the sensibility to a secondary insult during adult age such a prolonged increment in sodium or protein intake. The increase in sodium intake may induce the development of a sodium-sensitive hypertension during aging. The prolonged increment in protein intake may induce an accelerated deterioration of renal function in males but not in females.
- An increase of Ang II effects seems to be involved in the development of hypertension and in

increasing sympathetic activity, oxidative stress and inflammation in renal and vascular tissues in animals with developmental programming of hypertension.
- Sex hormones may modulate the activity of RAS, leading to a higher incidence of hypertension in males than in females. However, further investigations are needed to clarify the exact mechanisms involved in mediating the sexual dimorphism in the early origins and in the evolution of cardiovascular, renal and metabolic diseases during aging.
- The decrease in body growth found in developmental programming of cardiovascular and renal diseases may be secondary to changes in several hormonal factors such as GH, IGFs, PGH and insulin. These hormonal systems can be affected by different intrauterine injuries and may play a role in the future occurrence of insulin resistance and hypertension.
- Epigenetic modifications could be involved in some of the structural and functional alterations in vessels, heart and kidneys that predispose to cardiovascular and renal diseases at an adult age in developmental programming models. The epigenetic changes may also explain why developmental insults in one generation may have consequences for later generations. Future studies are needed to examine to what extent the cardiovascular, renal and metabolic diseases are transmitted to the next generations even in the absence of further insults.
- Future research need to be targeted to the search of potential therapies and preventive strategies that can be used clinically, to overcome or diminish the later cardiovascular and renal consequences of fetal insults.

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