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IMPORTANCE OF NEPHRON NUMBER IN THE REGULATION OF ARTERIAL PRESSURE AND RENAL FUNCTION DURING AGEING.

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INTRODUCTION.

The physiological importance of the kidneys in the long-term control of extracellular volume and arterial pressure has been demonstrated in studies showing that an alteration of renal function leads to the development of hypertension and other cardiovascular dysfunctions (1-4). It has also been proposed that the development of hypertension may be secondary to an altered nephron endowment during the nephrogenic period (3,4). A cause-effect link between nephron number at birth and hypertension has been proposed in clinical and experimental studies showing that essential hypertensive patients have a reduced nephron number (3-6), and that the alteration of nephrogenesis leads to the development of hypertension during the adult life (3,4,7-10). A deficient nephrogenesis has been observed in offspring of pregnant mothers taking a low protein diet, or treated with either corticoids or a cyclooxygenase-2 (COX-2) inhibitor (3,4). The renin-angiotensin system (RAS) seems to play an important role in the regulation of nephrogenesis because its activity is reduced in these situations (3,4), and it is known that angiotensin II (Ang II) is involved in regulating renal growth and differentiation (11). The role of Ang II in renal development has been confirmed in studies demonstrating an elevation of all RAS components during the nephrogenic period and showing that the administration of either a converting enzyme inhibitor or an Ang II AT_1 receptor antagonist during this period leads to a significant reduction in nephron number and an alteration of the normal kidney structure (7,8).

In this mini-review we will examine the evidences showing the role of the RAS in the normal nephron endowment, and the ageing and sex-dependent changes in renal function and arterial pressure when nephron number has been reduced during the nephrogenic period. To examine the role of the RAS in the regulation of nephrogenesis, and the ageing consequence of reducing Ang II effects during renal endowment, is important because it has been demonstrated that the intake of a high sodium or a low protein diet by the mother during pregnancy reduce the RAS activity in the offspring and predispose to hypertension and renal dysfunction in their adulthood (3,4,12,13). The available evidences suggest that these changes in sodium or protein intake, or other stimuli that reduce the RAS activity during the nephrogenic period, will lead to the development of hypertension and elicit important alterations in renal function that are age-dependent and greater in males than in females.

Role of angiotensin II in renal development.

The role of Ang II in the regulation of several mechanisms inducing vasoconstriction, sodium reabsorption, changes in other endocrine systems, inflammation, oxidative stress, etc, has been demonstrated by many research groups. Several experimental evidences also support the importance of Ang II in the regulation of kidney development. Some of these evidences are that 1) all components of the RAS are expressed in the immature kidney; 2) the activity and distribution of the RAS are developmentally regulated in a tissue-specific manner, with a spatio-temporal pattern of the expression of Ang II receptors; and 3) there is an elevated Ang II content during the neonatal period compared with the adult life (11,14). The role of Ang II has been confirmed in studies showing that the administration of an AT_1 receptor antagonist during the late nephrogenic period induces a significant reduction in nephron number and important renal histopathological abnormalities in the neonatal rat. The lower nephron number is accompanied by a compensatory increment in glomerular volume (**figure 1**), and by glomerulosclerosis, interstitial fibrosis, hypertrophy of the cortical radial arteries, tubular dilatation, and a perturbed medullary tubulogenesis (8,15).

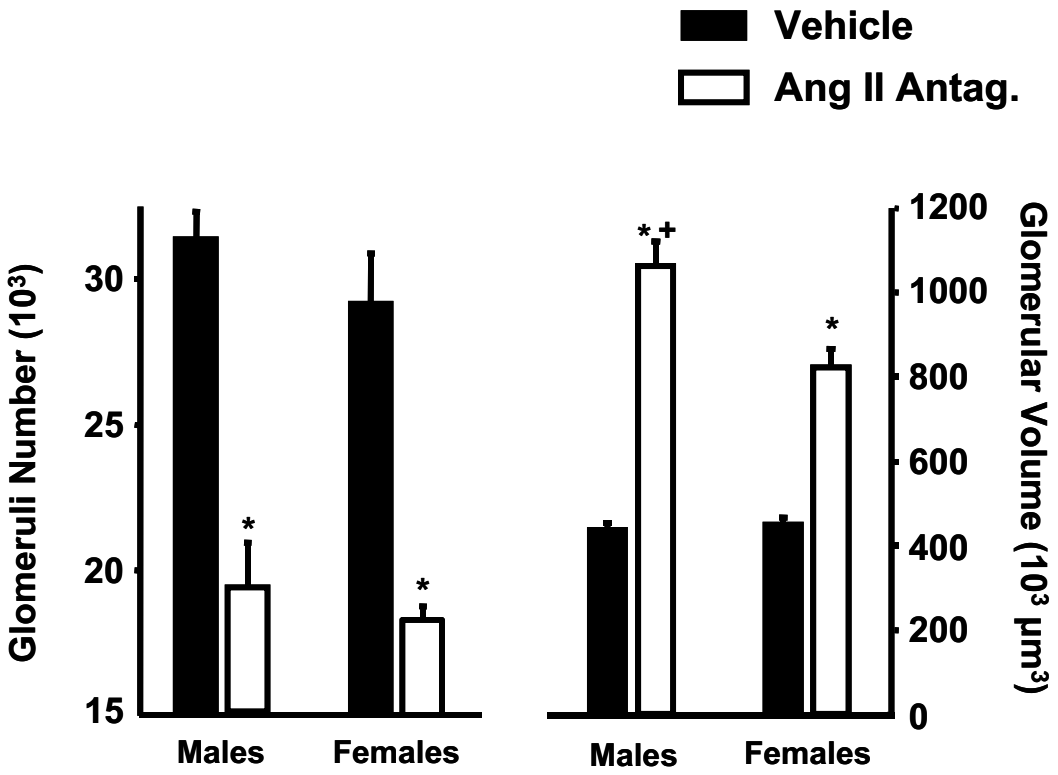

Figure 1. *Glomeruli number/kidney and glomerular volume in 3 months old rats treated with an angiotensin II AT_1 receptor antagonist or vehicle during the nephrogenic period. * P<0.05 vs vehicle. + P<0.05 vs females.*

The fact that the decrease in nephron number is associated with an increased renal apoptosis suggest the existence of a possible molecular mechanism whereby the reduction of Ang II effects during neonatal life leads to permanent changes in renal morphology (3). Since the blockade of Ang II effects also induces the development of

hypertension later in life (8-10) (**figure 2**), it is clear that the fetal programming of hypertension can be secondary to a reduction of Ang II effects during the nephrogenic period. The concept of fetal programming of hypertension refers to an adverse stimulus experienced during a critical period of development in utero with a following increase in arterial pressure (4). In support of the notion that an stimulus inducing a reduction of RAS activity during the nephrogenic period leads to the development of hypertension later in life, it has been demonstrated that the offspring of mothers taking a high sodium diet during pregnancy, develop hypertension during the adulthood (12,13).

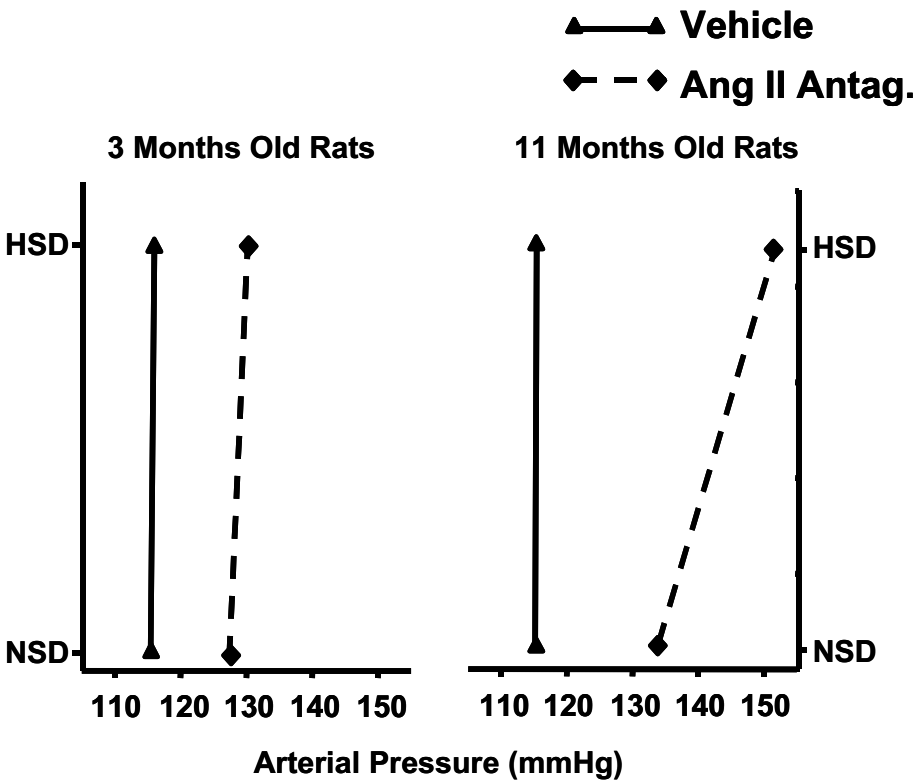

Figure 2. *Arterial pressure changes when sodium intake increased from a normal (NSD) to a high level (HSD) at 3 and 11 months of age in rats treated with an angiotensin II AT_1 receptor antagonist or vehicle during the nephrogenic period.*

The renal structural changes occurring as a consequence of the reduction in nephron number increase during ageing. These structural alterations seem to be modulated by sex-dependent mechanisms because the same decrease in nephron number is accompanied by a glomerular hypertrophy (figure 1), glomerulosclerosis and interstitial fibrosis that are greater in males than in females (8,16). Another important sex-difference in response to a reduction in Ang II effects during nephrogenesis is that only males have a significant papillary atrophy (8). Sex differences in the histopathological alterations until middle age cannot be attributed to the increments in arterial pressure or to the fall in total glomeruli number because both parameters changed similarly in males and females. However, the sex-difference in the histopathological alterations in aged rats may be partly secondary to the greater arterial pressure increment in males (16). There are also sex differences in the renal response to the alteration of other mechanisms involved in renal development (17,18). It has been shown that COX-2 deletion in mice induces an elevation in proteinuria only in males (17), and that a modest maternal protein restriction leads to a reduction in glomeruli number in the adult male but not in the adult female offspring (18).

The greater renal alterations in males than in females when there is a reduction in nephron number during renal development may be explained by the damaging influence of androgens in males and/or by the protective effects of estrogens. Female sex hormones have been postulated to be renal protective by decreasing renal inflammation and levels of oxidative stress (19), exerting a potent anti-growth effect on the glomerular mesangial cells and inhibiting the mesangial extracellular matrix accumulation (20). Estrogens seem also to protect females against the papillary atrophy by an activation of AT_2 receptors (8,16). On the other hand, male sex hormones have been linked with the progression of renal injury and it is known that men progress more rapidly in their renal diseases than women (20).

Aged and sex-dependent changes in renal function and arterial pressure when nephron number is reduced.

This section will examine the evidences showing that the decrease in nephron number during renal development leads to important age-dependent changes in renal function and arterial pressure. Glomerular filtration rate (GFR) does not change at the young age because there is a compensatory glomerular hyperfiltration and a significant increment in single nephron GFR (SNGFR) that seems to be secondary to an elevation in glomerular capillary pressure (**figure 3**) (4,8). It has been hypothesized that glomerular capillary pressure increases more in males than in females, and that this greater pressure could contribute to the greater age-dependent increment in proteinuria and to the important age-dependent decline in GFR found in males. Most probably, the reduction of Ang II effects during renal development may enhance the susceptibility to develop renal failure because proteinuria is considered an initial sign of renal damage and potentially a prognostic indicator for the future progression of renal disease (21). The greater capillary pressure in males would hasten the injury to functioning glomeruli and would perpetuate the vicious circle of ongoing nephron loss (**figure 3**). It is possible that compensatory adjustments to the decrease in nephron number were necessary for the preservation of a normal renal function but in the long run were central for the progressive nature of renal disease.

The results obtained by our group (8-10,16,22) support the notion that a reduction in functional glomeruli during renal development leads to an earlier age-dependent deterioration of renal hemodynamics in males than in females. The mechanisms responsible for the renal protection in females to the time dependent decline in renal function and elevation in proteinuria are unknown. However, as already mentioned, sexual hormones may be involved since there is a pronounced sexual dimorphism in the age-dependent renal injury and decline in renal function, with females protected due both to the protective estrogens and the lack of damaging androgens (23,24).

The decrease in glomeruli number during the nephrogenic period does not modify the basal renal hemodynamics at the young age because there is a functional overload of the existing units. This overload reduces the “renal functional reserve” and renders the lower nephron number kidney susceptible to failure when other stimuli inducing renal vasodilatation and hyperfiltration are superimposed (**figure 4**). That notion is supported by results showing that the renal response to an elevation in plasma aminoacids levels is abolished when nephron number decreases during renal development (21). One possible explanation why renal hemodynamics do not change in response to an elevation in

aminoacids levels is that glomerular pressures and flows are at maximal, and therefore potentially harmful, levels (**figure 3**).

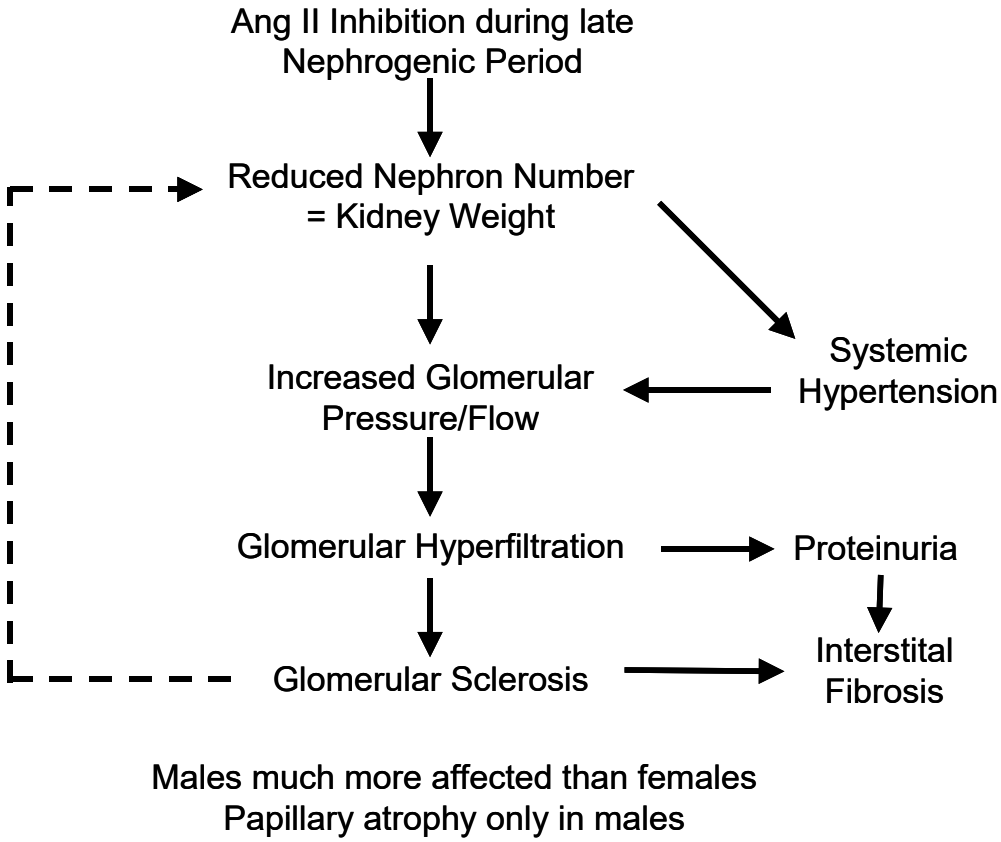

Figure 3. *Renal consequences of a reduction in nephron number elicited by the decrease of angiotensin II effects during renal development.*

The reduction of Ang II effects during the late nephrogenic period also leads to an important ageing-dependent deterioration of tubular reabsorption that is greater in males than in females (9,10,22). The urinary concentrating ability in response to a prolonged dehydration is significantly impaired and aggravated by ageing only in males (9). This alteration seems to be mainly secondary to the reduction in papillary volume that occurs only in adult males with a lower nephron number (8). The lower renal ability to concentrate urine in response to a prolonged dehydration may also be a consequence of the medullary interstitial fibrosis and the altered medullary tubulogenesis (8,14-16).

The renal ability to increase sodium and water excretion is also diminished when nephrogenesis is altered by a reduction of Ang II effects during the nephrogenic period (22). Our group has reported recently that the renal excretory response to an increase of extracellular volume or plasma aminoacids is reduced, and that this effect is similar in males and females (22). However, the aged-dependent deterioration of the renal ability to eliminate an acute volume expansion is accelerated in males but not in females with a lower nephron number. The lower excretory ability may be explained by an elevation of Ang II effects that could enhance tubule reabsorption and reduce the increment in renal interstitial hydrostatic pressure (4,10,22). The mechanisms responsible of the greater age-dependent deterioration of renal excretory function in males are unknown but it has been speculated that a decrease in nitric oxide (NO) production and the different sexual hormones might be involved (22). The importance of sexual hormones regulating the renal

excretory ability is supported by studies showing that the ratio NO/Ang II is enhanced by estrogens and reduced by androgens (1). The involvement of a decrease in NO is also supported by studies showing that NOS expression decreases in an age-dependent manner in males but not in females SD rats (23), and by studies demonstrating that the renal excretory ability is impaired when intrarenal NO synthesis is reduced (25).

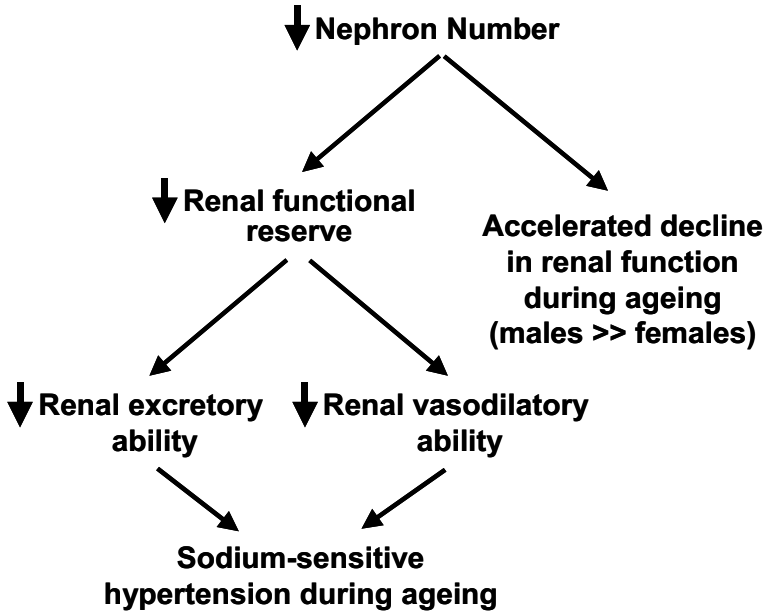

***Figure 4**. Changes in renal function and development of an aging-dependent sodium-sensitive hypertension when nephron number decreases during the nephrogenic period.*

The decrease of renal excretory function could contribute to the rise in arterial pressure found early in life, and to the development of an aging-dependent sodium-sensitive hypertension when nephron number decreases during the nephrogenic period, (**figures 1** and **4**) (9,10,16). The development of this sodium-sensitive hypertension may be explained by a decrease in NO, and an increase in both Ang II and oxidative stress (1,10,26). The importance of Ang II in the hypertension secondary to the reduction in nephron number is supported by results showing that the prolonged administration of an AT_1 receptor antagonist elicits a decrease of arterial pressure to normal levels (10).

In summary, there are strong evidences suggesting that a decrease of Ang II effects during the nephrogenic period leads to important age-dependent alterations of the renal structure and renal function that are greater in males than in females, and programs for the development of a hypertension that became sodium-sensitive later in life and that is also more important in males than in females.

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