Nitric Oxide, the Kidney, and Hypertension
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The acute administration of nitric oxide (NO) synthesis inhibitors reduces the renal capacity to excrete sodium under normal or volume expanded conditions and increases renovascular resistances in the absence of changes in systemic blood pressure (BP). This indicates a sensitivity of renal vasculature higher than that of systemic vessels to NO synthesis inhibition. Medullary circulation is the renovascular territory most dependent on NO availability. Thus, alterations in medullary blood flow seems to account for the blunted pressure-natriuresis and sodium retention during acute NO synthesis inhibition. By contrast, during chronic administration of L-arginine analogs, systemic BP rises and overrides initial sodium retention by a resetting of the pressure-natriuresis relationship. This BP increase appears to be dependent on an overexpression of the actions of vasoconstrictor systems due to an imbalance created by the diminished NO production. Prolonged NO synthesis inhibition not only elevates BP, but also produces renal vascular and parenchymal damage. Antihypertensive therapy impedes BP elevation and ameliorates kidney deterioration. Finally, there is evidence of the possibility that a certain alteration in the L-arginine-NO pathway exists in genetic models and in human essential hypertension. In conclusion, according to the data contained in the literature, NO plays a significant role in the regulation of systemic and renal hemodynamics and excretory function, and could participate in the development of hypertension.

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KEY WORDS: Nitric oxide, natriuresis, arterial hypertension, L-arginine, nitric oxide deficiency, proteinuria, angiotensin converting enzyme inhibitors.
renal capacity to excrete sodium. Furthermore, the existence of an impairment of renal function, with a decrease in renal blood flow and glomerular filtration rate, has recently been shown to precede the establishment of sustained hypertension in spontaneously hypertensive rats. These results are consistent with the hypothesis that BP increases to compensate for impaired renal function in genetic hypertension.

Evidence also exists relating the kidney and the development of arterial hypertension in humans. Such a relationship is certainly the case for the hypertension that accompanies renal failure. The elevated BP in this situation is consequence of the renal incapacity to fully excrete the sodium of the diet. In primary hypertension, Curtis et al. showed, in a manner similar to that previously done in animals, that cross-transplantation with a renal graft from a normotensive donor decreases BP in the absence of any therapy in patients with terminal renal failure resulting from nephrosclerosis. Indirect arguments favoring the hypothesis that the kidney participates in the origin of arterial hypertension involve the correlation between daily sodium excretion in urine and both systolic and diastolic BP and the BP lowering effect of dietary salt restriction.

Different theories have tried to explain the renal defect(s) accounting for the initiation of arterial hypertension. Hereditary hypertension is characterized, both in animals and humans, by the presence of generalized membrane abnormalities, thereby suggesting that membrane transport functions could be markers of individual susceptibility to the pressor effects of dietary salt. Brenner et al. proposed that hypertension may be the consequence of a congenital reduction in the number of nephrons or in the filtration area per glomerulus. A congenital reduction in the filtration surface area would contribute not only to a limited ability to excrete sodium, but also to an increased susceptibility to renal failure. Sealey et al. reported a theory based on the existence of nephron population heterogeneity, with a subpopulation of ischemic nephrons with reduced capacity for sodium excretion and with chronic hypersecretion of renin. Elevated renin secretion, by increasing tubular sodium reabsorption and enhancing tubuloglomerular feedback-mediated afferent vasoconstriction, would interfere with the capacity of remaining nephrons to excrete sodium.

In addition, we have recently published that, according to the literature, the most common renal manifestation of arterial hypertension in humans is an increase of intrarenal vascular resistance that is present since the very early stages of the disease. Furthermore, this renal vasoconstriction is functional in nature until renal vascular damage secondary to hypertension appears. Renal hemodynamics are very important in maintaining renal function and the renal capacity to excrete sodium. The mechanism by which elevations in preglomerular vascular resistance induce hypertension remains undefined. Hall has suggested that the systemic alterations are comparable to those produced experimentally by the constriction of the renal artery. In the one-kidney, one-clip model of hypertension developed by Goldblatt et al., a decrease in renal perfusion pressure, which increases renin release and produces sodium retention, is responsible for the elevation in systemic BP. This hypertension restores renal perfusion distal to the clamp and normalizes renin release and sodium excretion. The mechanism(s) underlying the appearance of renal vasoconstriction remain to be clarified. Nevertheless, we might point to a lack of modulation of renal vasculature to angiotensin II, an increased sympathetic activity, or a suppressed renal dopaminergic activity as being among the possibilities. Thus, renal vasoconstriction can constitute not an isolated phenomenon, but the consequence of cardiovascular adaptation in primary hypertension. In this sense it has been shown that, in parallel with the gradual pressure rise in SHR, preglomerular resistance becomes structurally elevated, while glomerular filtration capacity remains unaltered. This possibility does not exclude the pivotal role played by the kidney in the development of hypertension and does not exclude the hypothesis that the increase in BP is needed to maintain glomerular filtration rate and sodium excretion within normal limits.

The pioneering reports of Furchgott and co-workers showed that the responses of vascular preparations to acetylcholine and other agents were dependent on the integrity of endothelial function. Subsequent investigations, initially in animals and then in humans, have demonstrated that the endothelium significantly modulates vascular tone by regulating the contractile activity of the underlying smooth muscle. Moreover, this regulatory function of the endothelium has been shown to be abnormal in some cardiovascular conditions, suggesting the possibility that such endothelial dysfunction could play a pathophysiological role in those disease states. Essential hypertension is one of the conditions in which endothelium-dependent vascular relaxation has been shown to be abnormal. Previous studies have demonstrated that hypertensive patients have a reduced vasodilator response to the endothelium-dependent agent acetylcholine, in spite of the fact that response to sodium nitroprusside (a direct smooth muscle dilator) was similar to normal controls. These findings are compatible with either of two pathophysiological mechanisms: an endothelial dysfunction of patients with essential hypertension as a primary phenomenon that plays a causal role in the
hypertensive process, or a hypertension that injures the endothelium and thereby causes endothelial dysfunction as a secondary process. Considerable interest was raised by these two possibilities and an experimental model with chronic deficiency of nitric oxide (NO) production was created through the administration of L-arginine analogs that have the capacity to inhibit NO formation. Acute and chronic deficiency of NO production can be induced in animals by the administration of L-arginine analogs that inhibit NO synthesis in a competitive manner. It was initially shown that the administration of such compounds leads, in a dose dependent manner, to a rise in both BP and peripheral resistances. This allowed for introducing a new model in which arterial hypertension is obtained through the chronic inhibition of NO synthesis. Furthermore, the participation of a decreased NO production in the genesis of arterial hypertension in some animal models, such as the Dahl salt sensitive rat, has also been shown. All this generated a huge amount of interest in understanding the relationship between the kidney and NO in the development and maintenance of arterial hypertension.

The aim of this paper is to review the evidences in favor of or against a direct participation of the kidney in arterial hypertension occurring as a consequence of a deficiency in NO production.

EFFECTS OF NO SYNTHESIS INHIBITION ON THE REGULATION OF SODIUM EXCRETION AND ITS RELEVANCE FOR HYPERTENSION

The significance of NO as a mediator of renal function in the absence of changes in BP was explored in a previous study by giving intravenous infusions of progressively increasing doses of the NO synthesis inhibitor \( \text{N}^\text{G}\)-nitro-L-arginine methyl ester (L-NAME) to normal rats. The earliest and most sensitive alterations produced by small doses of L-NAME (0.1 to 1.0 \( \mu \text{g/kg/min} \)) consisted in decreases in urine volume and sodium excretion, which occurred 60 min after starting the infusion. By 120 min after beginning the infusion, intrarenal vascular resistance was found to be increased as suggested by a decrease of renal plasma flow. Glomerular filtration rate was also increased (Figure 1). All these changes occurred without any alteration in systemic BP, suggesting that kidney functions are more sensitive to NO synthesis inhibition than are peripheral resistances and BP. Administration of higher doses of L-NAME (10-50 \( \mu \text{g/kg/min} \)) reduced renal plasma flow and glomerular filtration rate and increased systemic BP. After an initial reduction, urinary volume and sodium excretion were normalized (Figure 2). Thus, this BP elevation can be regarded as an important compensatory mechanism that overcomes the initial antinatriuretic effect of NO synthesis inhibition, bringing sodium excretion back to normal. The effects of L-NAME on renal function appear to be dependent on a decreased availability of cGMP to the kidney. This was demonstrated by the ability of exogenous 8-Br-cGMP, but not by dibutyryl-cAMP, to prevent hemodynamic and excretory actions of L-NAME. These results support the concept of an NO-dependent continuous formation of cGMP responsible for maintaining the vascular tone and renal function.

The primary force determining glomerular filtration, as well as the amount of sodium to be excreted in the urine, is the renal perfusssion pressure. Elevation of renal perfusion pressure evokes an efficient autoregulatory response which maintains constant renal blood flow and glomerular filtration in spite of a markedly increased urinary sodium excretion. This pressure-induced natriuresis is a complex phenomenon in which changes in medullary circulation, interstitial pressure and intrarenal concentration of angiotensin II are mainly involved. The participation of NO in the natriuresis induced by acute increases of perfusion pressure was demonstrated by Salom et al, who showed that the intrarenal infusion of L-NAME in dogs abolished the increase in urinary sodium excretion produced by an elevation of the renal perfusion pressure. Since L-NAME was given at a dose that does not disturb either BP or autoregulation, it is proposed that NO is essential in coupling renal perfusion pressure with a decrease in tubular sodium reabsorption by mechanisms that are independent of vascular and glomerular events.

Effects on Medullary Blood Flow The consequences of NO inhibition on excretory function could also be a consequence of changes in renal medullary blood flow, which are associated with parallel changes in sodium and water excretion. This is consistent with biochemical reports that indicate that the renal medulla has a greater capacity than the cortex to synthesize NO. Matson et al showed that the acute infusion of L-NAME into the medullary interstitium of anesthetized rats selectively decreased renal inner medullary blood flow and sodium and water excretion without changing glomerular filtration rate, BP, or contralateral kidney function. In subsequent studies using uninephrectomized rats, these investigators demonstrated that administration of L-NAME for 5 days into the renal medullary interstitial space selectively and reversibly decreased renal medullary blood flow without altering cortical blood flow. During these maneuvers, the animals achieved a positive sodium balance, and their BP was increased. The onset of hypertension paralleled the observed reduction in medullary blood flow and the retention of sodium and water. However, it is unclear why the rats continued to retain sodium even on the fifth day of L-NAME infusion at a time when a state of electrolyte balance
FIGURE 1. Percent change from respective baseline values of mean arterial pressure (MAP), renal plasma flow (RPF), glomerular filtration rate (GFR), and urinary sodium excretion rate (UNaV) in control rats and in rats treated with 0.1, 1, 10, and 50 \( \mu \text{g/kg/min} \) L-NAME, and 50 \( \mu \text{g/kg/min} \) L-NAME + 100 \( \mu \text{g/kg/min} \) l-arginine; * \( P < .05 \) vs respective basal values.

would have been expected. It is likely that more than
one mechanism participates in the development of this
type of experimental hypertension, as will be discussed
later. Although interstitial L-NAME infusion signifi-
cantly decreased medullary blood flow, the site of NO
production in the renal medulla and the mechanism of
sodium retention are not clear, because both vascular
and tubular alterations could be involved in the de-
velopment of hypertension during interstitial L-NAME in-
fusion. Decreased renal medullary blood flow in the
vasa recta could indirectly alter tubular sodium and
water reabsorption by altering renal interstitial hydro-
static pressure or by changing the renal medullary con-
centration gradient. The physiological importance of
this renal medullary NO has been clearly shown in
other situations. The renal excretory response to an iso-
tonic saline load is blunted in the presence of a dose of
the NO inhibitor that reduces papillary blood flow and
renal interstitial hydrostatic pressure. The reduced
sensitivity of the pressure diuresis and natriuresis
mechanism found after blockade of NO can be related
to specific decreases in papillary blood flow. The
pressure dependency or lack of autoregulation of the
renal papillary circulation plays a pivotal role in the
pressure-natriuresis phenomenon and is reduced after
NO inhibition at all levels of arterial pressure. Therefore, renal NO, most specially NO produced within the
renal medulla or papilla, plays a prominent role in the
control of medullary hemodynamics and associated ex-
cretry changes.

Consequences of Sodium Load and Volume Expans-
on. The results mentioned above initially suggest the
possibility that a deficient renal synthesis of NO might
contribute to the development of systemic hyperten-
sion, because it interferes with the ability of the kidney
to excrete sodium and it also increases systemic and
renal vascular resistances. However, it is unlikely that
the increases in BP induced by acute L-NAME adminis-
tration could be related to the modest sodium retention
that occurs in such a short period of time, except that
the kidney would be challenged by maneuvers such as
sodium load or volume expansion. This concept was
used by Salazar in a subsequent study in dogs submit-
ted to an intravenous infusion of isotonic saline load
for 4 consecutive days in the absence and presence of
a nonhypertensinogenic dose of L-NAME. The concurrent
administration of L-NAME and the sodium over-
load induced a significant increase in arterial pressure
that seemed to be secondary to a significant sodium
retention, because the increment of cumulative sodium
balance was larger than that observed in the control
groups. Under these circumstances, the resultant
expansion of extracellular fluid volume elevates arterial
pressure in order to overcome this excretory deficit and
thereby to return body fluid volume to a normal state.
These observations might have important clinical implications because they show that the blockade of the synthesis of a single endogenous vasodilator can render BP volume dependent. The importance of NO in regulating sodium excretion during acute volume expansion was also shown by Alberola et al. 57 in dogs in which the left kidney was perfused with L-NAME, and the right kidney was used as a control. It was found that the sodium excretion rate by the kidney infused with L-NAME was 15% to 20% below the excretion rate of the control kidney. All these changes occurred in the absence of significant modifications in baseline renal hemodynamics and excretory function. These findings further support the importance of NO in the regulation of renal handling of sodium and extracellular fluid volume even in the absence of changes in systemic BP. The relationship between NO production and renal sodium handling was further demonstrated by Schultz and Tolins, 58 who showed that an enhanced NO production is needed for the renal adaptation to a high salt intake. Moreover, these investigators also showed that chronically salt loaded rats presented elevated renal hemodynamic responses to NO synthesis inhibition as compared with control rats.

MECHANISMS INVOLVED IN THE HYPERTENSION INDUCED BY CHRONIC DEFICIENCY OF NITRIC OXIDE

Gardiner et al. 59 first showed that oral administration of N(G)-monomethyl-L-arginine (LNMMA) for 7 days caused hypertension in Brattleboro rats. Other investigators 36, 37 also reported sustained hypertension during long-term oral administration of NO synthesis inhibitors. As a consequence of the studies described above, many investigators have tried to evaluate the renal mechanisms involved in the hypertensive effect produced by chronic inhibition of NO. Although an altered renal sodium handling could participate in the origin of the hypertension induced by acute administration of NO synthesis inhibitors, it appears not to be the case under chronic circumstances. In a previous study, 39 we evaluated the evolution of renal excretory function and circulating vasoactive systems during progressive increases in BP induced in rats by oral administration of L-NAME (5 to 30 mg/100 mL) for 5 weeks. L-NAME induced a stepped elevation $P < .05$ in BP levels without changing creatinine clearance, urine flow, or sodium excretion rate throughout
the study. Similarly, the groups of Manning\(^{60}\) and Mimran\(^{38}\) observed sustained hypertension during long-term intravenous infusion of L-NAME in both rats and dogs without altering sodium or volume balance. These results indicate that the increase in BP induced by chronic NO synthesis inhibition could be able to counteract any retention of sodium at the renal level, thus resetting the pressure-natriuresis relationship. However, the existence of a certain sodium retention during the first hours of L-NAME administration, as did occur in the above mentioned acute experiments, could not be ruled out. Illustrating this concept, we have recently shown a blunted natriuretic response to increases in perfusion pressure below the levels (100 to 150 mm Hg) observed in L-NAME hypertensive rats.\(^{61}\) Conversely, systemic administration of L-NAME to uninephrectomized rats produced hypertension accompanied by retention of sodium and water, as would be predicted from the analysis of the pressure-diuresis and -natriuresis relationships.\(^{62}\) These investigators demonstrated that these effects seem to be related to a selective reduction in medullary blood flow.\(^{63}\) An explanation for this apparent contradiction is that the presence of one or two kidneys might be a key factor for the differences found in renal sodium handling in this particular model of hypertension. In favor of this concept is the need of uninephrectomy for the development of hypertension in the DOCA-salt model.\(^{64}\) Thus, it is conceivable that a diminution of the total number of nephrons, as occurs with uninephrectomy, could render the medullary circulation particularly sensitive to NO synthesis inhibition in the remaining kidney. The absence of sodium retention in chronic NO-deficient animals with two kidneys could, therefore, be attributed to the changes in the systemic BP that overrides the renal defect impeding a normal sodium excretion.

**Vasoactive Systems During Chronic NO Inhibition**

The consequences of the hypertension induced by chronic NO synthesis inhibitors on circulating vasoactive neurohumoral systems have yielded controversial results. In vitro, NO directly inhibits renin release through the increase of cGMP hemodynamic and excretory alteration, such as structural damage in the juxtaglomerular cells.\(^{65}\) By contrast, during the stepped elevation in BP levels induced by oral administration of L-NAME (5 to 30 mg/100 mL) for 5 weeks, we observed reductions in either plasma renin activity or plasma aldosterone during treatment with 30 mg/100 mL of L-NAME, when the maximal BP increases were found.\(^{39}\) However, it has been reported\(^{66}\) that when the renal nerves and renal baroreceptor are controlled, endothelial NO appears to inhibit renin release. In addition, Persson et al\(^{67}\) reported that renin stimulation by reduced renal perfusion pressure below the range of autoregulation is blunted by NO synthesis inhibition, suggesting that NO may contribute to the stimulation of renin secretion, with diminished renal perfusion. Circulating catecholamine levels have been reported to be enhanced during chronic NO synthesis inhibition.\(^{58}\) This activation of the sympathoadrenal system might be dependent on the degree of inhibition of NO synthase because, during moderate inhibition of NO synthase, plasma concentrations of norepinephrine and epinephrine were elevated only during the administration of high doses of L-NAME.\(^{59}\) Previous studies already pointed out a central action of NO synthesis inhibitors.\(^{59}\) There is evidence that L-NAME crosses the blood-brain barrier when administered orally, and sympathetic activation might have consequently been triggered by the inhibition of NO synthase in the brain.\(^{68}\) Therefore, it is proposed that the effects produced by NO synthesis inhibitors on renal function and systemic circulation are produced by a decreased availability of NO, which leaves unbalanced the activity of pressor systems such as the renin-angiotensin or sympathetic nervous systems. Thus, an elevation of the circulating levels of these systems would not be necessary to observe the manifestation of their actions. Regarding the renin-angiotensin system, Ito et al\(^{70}\) and DeNicola et al\(^{71}\) have suggested that at least part of the systemic and renal effects produced by the inhibition of NO synthesis are the result of the biological activity of angiotensin II that becomes manifest after NO tissue availability is lowered. In fact, Sigmon et al\(^{72}\) showed that the retention of sodium seen during NO synthesis inhibition with L-NAME was significantly decreased by the prior administration of an angiotensin II receptor antagonist, whereas the increase in systemic BP remained unaltered. This issue has been further investigated by Oliveira et al and Pollock et al,\(^{73}\) who have shown that the administration of either an angiotensin II type 1 receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor minimizes the hypertension that develops after the inhibition of NO. Moreover, the reduction in BP induced by an angiotensin II type 1 receptor antagonist is further enhanced by the administration of an \(\alpha_1\)-receptor antagonist.\(^{74}\) These results suggest a contribution of the renin-angiotensin and sympathetic nervous systems to the L-NAME induced hypertension.

In addition, it has been observed that plasma concentrations of endothelin-1, and urinary excretion of prostaglandin (PG) \(E_2\), \(\alpha\)-keto-PGF\(_{1\alpha}\), and thromboxane \(B_2\) were not significantly affected by L-NAME treatment.\(^{39}\) Thus, it seems that L-NAME administration affects neither the production nor the release of endothelium derived constrictors nor that of vasodilatory prostanooids. However, administration of either an antagonist of endothelin receptors or endothelin converting enzyme inhibitors reduced BP and renovascular resistances during L-NAME administration in rats.\(^{75}\) This suggests the participation of endothelin in the vascular alterations induced by L-NAME administration.
The imbalance between NO and vasoconstrictor systems is further supported by the demonstration of altered vascular reactivity in the L-NAME-induced hypertension. Enhanced sensitivity of vascular smooth muscle to vasoconstrictors or decreased sensitivity to vasodilators might also account for BP elevation during chronic L-NAME administration. In fact, we observed increased constriction to angiotensin II and phenylephrine in isolated mesenteric vascular beds from rats treated for 8 weeks with L-NAME. However, sensitivity to sodium nitroprusside, bradykinin, or acetylcholine seemed to be unchanged. The elevated response was prevented by the treatment with either an ACE inhibitor or a calcium channel blocker.

Renal Damage Induced by Chronic NO Inhibition
Several investigators have reported that daily oral administration of L-NAME for 2 months was associated with arterial hypertension and diminished single nephron glomerular filtration rate. Elevation in glomerular hydraulic pressure as well as a decrease in glomerular ultrafiltration coefficient has also been observed. This long-term inhibition of NO synthase was associated with a mild degree of renal failure, as evidenced by proteinuria and glomerular sclerotic injury. Similarly, Fujihara et al reported that daily oral administration of an elevated dose of L-NAME for 30 days resulted in marked hypertension, interstitial expansion, and glomerular ischemia. These alterations were exacerbated by the concomitant sodium load, suggesting that additional glomerular stress impairs the damage induced by NO synthesis inhibition. In rats treated with L-NAME for 8 weeks, we have shown that the administration of the ACE inhibitor quinapril or the calcium channel blocker diltiazem reduced elevated BP and proteinuria. Since quinapril and diltiazem were not equally effective in preventing the increase in BP induced by L-NAME, their abilities to reduce proteinuria seems to be, at least partially, independent of their actions on BP. Similar results have been obtained with the administration of AT1 receptor antagonists suggesting that the renin-angiotensin system plays a prominent role in the development of renal damage in this model. Although in these experiments the glomerular filtration rate was normalized, the filtration fraction was not reduced by angiotensin II inhibition, suggesting that other vasoconstrictor agents might also have contributed to raise BP and to promote renal circulatory abnormalities in the setting of persistent NO inhibition. The participation of the renin-angiotensin system in the nephrosclerosis associated with chronic NO blockade has also been described in spontaneously hypertensive rats, where ACE inhibition prevents and reverses L-NAME-exacerbated severe nephrosclerosis.

We have also observed that the concurrent administration of indomethacin effectively prevents the effect of L-NAME on urine protein excretion (Figure 3). The antiproteinuric effect of indomethacin has been attributed to a fall in glomerular filtration rate. In addition, the participation of thromboxane (TX) A2 in the renal damage induced by chronic NO inhibition is proposed. In fact, many reports have emphasized the participation of TXA2 in glomerular injury, since treatments with TXA2/PGH2 receptor antagonists have been shown to ameliorate renal damage in diabetic rats and in rats with subtotal renal ablation. Therefore, the preventive effect of indomethacin on the proteinuria induced by chronic L-NAME administration might also be attributed to inhibition of TXA2 synthesis, whose actions would be overexpressed in the absence of NO in the kidney. Finally, L-NAME hypertension in rats has also been associated with rapid, local, and reversible development of sudanophilic lesions along renal preglomerular vessels. These lesions are characterized by medial cell proliferation, macrophage invasion, and infiltration of LDL, thus providing the hallmark of an early atherosclerotic process. Furthermore, sudanophilic lesions most likely develop from local pressure-induced aneurysms. The same investigators reported that
angiotensin II contributes to raising BP during the early phase of hypertension, whereas endogenous endothelin contributes little to raising BP, but endothelin selectively mediates the formation of sudanophilic lesions. The mentioned functional and structural changes induced by the chronic administration of NO inhibitors may be the expression, at the renal level, of a more general process occurring in the systemic vasculature. In fact, several studies have shown that chronic L-NAME treatment in the rat produces medial thickening and increased wall-to-lumen ratios. It should be mentioned that vascular hypertrophy also occurs during prolonged administration of L-NAME without producing persistent hypertension, suggesting that other functional hypertensiogenic mechanisms are also important. These vascular changes also have relevance for the kidney, since renal arteriolar and glomerular damage are present during long term L-NAME administration and contribute to the worsening of hypertension.

EVIDENCES OF NO DEFICIENCY IN GENETIC MODELS AND ESSENTIAL HYPERTENSION

Several groups of investigators have demonstrated the existence of an altered renal NO regulation in different models of arterial hypertension. Evidence for the existence of an abnormal renal NO synthase function in hypertension came from studies in a model of salt-sensitive hypertension, the Dahl rat. Studies from Chen and Sanders showed that the administration of the precursor of NO, L-arginine, abolished salt-induced hypertension in this strain of rats. In these animals, administration of L-arginine increased the elimination of NO-derived products and prevented the development of hypertension and associated renal lesions when salt intake was increased. Moreover, it has also been shown that long-term L-arginine administration normalized the right-shifted pressure-natriuresis relationship in this type of hypertension. Again, the improvement of pressure natriuresis seems essential to the beneficial effect of L-arginine in this salt-sensitive model. In spontaneously hypertensive rats, administration of the NO precursor, L-arginine, improves pressure natriuresis, and this is accompanied by an increased production of NO-derived metabolic products. Other authors have demonstrated that this beneficial effect of L-arginine on the spontaneously hypertensive rat is related to the restoration of the pressure dependency of the renal medullary circulation. Consequently, it could be proposed that NO production is needed in the kidney for a normal sodium excretion, and that a derangement of this function could lead to BP elevation.

Studies in essential hypertensive patients using forearm plethysmography suggested the existence of an alteration in the endothelium-derived NO system that may at least partly account for both the increased vascular resistance under basal conditions and the impaired response to endothelium-dependent vasodilators. This defect appears not to be related to a decreased availability of substrate for NO production nor to an alteration at the muscarinic receptor level. It could be due to the presence of constrictor prostanoids, according to Taddei et al, who showed that in essential hypertension patients the intrabrachial infusion of indomethacin increases forearm vasodilation in response to acetylcholine, indicating that the production of a cyclooxygenase-dependent endothelium-derived constricting factor could participate in the endothelial dysfunction. In addition, controversial results regarding the effects of antihypertensive therapy on impaired response to endothelium-dependent vasodilators have been published. While Panza et al reported no effect of antihypertensive drugs on forearm endothelial dysfunction, Schiffrin showed that ACE inhibitors, but not β-blockers, ameliorate acetylcholine-dependent relaxation in response to acetylcholine. The apparent contradiction between both studies could reside in the different vascular territories used.

The role of NO on kidney functions in humans has been investigated by the evaluation of the renal responses to systemic infusions of L-arginine. Initial results showed the existence of a blunted renal vasodilation in response to L-arginine in essential hypertensive patients as compared to normotensives. Moreover, an improvement of this blunted renal vasodilation was observed after prolonged treatment with ACE inhibitors. In a recent study, we tested the hypothesis that aging impairs kidney function in essential hypertension through a derangement of NO-dependent renal mechanisms. We observed that young essential hypertensives exhibited elevations in renal plasma flow,glomerular filtration rate and renal excretory function in re-
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