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The role of nitric oxide in hypertension and renal disease progression

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Abstract
Endothelial nitric oxide synthase (eNOS) serves a number of functions in the vasculature. In response to stimuli such as shear stress or acetylcholine, eNOS catalyses the production of nitric oxide (NO) from L-arginine. The NO diffuses across the endothelium into neighbouring smooth muscle and induces vasodilation. NO also acts locally to prevent platelet and leucocyte aggregation and inhibits vascular smooth muscle cell proliferation. It has been shown that mice lacking eNOS have decreased blood pressure, decreased heart rate and increased plasma renin activity. It has also been reported that NO production was reduced in patients with essential hypertension compared with normotensive individuals. In several animal models of renal disease (subtotal renal ablation, ureteral obstruction and diabetes), the administration of L-arginine, and probably the increase in NO synthesis, reduced the degree of glomerulosclerosis, ameliorated the changes in the tubulointerstitial compartment of the kidney and also decreased the infiltration of the kidney by invading macrophages. In summary, the L-arginine–NO pathway plays an important role in hypertension, renal disease, inflammation and atherosclerosis. This pathway also interacts with the renin–angiotensin system, the eicosanoid pathway, endothelin, cytokines and regulators of inflammation such as NF-κB.

Keywords: L-arginine; nitric oxide synthase; renal disease

Introduction

In addition to its role in protein synthesis, L-arginine is essential in the synthesis of creatinine, urea, nitric oxide (NO) and agmatine (see Figure 1). L-Arginine infusion influences the release of hormones and the synthesis of pyrimidine bases [1,2].

NO plays a role in the regulation of vascular tone, immune system function, neurotransmission and platelet aggregation and adhesion, among other processes [3,4]. Most of the effects of NO are mediated by second messengers, mainly GMP and protein kinases.

Nitric oxide and hypertension

It has been shown that brief pharmacologically induced elevations in blood pressure result in increased release of NO to the circulation, which can be detected by measuring small variations in plasma nitrate [5]. On the other hand, a fall in systemic pressure causes a decreased production of NO. The production of NO and the activity of constitutive nitric oxide synthase (NOS) have been shown to be greater in a genetic model of hypertension compared with normotensive controls. These findings suggest that high blood pressure up-regulates NO production. The mechanisms involved are not clear. It has been suggested that effects of blood flow, shear stress and other related mechanical stimuli account for the increased production of NO and the expression of endothelial NOS (eNOS).

Evidence for a role for eNOS was provided by the findings that disruption of the eNOS gene in mice led to hypertension [6]. It has also been reported that NO production was reduced in patients with essential hypertension compared with normotensive individuals. Also, in normal animals, the acute administration of antagonists of L-arginine causes a rapid and marked elevation of blood pressure, and a decrease in both glomerular filtration rate (GFR) and renal plasma flow. Administration of *N*-nitro L-arginine methylester (L-NAME), an antagonist of L-arginine, in the water for several weeks resulted in an increase in systemic blood pressure, an increase in glomerular capillary pressure and a reduction in the ultrafiltration coefficient (K_f) in rats [7]. These changes were associated with proteinuria and the development of glomerulosclerosis.

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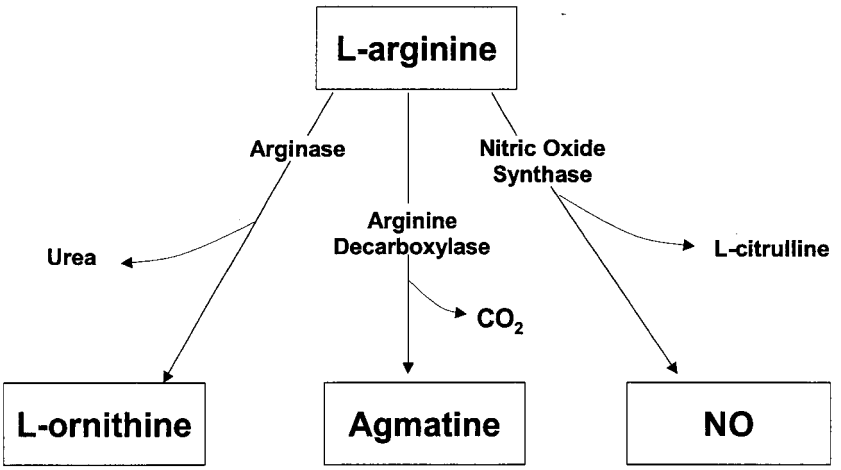

Fig. 1. Major pathways of L-arginine metabolism. L-Arginine may be metabolized by the urea cycle enzyme arginase to L-ornithine and urea, by arginine decarboxylase to agmatine and CO_2, or by nitric oxide synthase to NO and L-citrulline.

Several studies [8,9] have found that NOS is present in a specific area of the brain involved in the neurogenic control of blood pressure. The neuronal isoform of NOS (nNOS) is involved in the transduction pathways that tonically inhibit the sympathetic outflow from the brainstem [10]. In normal rats, the activity of the central sympathetic nervous system is regulated by local NO production. The expression of nNOS is increased in the brain of rats with chronic renal failure compared with control rats. This may attenuate the increased sympathetic nerve firing [11]. Fugihara *et al.* [12] examined the renal effects of NO blockade for a month in Munich–Wister rats, by the administration of L-NAME in the drinking water. They found that rats given L-NAME developed hypertension glomerulosclerosis and renal interstitial fibrosis. Similar results were reported by Kashiwagi *et al.* [13].

Ribeiro *et al.* [14] found a marked elevation of renin activity in rats given L-NAME for a month. Administration of an angiotensin II antagonist (losartan) largely attenuated the development of systemic hypertension and prevented the changes in renal function and the pathological changes in the kidney.

Nitric oxide and progression of renal disease

In rats with ureteral obstruction, the administration of L-arginine, before the ligation of the ureter, resulted in nearly complete restoration of blood flow and GFR [15]. Also, administration of L-arginine to rats with unilateral ureteral obstruction resulted in a marked decrease in macrophage infiltration in the obstructed kidney [16]. Similar findings were observed in a model of the nephrotic syndrome induced by the administration of the aminonucleoside of puromycin [16]. Administration of L-arginine in the drinking water significantly blunted the increased interstitial volume, monocyte infiltration, interstitial collagen IV deposition and α-smooth muscle actin expression in the kidney with ureteral obstruction [17].

We also examined a rat model with subtotal nephrectomy. These rats had higher blood pressure, greater proteinuria and lower plasma albumin than sham-operated rats. Rats with a remnant kidney given 1% L-arginine in the drinking water had significantly greater values of GFR and renal plasma flow [18]. These rats also had a greater number of normal glomeruli and fewer tubulointerstitial changes. The administration of L-arginine also decreased proteinuria and glomerular hypertension in the rats with subtotal nephrectomy [18].

We also examined the effect of L-arginine administration on the renal function of rats with untreated diabetes mellitus. Diabetic rats given L-arginine in the drinking water had significantly lower protein and cGMP excretion in the urine than diabetic rats given water alone [19].

Despite the persistent hyperglycaemia, the administration of L-arginine prevented the development of hyperfiltration and ameliorated the degree of proteinuria in diabetic rats. L-Arginine prevented the increase in whole kidney GFR in diabetic rats either when expressed in absolute terms or when factored per total body weight or kidney weight. The effects of L-arginine administration on renal function in diabetic rats (lower GFR and lower filtration fraction with no significant changes in effective renal plasma flow or mean arterial pressure) suggest that hyperfiltration may not occur after L-arginine administration because of changes in intraglomerular haemodynamics.

Bank and Aynedjian [20] reported that NO synthesis is increased in diabetic rats with hyperfiltration. There may be two, not necessarily exclusive, possibilities to explain the role of NO in the renal changes observed in diabetes. (i) NO may directly mediate hyperfiltration through its vasodilatory properties. In this respect, it has been shown that the administration of aminoguanidine, a putative inhibitor of the inducible form of NOS and of NO formation, prevents some of the morphological alterations seen in diabetes. (ii) It is possible that the activation of the NO pathway

excerts a counter-regulatory effect on vasoconstrictors, glycosylated products and/or thrombogenic substances known to be active in the setting of diabetes. NO is considered by some to be an antagonist of the renin–angiotensin system. Dietary supplementation of L-arginine also ameliorated renal hypertrophy in rats fed a high protein diet.

It is clear that the L-arginine–NO pathway has an important role in blood pressure control, progression of renal disease, inflammation and atherosclerosis. This pathway also interacts with the renin–angiotensin system, the eicosanoid pathway, endothelins, cytokines and regulators of inflammation such as nuclear factor-κB (NF-κB).

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