L-Arginine as a Therapeutic Tool in Kidney Disease

By Saulo Klahr and Jeremiah Morrissey

Infusion of L-arginine in experimental animals increases renal plasma flow (RPF) and glomerular filtration rate (GFR). It is likely that a component of these hemodynamic changes are mediated by nitric oxide (NO) as suggested by studies with specific antagonists of L-arginine metabolism. L-arginine administration ameliorates the infiltration of the renal parenchyma by macrophages in rats with obstructive nephropathy or rats with puromycin-induced nephrotic syndrome. L-arginine administration also blunts the increase in interstitial volume, collagen IV, and α-smooth muscle actin. Rats with a remnant kidney given 1% L-arginine in the drinking water had a greater GFR and RPF. L-arginine administration also decreased proteinuria. Diabetic rats given L-arginine had significantly lower excretion of protein and cyclic guanosine monophosphate than diabetic rats not receiving L-arginine. Despite persistent hyperglycemia, the administration of L-arginine prevented the development of hyperfiltration and ameliorated proteinuria in diabetic rats. In the setting of ischemic acute renal failure, the administration of L-arginine had a beneficial effect on GFR and RPF, decreased O_2^- production, diminished up-regulation of soluble guanylate cyclase, and prevented up-regulation of inducible NO synthase (iNOS). The pharmacokinetics of L-arginine indicate that side effects are rare and mostly mild and dose dependent.

THE AMINO ACID L-arginine is essential for the synthesis of creatine, urea, polyamines, nitric oxide (NO), and agmatine. L-arginine also influences the release of several hormones such as insulin, glucagon, growth hormone, somatostatin, prolactin, and aldosterone. The major pathways of L-arginine metabolism are depicted in Figure 1.

NO has a pivotal role in the regulation of vascular tone, immune system function, neurotransmission, and platelet aggregation and adhesion, among other processes.[1] Most of the effects of NO are mediated by second messengers, mainly cyclic guanosine monophosphate and protein kinases. NO is synthesized from L-arginine in a reaction catalyzed by one of a family of NO synthase (NOS) enzymes.

L-ARGININE AND SODIUM HOMEOSTASIS

Infusion of L-arginine in experimental animals increases renal blood flow and induces natriuresis and diuresis. Barri and Wilcox[2] compared the infusion of 30 g of L-arginine with that of 30 g of branched chain amino acids (control) in 8 normal subjects after 5 to 7 days of equilibration to a low-salt (20 mmol/24 hr) or high-salt intake (200 mmol/24 hr). The effects of arginine administration depended on salt intake. L-arginine infusion decreased renal sodium excretion during the low-salt intake, but it increased sodium excretion during the high-salt intake. L-arginine administration increased the excretion of NO and cyclic guanosine monophosphate in the urine and increased the levels of circulating insulin. L-arginine in the setting of a low-salt diet increased sodium reabsorption in the proximal and distal tubules, but inhibited the reabsorption of sodium during the high-salt intake. This study in normal subjects implies an effect of salt intake on the tubular response to the administration of L-arginine. These effects, however, appeared to be independent of blood pressure, renal hemodynamics, or the renin-angiotensin system.

The administration of L-arginine to normal animals causes significant changes in kidney function, including a marked increase in renal plasma flow (RPF) and glomerular filtration rate (GFR).[3] It is likely that a component of these hemodynamic changes are mediated by NO as suggested by studies with specific antagonists of L-arginine metabolism. Presumably, these competitive antagonists of L-arginine reduce the synthesis of NO. In normal animals the acute administration of antagonists of L-arginine causes an immediate and marked increase of blood pressure, a decrease in GFR, and a decrease in RPF. Rats given an antagonist of L-arginine, N^G-nitro-L-arginine methyl ester (L-NAME), in their drinking water for several weeks developed significant systemic hypertension, an increase in glomerular capillary pressure, and a re-

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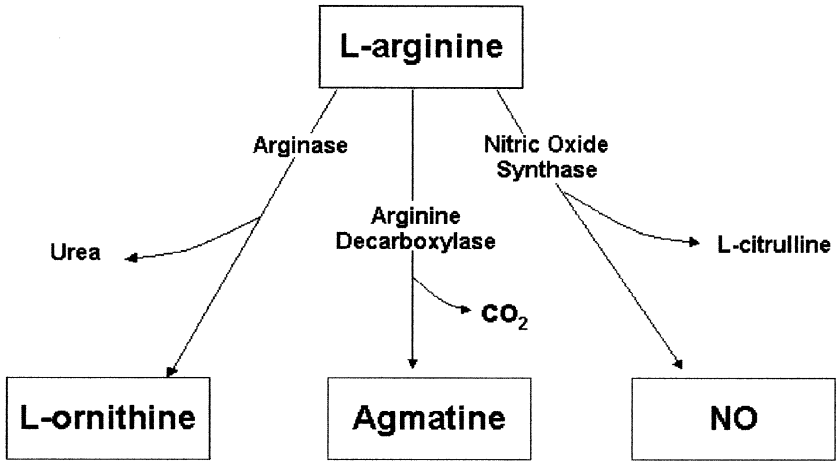

Fig 1. Major pathways of L-arginine metabolism. L-arginine may be metabolized by the urea cycle enzyme arginase to L-ornithine and urea by arginine decarboxylase to agmatine and CO_2, or by NOS to NO and L-citrulline. Reprinted with permission from Klahr.[22]

duction in the ultrafiltration coefficient. These changes were associated with proteinuria and the development of glomerulosclerosis.[4]

ROLE OF L-ARGININE IN RENAL DISEASE

Ureteral Obstruction

Ureteral obstruction leads to a substantial decrease in RPF and GFR and major changes in the tubulointerstitial compartment of the kidney.[5] Renal interstitial fibrosis develops as a consequence of long-standing obstructive uropathy. Leukocyte infiltration of the kidney of rats with bilateral ureteral obstruction (BUO) is detected as early as 4 hours after the onset of obstruction and peaks at 24 hours. Activated macrophages metabolize L-arginine to reactive nitrogen intermediates including nitrite, nitrate, and nitric acid.[6]

During the course of hemodynamic studies delineating the effect of NO on renal function and blood pressure in rats with BUO, we noted that plasma levels of L-arginine were significantly lower in rats, and that administration of L-arginine to rats with BUO ameliorated the decrease of GFR and the increase of systemic blood pressure observed in these rats.[7] These findings, and the fact that the proximal tubules are the major site of synthesis of circulating L-arginine,[8] led us to postulate that the decreased activity of the NO system in rats with BUO was caused, at least in part, by decreased availability of the substrate for its synthesis.

We also reported that L-arginine ameliorates the infiltration of the parenchyma of the kidney by macrophages in rats with obstructive nephropathy and in rats with puromycin-induced nephrotic syndrome.[9] This effect of L-arginine may be owing to several factors including a decrease in the intrinsic capacity of macrophages to migrate when exposed to L-arginine and/or increased release of endogenous corticosterone after administration of L-arginine in vivo. Administration of L-arginine to rats before induction of BUO or before and during puromycin resulted in values of GFR that were 61% and 133% greater, respectively, than the values obtained in similar rats not given L-arginine. Normal rats given L-arginine in the drinking water also had a significant increase in GFR (by 26%) when compared with normal rats given tap water alone. From these results it is unclear if the greater values of GFR seen in rats with BUO or those given puromycin and drinking water with L-arginine were caused by hemodynamic factors. Immunohistochemistry studies using a monoclonal antibody that recognizes tissue macrophages but not mononuclear cells[10,11] showed that the infiltration of glomeruli by macrophages in rats with BUO of 24 hours duration was reduced markedly, to about 10% of control.

Hegarty et al[12] studied the inhibition of NOS in the setting of ureteral obstruction in rats. Control blood flow in the renal cortex was 806 ± 63 mL/100 g tissue/min and 373 ± 38 mL/100 g tissue/min in the medulla. Inhibition of NO production by N^G-monomethyl-L-arginine resulted in a decrease in blood flow, in both the cortex (28% decrease) and the medulla (42% decrease), without causing any significant change in blood pressure

(105 ± 7 mm Hg in controls versus 108 ± 12 mm Hg) after 24 hours of ureteral obstruction.

In summary, NO plays an important role in the regulation of blood flow in the normal and the diseased kidney. In ureteral obstruction, the renal vasculature remains responsive to the vasodilatory actions of NO and blood flow changes associated with ureteral obstruction involve impairment of the NO synthetic pathway in the kidney. Increased expression of both endothelial NOS (eNOS) and inducible NOS (iNOS) is seen with increasing duration of obstruction, but may not correspond to a sufficient increase in enzyme activity when availability of substrate and cofactors are considered.

In a study by Morrissey et al,[13] administration of L-arginine in the drinking water significantly blunted the increase in interstitial volume, monocyte infiltration, interstitial collagen IV, and α-smooth muscle actin expression in the kidney with ureteral obstruction. However, in contrast to angiotensin-converting enzyme inhibitors, arginine administration did not decrease the expression of transforming growth factor-β1 messenger RNA in the obstructed kidney of rats with ureteral ligation.

Remnant Kidney

A decrease of 85% to 90% of the total kidney mass results in functional and structural changes in the remnant renal tissue. Rats with a remnant kidney develop systemic hypertension and exhibit a decrease in both GFR and effective RPF.[14] We examined the effects of dietary supplementation with L-arginine for 6 weeks on the progression of renal disease in rats subjected to sham operation or ablation of 85% to 90% of the total renal mass.[15] Sham-operated rats served as controls and were given tap water with or without 1% L-arginine added. Sham-operated rats given L-arginine in the drinking water had significantly greater urine urea excretion than similar rats drinking tap water. Rats with subtotal nephrectomy had a higher blood pressure, greater proteinuria, and a significantly lower plasma albumin level than sham-operated rats. Rats with remnant kidneys given 1% L-arginine in the drinking water had a significantly greater GFR and RPF (using para-amino hippurate clearance as a marker) than similar rats given tap water alone. The remnant kidney of rats given L-arginine had a greater number of normal or minimally abnormal glomeruli and fewer tubulointerstitial changes than rats given tap water alone. The beneficial effect of L-arginine was not related to differences in systemic blood pressure or lipid profile and was not associated with changes in protein or caloric intake.

Another study in which administration of L-arginine was at a much lower dose than in the previous study showed an effect in decreasing proteinuria and increasing renal function in rats with a remnant kidney.[16] It appears that chronic renal failure in rats is characterized by decreased synthesis of NO by the kidney and the correction of this abnormality slows the progression of renal disease.[17] In contrast, studies in patients or animals with uremia indicate increased levels of NO in the systemic circulation. Aiello et al[17] found that renal ex vivo production of NO, measured as the conversion of [^{3}H] L-arginine to [^{3}H] citrulline, was lower than normal in rats with a remnant kidney 7 days after surgery, and worsened with time in correlation with greater renal damage. They also found that the excretion of the NO metabolites, NO_2^-/NO_3^-, decreased significantly in the urine of rats with a remnant kidney.

In the rat model of subtotal renal ablation there was a decrease in NO synthesis in the kidney, apparently caused by a progressive decrease in the amount of iNOS. In this setting, a decrease in NO synthesis and the local generation of vasoconstrictors and cytokines may contribute to progressive renal insufficiency.

Diabetic Nephropathy

We also examined the effect of L-arginine administration on renal function of normal rats and diabetic rats.[18] Four groups of rats were studied: (1) normal rats given L-arginine in the drinking water, (2) normal rats given water alone, (3) diabetic rats given L-arginine, and (4) diabetic rats not given L-arginine. Diabetic rats had significantly lower levels of albumin and L-arginine in plasma than did normal rats. Diabetic rats had greater urine volumes and greater excretion of glucose, protein, nitrate, and nitrite than normal rats.

Diabetic rats given L-arginine had significantly lower excretion of protein and cyclic guanosine monophosphate than diabetic rats not receiving L-arginine. Despite persistent hyperglycemia, the administration of L-arginine prevented the development of hyperfiltration and ameliorated proteinuria in diabetic rats. L-arginine prevented the increase in whole-kidney GFR in diabetic rats when

expressed either 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 RPF, mean arterial pressure, or renal vascular resistance) suggest that hyperfiltration did not occur after L-arginine administration, perhaps because of changes in intraglomerular hemodynamics.

This study suggests, but does not prove, a greater use of L-arginine through the NO metabolic pathway in diabetic rats than in normal rats. Three findings support this postulate: (1) significantly lower plasma levels of L-arginine that cannot be attributed completely to losses of this amino acid in the urine, (2) significantly greater excretion of reactive nitrogen intermediates, and (3) significantly greater excretion of cyclic guanosine monophosphate in the urine. Bank and Aynedjian[19] reported that NO synthesis is increased in diabetic rats manifesting hyperfiltration. There may be 2, not necessarily exclusive, possibilities to explain the role of the NO system in the renal changes observed in diabetes. First, NO may mediate hyperfiltration directly through its potent vasodilatory properties. In this respect, it has been shown that the administration of aminoguanidine, a putative inhibitor of the inducible form of the NOS enzyme and of NO formation, prevents some of the morphologic alterations seen in diabetes.[20] Second, it is possible that the activation of the NO pathway exerts a counterregulatory effect on vasoconstrictors, glycosylated products, and/or thrombogenic substances known to be active in the setting of diabetes.

L-Arginine Supplementation

Xia and Zweier[21] found that low L-arginine concentrations also could lead to superoxide (O_2^-) production by iNOS and the formation of peroxynitrate in macrophages, which suggests a rationale for L-arginine supplementation in models in which iNOS is up-regulated. L-arginine supplementation in diverse models of renal disease is associated consistently with improvement of GFR and a reduction in macrophage infiltration.[22] L-arginine also protects against ischemia-reperfusion injury when administered before the occurrence of renal ischemia.[23-25] In an allogeneic renal transplant model a beneficial effect of 1% L-arginine in the drinking water on renal function and a reduction of vascular and tubulointerstitial injury was found.[26] The L-arginine was administered for 7 days, starting 5 hours after transplantation, well after the phase of ischemia-reperfusion. These observations suggest that in this phase the intrarenal availability of NOS cofactors were not a limiting factor. However, it should be pointed out that in addition to enhancing NO synthesis, there are several other pathways through which L-arginine could influence function and morphology of the (transplanted) kidney.[27] Beneficial effects include modulation of NO production, conversion into agmatine,[28] or stimulation of glucagon secretion.[29] Detrimental effects include conversion to citrulline and NO under influence of iNOS, and enhancing effects, via L-ornithine formation, on proliferation and collagen formation.[30] However, observations in the allogeneic transplant model show that in the early phase beneficial effects of L-arginine supplementation clearly outweigh the putative detrimental effects. Moreover, in renal transplant recipients who are highly predisposed to cardiovascular diseases,[31] the beneficial effects of L-arginine also are manifest for a number of risk factors.[32]

In conclusion, recent data have shown iNOS can act as a superoxide, a peroxynitrite, as well as a NO-producing enzyme, while the biologic effects of iNOS probably depend on the type of radical species released by the enzyme as well as the antioxidant capacity of the cellular microenvironment of the enzyme. Manipulation of this microenvironment may modulate the function of iNOS and thus could be used to reduce acute rejection in the kidney.

The Role of L-arginine in Ischemic Acute Renal Failure

Acute renal failure (ARF) is a common clinical complication with uncertain outcome, ranging from complete restitution of function to high mortality.[33] Previous studies suggested that L-arginine has beneficial effects on renal function.

Schneider et al[34] induced ARF in rats by bilateral clamping of renal arteries for 45 minutes. L-arginine was applied intraperitoneally during clamping and orally for 14 days. GFR and RPF were measured. Clamping resulted in a 70% to 90% reduction of GFR and RPF, with a gradual recovery by day 14. By using an in situ assay with a fluorescent dye (hydro ethidene), increased tubular generation of O_2^- was detected in the early

course of ARF, indicating enhanced oxidative stress. In this setting, L-arginine had a beneficial effect on GFR and RPF, decreased O_2^- production, diminished up-regulation of soluble guanylate cyclase, and prevented up-regulation of iNOS. In summary, L-arginine supplementation reduces O_2^- generation and significantly improves the expression of NO signaling proteins as well as the recovery of ARF.

ARF results in the permanent loss of peritubular capillaries, which may exacerbate the progression of chronic renal failure. A recent study by Basile et al[35] found that renal hypoxia, which is an important mediator in disease progression, is increased persistently after recovery from ARF. Rats were subjected to ischemia-reperfusion injury and allowed to recover for 5 or 20 weeks. Immunohistochemistry with the hypoxia-sensitive marker 2-pimonidizole at 5 weeks revealed an overall increase in incorporation in the outer medullary region after recovery from ARF compared with sham-operated controls. Unilateral nephrectomy, in combination with ischemia-reperfusion injury, resulted in a larger hypoxic area in the outer medulla than that observed in the bilateral injury model. In addition, in the unilateral ischemia-nephrectomy model, proteinuria, interstitial fibrosis, and renal functional loss developed at an accelerated rate compared with the bilateral model of ARF when animals were allowed to recover for 20 weeks. L-arginine in the drinking water (~0.5 g/d) increased total renal blood flow approximately 30%, decreased hypoxic regions, and attenuated manifestations of chronic renal disease. These data suggest that a reduction in the peritubular capillary density after ARF results in a persistent reduction in renal P_{O_2} levels and that hypoxia may play an important role in the progression of chronic renal disease after ARF.

L-Arginine: From Bench to Bedside

Soon after the first experiments had proven a beneficial effect of L-arginine on endothelium, it was reported that intracoronary infusion of L-arginine normalized coronary vasomotor responses to acetylcholine in subjects with hypercholesterolemia.[36] A similar observation also was made with systemic infusion of L-arginine in hypercholesterolemic individuals, in whom endothelium-dependent forearm vasodilation was improved.[37] Recent evidence from prospective clinical trials suggests that endothelial dysfunction is a predictor of future coronary events.[38,39] Therefore, reversal of endothelial dysfunction by L-arginine in vivo may suggest that this amino compound exerts antiatherosclerotic effects in humans

The pharmakinetics of L-arginine have been investigated recently. Side effects are rare and mostly mild and dose dependent. The mechanism of action of L-arginine may involve NOS substrate provision, especially in patients with increased levels of the endogenous NOS inhibitor, asymmetric dimethyl arginine. Several long-term studies have been performed that show that chronic oral administration of L-arginine or intermittent infusion therapy with L-arginine can improve some cardiovascular symptoms in humans. Although the physiologic roles of NO are becoming well defined, a role for the arginine metabolite agmatine remains to be elucidated.

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