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«HIPERTENSIÓN Y PROGRESIÓN DEL DAÑO RENAL»

The Role of Nitric Oxide in Hypertension and Renal Disease Progression

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Bedsides its role in protein synthesis, L-arginine is essential in the synthesis of creatinine, urea, nitric oxide (NO), agmatine and polyamines. L-arginine infusion influences the release of hormones and the synthesis of pyrimidine bases.

NO plays a role in the regulation of vascular tone, immune system function, neuro-transmition and plaletet aggregation and adhesion, among other processes. Most of the effects of NO are mediated by second messengers, mainly GMP and protein kinases.

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. On the other hand, a fall in systemic pressure causes a decreased production of NO. The production of NO and the activity of constitutive NOS have been shown to be greater in a genetic model of hypertension compared to normotensive controls. Theses findings suggest that high blood pressure upregulates 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 increase production of NO and the expression of endothelial NOS.

Evidence for a role of endothelial constitutive No synthase (ecNOS) was provided by the findings that disruption of the ecNOS gene in mice led to hypertension. 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 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 (Kf) in rats. These changes were associated with proteinuria and the development of glomerulosclerosis. 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. Also, administration of L-arginine to rats with unilateral ureteral obstruction resulted in a marked decrease in macrophage infiltration in the obstructed kidney. Similar findings were observed in a model of the nephrotic syndrome induced by the administration of the aminonucleoside of puromycin. 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.

We also examined a rat model with subtotal neprectomy. These rats had higher blood pressure, greater proteinuria and lower plasma albumin than sham-operated rates. Rats with a remnant kidney given 1% L-arginine in the drinking water had significantly greater values of GFR and renal plasma flow. These rats also had a greater number of normal glomeruli and fewer tubulo-interstitial changes. The administration of L-arginine also decreased proteinuria in the rats with subtotal nephrectomy. Also diabetic rats given L-arginine had significantly lower excretion of protein than rats not receiving L-arginine.

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