Renal localization of NO synthesis

Endogenous NO is synthesized by nitric oxide synthases (NOS) which use L-arginine as substrate. The various isoforms of NOS are widely distributed within the kidney. Brain NOS (bNOS) and endothelial NOS (eNOS) are constitutively expressed and are both distributed in glomeruli and vasculature. In addition bNOS is found in epithelial tissue including macula densa and the collecting duct. Two structurally distinct inducible NOS (iNOS) are ‘constitutively expressed’ at the juxtaglomerular apparatus (JGA) and in tubules and after immune stimulation iNOS has been located in glomerular mesangial cells and several locations in the tubule [1,2].

Physiological actions of NO on the kidney

NO synthesized by eNOS, and possibly bNOS, has a major role in control of renal vascular tone, via its vasodilatory actions. NO produces vasodilatation via a cyclic guanosine, 3',5' monophosphate (cGMP) mechanism and also by stimulating calcium-dependent potassium channels [1]. Generalized systemic NO inhibition (NOI) leads to dose dependent increases in blood pressure (BP) and renal vascular resistance (RVR), a large fall in renal plasma flow (RPF) and a slight fall in glomerular filtration rate (GFR) [1]. The kidney is particularly sensitive to NO inhibition, which leads to increases in afferent arteriolar resistance (R_A), decreases in the ultrafiltration coefficient (K_f), possibly via mesangial cell contraction [1] and a variable effect on the efferent arteriolar resistance (R_E). When systemic NO inhibition leads to increased BP, R_E rises and causes marked elevation in the glomerular blood pressure (P_Gc). In addition to directly influencing vascular tone via eNOS, NO at the JGA controls glomerular hemodynamics via the tubuloglomerular feedback mechanism (TGF). JGA NO blunts the increase in R_A seen when the macula densa is perfused with high NaCl [3]. Also, NO plays complex roles in control of JGA renin release [1-3] and the physiological relationship between NO and renin has not yet been defined.

NO also influences sodium excretion and may play a physiological role in control of sodium balance. NO has a direct tubular effect to inhibit sodium reabsorption in the collecting duct. Also local administration of NOI into the renal medullary interstitium selectively decreases papillary blood flow and lowers urinary sodium excretion with no change in GFR or BP. It is likely that NO controls sodium excretion both by direct tubular actions and also by regulating the vascular tone in the medullary circulation and the pressure natriuresis. There is some evidence that increased NO production is stimulated by increased dietary salt intake in normal animals, and may function as a ‘natriuretic hormone’ although the origin of this NO remains to be determined [2].

NO also influences growth and is generally reported to function as an anti-growth factor, although this has recently been disputed [1,2,4].

Deranged NO production in renal pathology

Overproduction of NO

There is increasing evidence that elevated levels of NO play a primary pathogenic role in some forms of immune-mediated glomerular injury. The injurious NO in glomerular inflammation probably originates from iNOS and may come from a variety of cell types including infiltrating macrophages and resident glomerular cells including mesangial cells [1]. NO appears to play a primary pathogenic role in the glomerular injury caused by antithymocyte serum; an acute glomerulonephritis that primarily involves the glomerular mesangial cells. Both NOI and dietary arginine deprivation are protective, and in this model excess NO actually promotes glomerular extracellular matrix accumulation [5]. Excessive NO is cytotoxic by several mechanisms, including formation of peroxynitrite and...
nitrosylation and inactivation of various enzymes [1]. Excessive NO production in sepsis and even normal pregnancy can lead to glomerular thrombosis, possibly because of substrate depletion and inadequate local eNOS generation of NO, which serves as antiagregant [1]. Some end-stage renal failure patients develop severe hypotension during haemodialysis due to iNOS activation in vascular smooth muscle, secondary to bioincompatibility of the dialysis membranes [6]. Renal allograft rejection may be mediated in part by cytotoxic effects of NO generated by iNOS [7]. Also the early diabetic hyperfiltration, which contributes to eventual development of diabetic glomerulopathy, may be partly due to excessive glomerular NO production [1].

**NO deficiency states**

Studies involving the Dahl salt-sensitive rat suggest that an inadequate NO production in response to high dietary salt intake, contributes to the hypertension, renal dysfunction, and injury in this strain [1,2]. Extracellular fluid volume expansion and salt-dependent hypertension can be experimentally induced in animals given chronic low doses of NOI and a high salt intake [1,2]. With increasing doses of chronic experimental NOI in animals, hypertension and renal injury can be produced on normal or low-salt diets. Partial NOI for 8 weeks produced moderate hypertension, renal vasoconstriction, increased P_eG, and eventual proteinuria and focal and segmental glomerular sclerosis [1,2]. Near complete NOI in rats for 4–6 weeks caused malignant hypertension with widespread arterial, arteriolar and glomerular structural damage [1,2]. In addition to glomerular hypertension, NO deficiency may lead to mesangial and vascular smooth muscle expansion and overproduction of extracellular matrix, which also predisposes to glomerular injury [1,2].

The clinical importance of NO deficiency in essential hypertension is not yet clear although functional studies suggest that NO-mediated vasodilatation is attenuated in some vascular beds of some individuals with essential hypertension [2]. Based on animal studies, NO deficiency may play a primary role in low-renin essential hypertension [1,2]. There is evidence suggesting that NO deficiency occurs in end-stage renal patients, since the 24-h production of the stable NO oxidation products NO_2 + NO_3 are reduced in peritoneal dialysis patients [8] and may contribute to the refractory hypertension sometimes seen in this population. NO deficiency would also be predicted to contribute to the progression of renal disease prior to end-stage. In renal failure NO deficiency presumably results both from reduced arginine availability (since the kidney is a major site of endogenous arginine synthesis), and accumulation of endogenous NOIs secondary to decreased renal clearance [9].

Many models of experimentally induced renal disease are improved by chronic dietary supplementation of the NO substrate L-arginine. These include cyclosporin-induced nephropathy, puromycin-aminonucleoside-induced nephrosis, diabetic nephropathy, severe ablation of renal mass and ureteral obstruction [9]. Perhaps the protective effect of arginine indicates that NO deficiency plays a primary role in the pathogenesis of these various, quite distinct models of kidney damage? However, L-arginine is unlikely to be rate limiting for constitutive NO synthesis [2], unless L-arginine utilization is dramatically increased by some other pathway [10], thus the mechanism of the protective effect of L-arginine remains to be determined. Nevertheless, L-arginine supplementation provides a promising therapeutic avenue for patients with various forms of progressive renal disease [9]. Acute L-arginine infusion in patients with chronic glomerulonephritis has already been shown to substantially reduces the proteinuria [11].

It is tempting to ascribe a primary role for NO deficiency to any renal disease in which renal vasocstriction plays a part. A recent study by Conger and colleagues provides a cautionary note [12]. Postischaemic (noradrenaline-induced) acute renal failure is characterized by reduced renal blood flow and a loss of responsiveness to endothelial-dependent vasodilators. Although this could be interpreted as evidence for NO deficiency, basal NO production and constitutive NOS protein were actually enhanced in postischaemic kidneys [12]. Renal NO synthesis is also elevated in cyclosporin-induced nephropathy, and the protective effect of L-arginine supplementation may occur by preventing substrate limitation of NO synthesis at crucial intrarenal sites [13].

In conclusion, NO plays a key role in the physiological regulation of renal blood flow and glomerular haemodynamics and possibly also in control of sodium excretion. In some disease states NO over- or underproduction may play a primary role in the disease process and chronic L-arginine supplementation may provide a useful tool in the treatment of various forms of renal disease.

**Note**

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**References**