NITRIC OXIDE IN RENAL PHYSIOLOGY AND CHRONIC RENAL FAILURE

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RENAL PHYSIOLOGY

In the late 1980's, many experiments were performed in different countries to demonstrate an effect of endothelial-derived relaxing factor (EDRF) on the vascular resistance of isolated organs such as the kidney (1, 2). The discovery of arginine analogues which inhibit nitric oxide (NO) synthase (NOS), including monomethyl arginine (L-NMMA) and nitroarginine methyl ester (L-NAME) allowed similar experiments to be performed in vivo. The systemic administration of NOS inhibitors produce large acute falls in both renal blood flow (RBF) and glomerular filtration rate (GFR) suggesting that NO may play an important role in the maintenance of renal function. However, the local administration of l-NAME to the kidney in the conscious dog produces much smaller changes in renal function, RBF declining by 10% with no change in GFR (3). This suggests that a large proportion of the change in renal function seen following intravenous administration of NOS inhibitors may be indirect, secondary to other effects of L-NAME including systemic hypertension. In healthy man, the intravenous administration of L-NMMA (3mg/kg) was associated with a 15% reduction in RPF measured using I^{125} hippuran clearance (4). Micropuncture experiments in the anaesthetised, laparotomised Munich-Wistar rat showed that an intrarenal infusion of L-NMMA increases afferent resistance (RA) by some 25% without affecting resistance of the efferent arteriole (RE). The glomerular hydrostatic and oncotic pressure gradients remained unchanged while single nephron GFR fell by 16% principally, due to a fall in the ultrafiltration coefficient (Kf) (5). Such data suggests that NO may have independent roles in the control of afferent arteriolar resistance and glomerular ultrafiltration.

Renin-Angiotensin System (RAS)

NO may interact with RAS in two specific ways influencing both renin release and the biological activity of angiotensin II (AII). Studies in isolated mouse juxtamedullary cells suggest NO exerts a dual effect on renin release of a transient inhibition mediated by cyclic GMP followed by a sustained increase requiring extracellular calcium (6). Studies in the conscious dog show a marked inhibition of renin release following l-NAME administration as renal arterial pressure was reduced from 90 to 50mmHg suggesting that NO stimulates renin release in vivo (7). While the renal effects of NOS inhibition are not thought to be mediated by AII (8), NO may be involved in the selectivity of AII as a vasoconstrictor for the efferent arteriole. The selectivity of AII as an efferent vasoconstrictor may be based on the selective inhibitory effect of NO as a vasodilator of the afferent arteriole in response to AII (9). NO may therefore be important in the renal response to angiotensin converting enzyme (ACE) inhibitors, proposed to protect the kidney from glomerular hypertension through a selective effect on the efferent arteriole. Since NO mediates the renal response to bradykinin, NO may also be a determinant of the beneficial effects of ACE inhibitors through inhibition of renal kininase II, enhancing bradykinin release.

Autoregulation and Tubuloglomerular Feedback (TGF)

The discovery of a renal vasodilator which selectively influences afferent arteriolar tone makes NO a potential candidate as a mediator of renal autoregulation. Although NOS inhibitors reduce the autoregulation plateau for RBF in both anaesthetised and conscious dogs, no evidence for inhibition of autoregulation per se for either GFR or RBF was obtained (10, 11). TGF is a separate event from autoregulation being mediated through the sensing of tubular chloride by the macula densa. The macula densa is an important site for NO production in the kidney generated by the brain type of the constitutive form of NOS (bNOS) (12). An increased tubular delivery of sodium chloride, increases macula densa chloride content which in turn enhances NO release, constituting the vasodilator arm of TGF (13). Alternatively NO may itself inhibit the macula densa transport of chloride (14). The precise function of the vasodilator arm of TGF remains to be established but it could control the sensitivity of the TGF pathway modified in physiological states such as volume expansion, diabetes, pregnancy and growth (15).

Glomerular Hyperfiltration

The glomerular capillary is unusual in possessing resistance arterioles at both its afferent and its efferent ends. As a conseqeuence, the glomerular hydrostatic pressure does not decline along the length of the glomerular capillary and filtration normally ceases when an equilibration point is reached partway along the capillary loop where the oncotic and hydrostatic gradients are in balance (16). GFR can therefore increase by using a greater proportion of the filtering surface ie by driving the equilibration point toward the efferent end of the capillary and such hyperfiltration has been termed renal functional reserve (RFR). In man, RFR is defined as the increase in GFR in response to a meat meal or amino acid infusion, both of which are prevented by NOS inhibitors and therefore mediated by NO. Studies in the diabetic kidney show hyperfiltration to be prevented by both NOS inhibitors and antagonists of the insulin-like growth factor-1 (IGF-I) receptor (17). Diabetic hyperfiltration is thought to be generated by the transcriptional activation of IGF-I induced by hyperglycaemia but mediated through the activation of cNOS by IGF-I (18). NO then increases the ultrafiltration coefficient of the glomerular filter probably through an effect on the podocyte at the level of the filtration slit diaphragm.

Tubular NO

Involvement in the control of renal haemodynamics inevitably gives NO a place in the homeostasis of salt balance, an increase in dietary salt potentiating the renal vascular effects of l-NAME in both man and the rat (19). However, in addition to its vascular properties, NO can also influence solute excretion by direct effects on the renal tubule. NO inhibits Na/K ATP-ase and chloride transport in the thick ascending limb but, stimulates the Na/HCO3 co-transporter in isolated proximal tubules (20-22). Tubular NO deficiency may therefore result in volume expansion. NO may also be involved in the inhibitory tubular effects of other hormones mediating for example, the inhibitory effects of AII on proximal sodium transport.

Chronic Renal Failure

The contribution of NO to the etiology of renal disease requires a broader understanding of its biochemistry and the biological properties. In renal disease, the involvement iNOS activated by both resident and infiltrating cell types becomes increasingly important. Additional biological properties to consider include, inhibition of platelet aggregation, leukocyte adhesion and matrix protein accumulation, modification of the immune response and the cytotoxic effects of large amounts of NO. The vascular effects of NO play a role in acute renal failure where medullary NO synthesis has been proposed to prevent hypoxic injury and in the renal and systemic effects of cyclosporin and erythropoetin. Inhibition of leukocyte adhesion may be important in reperfusion injury. NO plays a major role in the development of renal inflammation associated with glomerulonephritis

(23) but the implications of the potential deficiency of NO in chronic renal failure are less well documented.

Haemodialysis

Haemodialysis patients have increased plasma concentration of arginine and platelets which generate increased amounts of NO and cyclic guanosine monophosphate (cGMP). Uraemic serum can induce NO synthesis in human umbilical vein endothelial cells (HUVEC) and the induction of NO synthesis may explain defects in platelet aggregation and the hypotension associated with the dialysis patient (24). Elevation of plasma NO metabolites and total body NO generation during haemodialysis may result from enhanced cNOS activity in neutrophils activated by interaction with the dialysis membrane (25). Cardiovascular instability is observed more frequently when acetate dialysis solutions are used and NO synthesis remained unchanged when acetate free biofiltration was employed (26).

Peritoneal Dialysis

NO production may also be modified in patients on peritoneal dialysis. Patients on CAPD with acute peritonitis develop l-arginine deficiency with increased levels of nitrite in the dialysate (27). iNOS can be induced by cytokines such as IL-1 in both peritoneal macrophages and human peritoneal mesothelial cells (28). NO is therefore thought to be a mediator of peritoneal inflammation contributing to dialysis defects during peritonitis. However, under non-inflammatory conditions, the addition of an NO-donor to the peritoneal dialysis solution can increase the filtration surface area especially for larger molecules (29).

Transplant Rejection

Large quantities of NO are produced during allograft rejection and urinary tract infection with a 10-50 fold increase in NOS activity. NOS is also induced in cells present in the urine of patients undergoing allograft rejection (30). However whether NO functions as a mediator or a feedback inhibitor of alloreactivity remains a controversial issue. NO and the macrophage could function as regulators of alloreactivity possibly by preventing the activation of promotor sequences associated with some interferon response genes (31).

NO Deficiency in CRF

In patients with CRF, undergoing CAPD in the absence of peritonitis, whole body production of NO and cGMP is markedly reduced suggesting that CRF is a disease deficient in NO (32). A reduction in renal NO has been proposed to contribute to chronic renal insufficiency in patients with sickle cell disease and glomerulosclerosis is a feature of chronic NOS inhibition in the rat (33). Chronic NOS inhibition is associated with profound systemic hypertension which could itself generate glomerulosclerosis. The hypertension of chronic renal failure in man has been suggested to result from NOS inhibition through accumulation of dimethylated arginies, endogenous inhibitors of NO production (34). In the rat following subtotal nephrectomy, differential effects on systemic and renal NO production have been demonstrated renal NO, particularly iNOS activity is decreased, whereas cNOS activity was preserved (35). The fibrogenic growth factors transforming growth factor beta (TGFbeta) and IGF-I are both known to inhibit iNOS (36) but activate cNOS by independent mechanisms. TGF beta increases the expression of cNOS protein (37) while the effects of IGF-I are much more rapid occuring in HUVEC cells interestingly in the absence of measurable changes in intracellular calcium (38).

The NO-donor molsidomine slows renal progression and prolongs survival in rats with subtotal nephrectomy. NO is an inhibitor of matrix protein production (39) which has been demonstrated to entirely prevent the effects of fibrogenic growth factors, such as IGF-I on renal collagen accumulation in vivo (40). In fact, studies in the normal rat would suggest that in addition to vasodilatation and inhibition of platelet aggregation, keeping an inhibitory brake on matrix protein production may be a basic property of NO synthesised in the vascular endothelium. Diseased states deficient in NO such as diabetes may therefore be devoid of this property, increasing their susceptiblity to renal disease. Such a property may also explain the beneficial effects of dietary supplementation with l-arginine in experimental models of CRF (41).

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