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EDITORIAL REVIEW

Glomerular actions of nitric oxide

The discovery of the L-arginine-nitric oxide (NO) pathway has been one of the major scientific accomplishments of the last 10 years [1–7]. NO, a simple molecule, has been identified as having roles in cell communication as well as cell defense and injury. This has changed our understanding of important aspects of the physiology and pathophysiology of the cardiovascular, nervous and immune systems [5, 8–14].

A family of enzymes named NO synthases (NOS) are capable of generating NO from the terminal guanidino nitrogen of L-arginine. NOS require reduced nicotinamide adenine dinucleotide, flavine dinucleotide, flavine mononucleotide and tetrahydrobiopterine as co-factors in the oxidative process which results in production of citrulline and NO from L-arginine [2, 4, 5, 13–17]. Four isoforms of NOS have so far been identified: in the brain, vascular endothelial cells, macrophages and in hepatocytes. The brain NOS, which is also present in peripheral neural tissue, and the endothelial NOS are constitutive (c) enzymes which are calcium and calmodulin dependent [13, 14, 17]. The macrophage NOS is calcium and calmodulin independent and is not constitutive but can be induced (iNOS) by certain cytokines and bacterial products, such as endotoxin [15, 18–21]. Most recently a structurally distinct iNOS has been induced in hepatocytes (with endotoxin), which is calcium independent but requires calmodulin [22, 23]. iNOS have also been identified in other cells, including glomerular mesangial cells [24–26], vascular endothelial cells [5] and vascular smooth muscle cells [27]. Thus far transcription factors NF-κB and IRF-1 have been shown to particpate in the induction of iNOS [7].

The endothelial cNOS, which is predominantly membrane bound, is activated by mechanisms that result in calcium mobilization, including activation of receptors by various agonists such as acetylcholine (ACh), bradykinin (BK) and ADP as well as by physical forces, specifically shear stress [5, 14, 28, 29]. The amount of NO generated by cNOS is small, in nmol quantities, and its effects are transient since NO is rapidly inactivated by superoxide anions and binding to hemoglobin [5]. However, since endothelial cNOS is tonically active *in vivo*, there is a continual basal production of NO by vascular endothelium [5, 11, 12]. On the other hand, iNOS synthesize NO in large (mmol) quantities. Since iNOS are regulated at the transcriptional level the initiation of NO synthesis/release is delayed after the stimulus (by several hours) but once initiated the synthesis of NO is long lasting (hours) [5, 15, 19, 24].

In early studies differentiation between cNOS and iNOS was based upon its dependence or independence, respectively, of calcium for activation. However, recent studies have shown that certain calcium dependent NOS are inducible [30, 31]. L-arginine analogs compete with L-arginine for binding sides in the NOS and can inhibit NO synthesis by both cNOS and iNOS [5, 32, 33]. Several L-arginine analogs have been synthesized and some of these analogs may have more affinity for either the constitutive or inducible enzymes [5, 32, 33]. Actinomycin D and cycloheximide, inhibitors of DNA transcription and of protein synthesis, respectively, prevent the induction of NOS. Glucocorticoids and certain cytokines such as TGFβ, IL-4 and IL-10 have also been found to inhibit iNOS without affecting cNOS [7, 34–37]. In human monocytes cross linking of the surface receptor CD69 which is constitutively expressed leads to production of NO in large quantities by these cells [38].

NO acting as a messenger molecule mediates vascular relaxation, inhibits platelet aggregation and adhesion to the endothelium and modulates leukocyte chemotaxis and adhesion [5, 39, 40]. All these effects of NO are mediated by activation of soluble guanylate cyclase after NO binding to its heme iron, resulting in increased levels of cyclic guanosine, 3′, 5′, monophosphate (cGMP) [5, 32]. NO also mediates relaxation of vascular smooth muscle by directly activating calcium-dependent potassium channels [39]. In peripheral blood mononuclear cells NO may act as a signaling molecule by activating G proteins through a cGMP-independent pathway [40–42]. NO, when released in large quantities by the iNOS, can inhibit enzymes such as aconitase and ribonucleotide reductase by nitrosylation of Fe-S centers [43–45]. It needs to be stressed that a differentiation has to be made between NO action and the activity of NO synthases. The actions of NO are dependent upon: (1) the amount of NO produced, which is conditioned by the availability of its substrate L-arginine as well as the activity of the NOS; (2) the rate of NO inactivation by either superoxide anions or NO sequestration due to binding to reactive groups such as heme groups; and (3) the availability of substrates such as guanylate cyclase which participate in mediating NO actions. Increments in NOS are often accompanied by increased NO action; however, increased NO production and activity may under certain circumstances be due to changes in NOS activity without changes in NOS mass [46, 47].

In the kidney cNOS, identified by immunohistochemical staining or by reverse transcription and polymerase chain reactions, has been found in glomeruli and vasculature as well as the macula densa, the collecting duct and the inner medullary thin limb [47, 48]. In addition, iNOS occurs in vascular smooth muscle and granular cells at the juxtaglomerular apparatus (JGA) [48], and cytokine induced iNOS have been reported in cultured proximal and collecting duct cells [48–51].

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Glomerular hemodynamic actions of NO

The pressures and flows at the glomerulus that determine single nephron GFR (SNGFR) are controlled by the tone of preglomerular (afferent) and postglomerular (efferent) arteriolar resistance vessels (R_A and R_E). The ratio of the tone of these

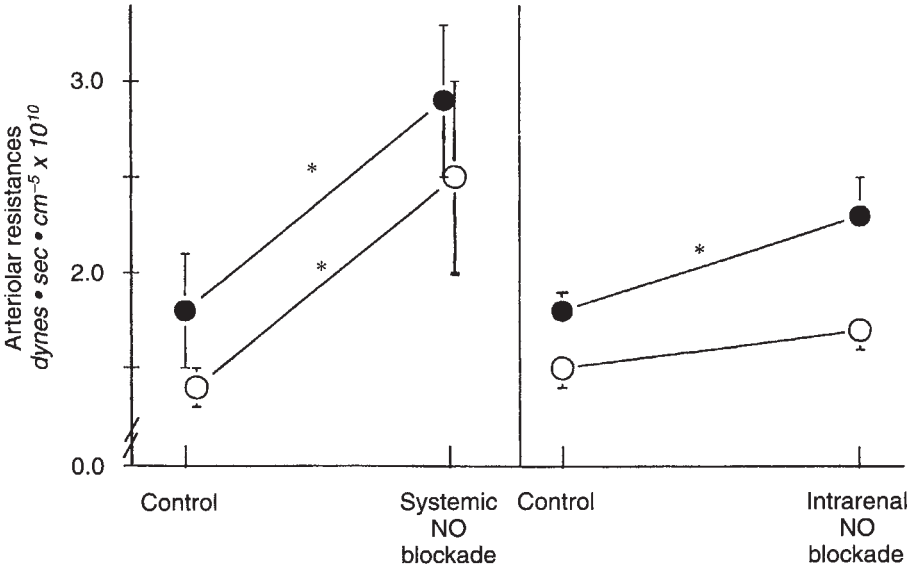

Fig. 1. *Comparison of the effects of systemic versus intrarenal NO blockade on afferent and efferent arteriolar resistances in the euvolemic Munich Wistar rat.* *Significant change versus control by paired *t*-test. These studies are reported in [76].

resistances determines the glomerular blood pressure, P_{gc} and the overall level of tone in the renal resistance vessels controls glomerular plasma flow [52–54]. The glomerular capillary ultrafiltration coefficient, K_f, is another variable that can directly influence SNGFR and dynamic control may occur via alterations in tone of glomerular mesangial cells which cause alterations in filtration surface [52, 53].

The glomerular mesangium is located centrally in the glomerulus and plays an important role in regulation of the glomerular microcirculation [55–57]. The fenestrated glomerular endothelium lies in direct contact with the mesangium, hence, substances released by the endothelium or circulating in the plasma have easy access to the mesangial cells. In addition, substances released by either endothelial or mesangial cells can act in a paracrine fashion [56–61]. Mesangial cells have actin and myosin, and similarly to vascular smooth muscle cells, can contract and relax. Vasoactive agents such as angiotensin II, vasopressin, endothelin and thromboxane A2, induce mesangial contraction subsequent to binding to specific receptors and activation of phospholipase C, ultimately leading to calcium mobilization [59].

Effects of acute blockade of NO

In several species, systemic administration of L-arginine analogs produces dose dependent and prolonged increases in arterial blood pressure (BP) and renal vasoconstriction with falls in renal plasma flow (RPF) and smaller declines in GFR [5, 12, 62–67]. These effects can be reversed by excess L-arginine, which suggests that the L-arginine analogs are functioning as specific NO synthesis inhibitors [5, 62, 63, 66, 68]. Direct infusion of NO synthesis inhibitors into the renal artery of the isolated perfused rat kidney and L-arginine depletion in the perfusion medium produces renal vasoconstriction and falls in GFR [65, 69–72]. There are regional differences in the extent to which NO controls the circulation and the renal vasculature seems to be particularly sensitive to regulation by NO. Systemic infusion of low doses of NO inhibitors, which have no effect on BP, produce increased renal vascular resistance (RVR) and reductions in renal blood flow (RBF) and cortical blood flow [64, 73, 74].

In vivo micropuncture experiments have shown that systemic administration of pressor doses of NO synthesis inhibitors produce complex effects on the glomerular microcirculation. Both R_A and R_E increase and as a result glomerular plasma flow falls; however, SNGFR is relatively protected due to a large rise in P_{gc} [75, 76]. In addition, the glomerular capillary ultrafiltration coefficient (K_f) is reduced to ~50% of control with NO blockade [75, 76]. *In vitro* studies utilizing co-incubation of either glomerular or aortic endothelial and mesangial cells have shown that agonist-induced release of NO from endothelial cells is accompanied by increases in mesangial cell CGMP [60, 61]. Increases in cGMP induced by NO are sufficient for antagonizing angiotensin II (Ang II) evoked mesangial cell contraction [60]. Atrial natriuretic peptide which increases mesangial cell cGMP via activation of the particulate guanylate cyclase, also antagonizes the effects of Ang II [77]. Thus, independent of the triggering stimulus, increases in cGMP antagonize mesangial cell contraction (or induce its relaxation) probably due to inhibition of cellular calcium mobilization.

Systemic administration of NO blockers produce widespread inhibition of NO synthesis and increases in BP, which will have indirect effects on the kidney. Local intrarenal inhibition of NO generation leads to much smaller increases in RVR than are seen during systemic NO blockade; thus, a substantial part of the renal vasoconstriction seen with systemic NO inhibition is due to secondary phenomena perhaps mediated via the renal nerves. Micropuncture studies in the rat [76] have shown that whereas both R_A and R_E increase with systemic NO blockade, a smaller increase in R_A is seen during intrarenal blockade (Fig. 1). The smaller increase in R_A with intrarenal versus systemic NO blockade probably reflects an autoregulatory component of the increase in R_A when BP rises [78]. Although R_E increases with systemic NO blockade, there is no effect on R_E when NO synthesis is blocked locally within the kidney (Fig. 1). These observations suggest that in the euvolemic rat the cortical afferent arteriole is tonically under the control of locally produced NO whereas R_E is not [76]. *In vitro* studies on isolated microperfused cortical rabbit arterioles have supported these findings [79–81], although in

contrast to cortical vessels, NO synthesis inhibition produced constriction of both afferent and efferent arterioles of juxtamedullary nephrons [82]. Thus, *in vivo* and *in vitro* studies suggest that tonic release of NO and control of basal tone by NO is confined to the afferent arteriole and mesangial cell in the cortex, but in the juxtamedullary nephron preparation, efferent arterioles are also under tonic NO control.

In some situations the efferent arteriole from the cortex can make and respond to NO. In the isolated perfused rat kidney, the extremely high perfusion rate causes a high shear stress effect throughout the renal microcirculation and shear is a potent stimulus to release of endothelial NO [5, 29]. In this setting both R_A and R_E increase with NO blockade [83]. There is also evidence that agonists stimulate NO release from efferent arterioles (see below).

NOS is abundant in the juxtaglomerular apparatus [48, 51, 84, 85] and NO generated within the macula densa may control glomerular hemodynamics. The macula densa provides the sensor for the tubuloglomerular feedback system (TGF), and when NO synthesis in the macula densa is locally inhibited, P_{gc} decreases due to constriction of the afferent arteriole [86]. *In vitro* studies have shown that inhibition of macula densa NO synthesis during delivery of high NaCl produced afferent arteriolar constriction but had no vasoconstrictor effect during delivery of low sodium chloride [87] (Fig. 2). These studies suggest that TGF-induced afferent arteriolar vasoconstriction produced by increased NaCl reabsorption at the macula densa is blunted or modified by NO, which is also stimulated by high NaCl [86, 87]. Conflicting preliminary observations suggest that decreased macula densa NaCl reabsorption stimulates NO synthesis [88, 89]. Resolution of these differences, as well as defining the role and regulation of an iNOS in the afferent arteriole [48] remains to be determined. The relationship between NO and renin release is discussed below.

Effects of chronic blockade of NO

Chronic blockade of NO produces a dose dependent, chronic hypertension [90]. Partial NO blockade over a two month period produced a moderate, stable systemic hypertension with renal vasoconstriction, proteinuria and mild glomerular sclerotic injury [90]. Micropuncture revealed that P_{gc} was high, K_f was low and both R_A and R_E were elevated [91], which is a similar pattern of change to that seen after acute systemic NO blockade [75, 76]. More complete NO blockade for four to six weeks produced severe hypertension with renal vasoconstriction and substantial microvascular and glomerular damage, characteristic of hypertensive microangiopathy [92]. After only two weeks of severe NO blockade, BP and P_{gc} were higher than after two months of the more moderate dose of NO blocker [90, 93]. With severe chronic NO blockade there is a progressive increase in BP and RVR, declines in GFR and development of proteinuria, within three weeks [94]. With even shorter periods of chronic NO inhibition (3 to 7 days), sustained renal vasoconstriction has been reported [95, 96], although in the Brattleboro rat, the increase in RVR is not maintained over a three day period [97].

Overall, the studies with acute and chronic NO blockade suggest that NO plays important short- and long-term roles in control of glomerular hemodynamics by controlling R_A and the tone of glomerular mesangial cells and in some circumstances, R_E. Thus all contractile cells which control glomerular filtration are potential targets for endogenous NO.

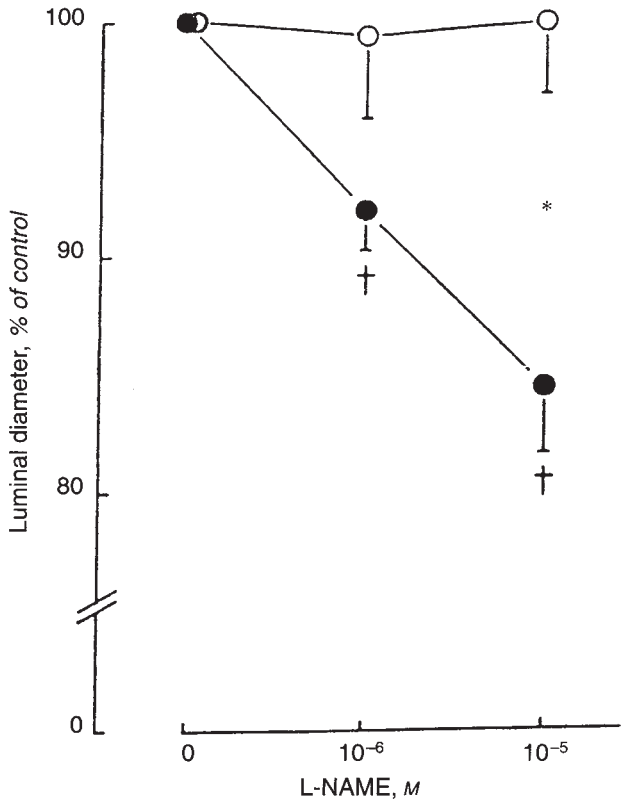

Fig. 2. *Changes in the internal diameter of the isolated rabbit afferent arteriole during local NO synthesis inhibition at the macula densa using L-NAME.* L-NAME was added to the macula densa perfusate which contained either a high NaCl (●) or a low NaCl (○) solution. †$P < 0.001$ versus control (that is, intact NO system), *$P < 0.003$ for low versus high NaCl. This Figure is reproduced from the *Journal of Clinical Investigation* 92:1093–1098, 1993 by copyright permission of the American Society for Clinical Investigation and permission from the authors [87].

NO and renal autoregulation

A combination of myogenic and TGF mechanisms increase R_A during increases in systemic BP, which leads to autoregulation of RBF, GFR and P_{gc} [78]. In addition to controlling TGF (see above) it is possible that NO also influences the myogenic component of autoregulation. The isolated rabbit ear is a weakly autoregulating vascular bed under normal conditions, but blockade of local NO production leads to improved pressure-dependent autoregulation [98]. In the kidney, NO synthesis inhibition leads to increases in RVR but autoregulation of RBF and appropriate changes in tone in afferent arterioles of the rat juxtamedullary nephrons persist over a wide range of arterial BP [82, 99–102]. There is a suggestion that in dogs and rats, NO might contribute to the vasodilation which occurs at low pressure [101, 103, 82]; however, renal autoregulatory ability is relatively unaffected by the activity of the NO system.

Effects of vasodilators that stimulate NO

The vasodilatory action of ACh and BK is mediated in part by NO [1, 5, 12]. Both ACh and BK are potent renal vasodilators and glomerular micropuncture studies indicate that both R_A and R_E respond to ACh and BK with a vasodilation [104]. *In vitro* studies

have also indicated that R_A vasodilates to ACh, [82, 105, 106] and R_E relaxes in response to ACh and BK [106]. In contrast to these observations, studies by Kon, Harris and Ichikawa suggested that the main renal artery was the primary site of NO release in response to ACh, since endothelial denudation of the renal artery impaired the vasodilatory response to ACh by R_A and R_E [107]. However, the *in vitro* evidence indicates that NO can be generated in the renal arterioles, thus, a vasoconstrictor may have been released by endothelial rubbing of the renal artery [107].

Despite renal vasodilation and increased plasma flow with both ACh and BK, SNGFR did not rise due to an offsetting decline in K_f [104]. The reduction in K_f with BK (and possibly ACh) probably resulted from a direct action on the mesangium to increase intracellular free calcium and inositol trisphosphate [108, 109], which overwhelmed the endothelial NO-stimulated effect to relax the mesangial cell [60].

The increase in urinary cGMP and the renal vasodilatory action of ACh and BK can be attenuated or abolished by simultaneous NO synthesis inhibition [12, 110]. ACh induced increases in cortical and papillary blood flow and falls in R_A in juxtamedullary nephrons are also inhibited by simultaneous NO inhibition [73, 82]. However, NO is not the only mediator of ACh and BK induced renal vasodilation, since a significant arachidonic acid component has been identified in rat and dog kidney [72, 111–113].

ACh and BK produce widespread vasodilation but amino acid infusion and high protein feeding produce a selective renal vasodilation which is linked to increases in urinary cyclic GMP excretion [114]. In the anesthetized rat, the renal vasodilatory response to an infusion of amino acids is inhibited by NO blockade [115, 116], although mechanisms in addition to NO may contribute to the renal vasodilation in response to amino acid infusion [117]. Why NO release in response to amino acid infusion should be confined to the kidney, has yet to be described.

Interactions between NO and other vasoactive systems

The greater the level of vascular tone, the greater the amount of endothelial NO produced [118]. How much the vasoconstrictor response to NO blockade results from withdrawal of an "active" NO vasodilatory stimulus and how much is secondary to amplification of underlying vasoconstrictor systems, is not clear. Below interactions between NO and other vasoactive control systems will be considered.

Angiotensin II

In the anesthetized rat and *in vitro* juxtamedullary nephrons, part of the renal vasoconstriction in response to NO synthesis inhibition is due to the unopposed vasoconstrictor effect of endogenous Ang II [82, 115, 119]. In contrast, Ang II blockade has no effect on the renal vasoconstrictor response to acute NO inhibition in the conscious, unstressed rat [120] and similar findings have been reported in the anesthetized rat [121]. Sigmon and Beierwaltes have indicated that the Ang II dependence of the renal vasoconstriction seen with NO blockade varies according to the preparation, being much less pronounced in the awake animal [122]. Inhibition of Ang II has no attenuating effect on the vasoconstriction due to NO blockade in isolated rat afferent arterioles [123] and in glomerular micropuncture studies, Ang II inhibition had no effect on the increase in R_A although blunting of the increase in R_E was seen [124]. Thus, the renal vasoconstriction produced by acute NO blockade does not require the participation of the Ang II system; however, when Ang II levels are sufficiently high to control renal vascular tone, NO is important in maintaining renal perfusion. In the conscious rat and dog, infusions of Ang II that have little effect on RVR when given alone, cause massive renal vasoconstriction when the NO system is also acutely inhibited [125, 126]. In rabbit isolated afferent arterioles, locally produced NO blunts the response to administered Ang II but R_E, which is also responsive to Ang II, is unaffected by NO blockade [79, 80]. When endogenous Ang II levels are elevated in two kidney, one-clip Goldblatt hypertension, tonically produced NO helps maintain perfusion to the contralateral kidney but does not apparently have an impact on resistance in the clipped kidney which is mainly controlled by Ang II [127]. In fact, NO may not have a long- term protective vasodilatory effect on the renal vasculature when intrarenal Ang II levels are chronically high [128].

In chronic NO blockade, Ang II plays an important role in the maintenance of the hypertension since chronic Ang II inhibition prevents the hypertension and the kidney damage during NO blockade [91, 123, 129]. When the Ang II system is acutely inhibited in chronic NO blockade induced hypertension, there is no beneficial effect on BP or RVR [151] but when both Ang II and the sympathetic nervous system (α1-adrenergic receptors) are inhibited simultaneously, normalization of BP occurs although the renal vasoconstriction is largely maintained [130].

In addition to influencing the renal vascular effect of Ang II, NO may also influence the levels of Ang II via control of renin release. This is a controversial area and some observers have suggested that NO stimulates renin release [131–133] whereas others suggest that NO is inhibitory on renin release, thus acute NO blockade increases renin production [134–136]. Although the reasons for these discrepancies regarding the directional effect of NO on renin release remain unclear, there is recent evidence to suggest that NO may have a dual effect on renin production. When applied directly to the granular cells NO inhibits renin secretion, however, stimulation of macula densa NO production, leads to a stimulation of renin secretion [85]. In models of chronic NO blockade, renin levels are variable and have been reported as low, unchanged or elevated, which probably reflects the severity and extent of the hypertension and underlying renal pathology as well as any direct actions of NO deficiency on renin release [89, 91, 129].

Sympathetic nervous system (SNS)/catecholamines

Although NO will blunt any vasoconstrictor tone present, several groups have shown that the acute increase in BP with NO blockade is not dependent on the sympathetic nervous system. Ganglion blockade, pithing or adrenergic receptor blockade had little effect on the increases in BP or RVR [121, 137], although this contrasts with one report which suggests that the hypertension and renal vasoconstriction can be abolished by ganglion blockade [138]. There is some evidence to suggest that efferent renal sympathetic nerve activity plays an important role in mediating the renal vasoconstriction during acute systemic NO blockade, and the hypertension during chronic NO blockade [65, 139]. The combination of acute Ang II and SNS blockade also normalize BP in chronic NO blockade-induced hypertension [130] Thus, as with Ang II, the SNS in some circumstances plays an important role in NO dependent peripheral and renal vasoconstriction.

Endothelin (ET)

There are both ET_A and ET_B receptors in the kidney and is some evidence suggests that ET-induced renal vasoconstriction is via ET_B stimulation [140, 141]. ET1 administration produces renal vasoconstriction in the rabbit, dog and rat, and in all cases inhibition of either NO synthesis or cGMP potentiates the renal vasoconstrictor effects of ET1 [142–145] However, the interrelationship between the vasodilation mediated by NO and vasoconstriction elicited by several vasoconstrictor substances is further complicated by the fact that vasoconstrictors such as ET1 and platelet activating factor (PAF), trigger endothelium dependent relaxations mediated by NO. In the isolated rabbit afferent arteriole, ET1 causes a dose dependent vasoconstriction which is amplified by NO synthesis inhibition and attenuated by the NO stimulator ACh [146]. PAF vasodilates preconstricted isolated rabbit afferent arterioles via increased local NO production [147], and lowers R_E via NO produced in the glomerulus [148]. Of interest, ET and PAF, as well as substances released by platelets during aggregation, that is, serotonin and ADP, and by-products of blood coagulation such as thrombin, stimulate NO synthesis/release in the presence of an intact endothelium but trigger vascular smooth muscle and mesangial cell contraction when acting directly on these cells [28]. Therefore, the ultimate action of these substances depends upon whether or not a functionally intact endothelium is interposed between the agonist and the mesangial or vascular smooth muscle cell. Obviously, this has important pathophysiologic implications. It is known that in coronary vessels serotonin, for instance, is a mild vasodilator in the presence of an intact endothelium and a vasoconstrictor when the endothelium is dysfunctional [149]. If the same situation occurs within the glomerulus, a given substance may induce opposite changes in the glomerular microcirculation depending upon whether the glomerular endothelium is functionally intact.

Prostaglandins

There are a number of agents with receptors on the vascular endothelial cell which release both NO and vasodilatory prostanoids, such as ACh, BK [5]. There is also evidence to suggest that the endothelial prostaglandins may control the synthesis of NO. Prostacyclin (PGI_2) inhibits NO release from cultured bovine aortic endothelial cells and modulates LPS stimulated iNOS in mouse macrophages [150, 151]. It has been suggested that agents which increase cAMP, such as PGI_2, decrease NO production [152]. There is also *in vivo* data to suggest that in the dog kidney the full renal vasodilatory potential of NO is expressed only in the presence of PG blockade [112, 113]. In contrast to these findings, however, an *in vitro* study suggests that PGE_2 actually mediates cytokine stimulated activation of iNOS in rat liver macrophages [153], and it has also been shown that NO stimulates the inducible cyclooxygenase enzyme (COX_2) *in vitro* [154]. Functional studies in the normal and chronically NO blocked conscious rat have shown that indomethacin has little potentiating effect on either the pressor or the renal vasoconstrictor response to either acute, low dose or systemic chronic NO blockade [74, 155]. Thus, according to the circumstance, inhibition or stimulation have been observed between NO and cyclooxygenase products.

In control of vascular tone and renal hemodynamics NO has a complex relationship with other vasoactive systems, which vary according to experimental preparation, volume status, anesthesia, etc. Tonically produced NO both attenuates the renal vasoconstrictor effects of any activated pressor systems and provides an active renal vasodilatory stimulus.

Role of NO in some disease states where glomerular hemodynamics are deranged

Since chronic pharmacologic NO inhibition causes hypertension, renal vasoconstriction and kidney damage, NO deficiency might also be causal in other forms of hypertension. There is evidence to suggest that the normal, "normotensive" response to high dietary salt intake includes stimulation of NO production [156]. Studies in the Dahl salt sensitive (SS) hypertensive rat suggest that malignant hypertension with renal function impairment and damage develops due to a deficient NO response to dietary salt [157]. Low dose NOS inhibition, which has no effect on BP in dogs on normal salt intake, leads to hypertension during high salt intake [158, 159]. Also, salt loading greatly potentiates the hypertension and glomerular injury in rats receiving high dose NO blockade [159], although sodium restriction does not ameliorate the hypertension [160]. Despite the findings described above, it is unlikely that alterations in NO synthesis or release can fully explain salt dependent hypertension. Moreover, in hypertensive Afro-Americans without renal failure, salt loading suppressed serum levels of NO_2/NO_3 [161].

The role of NO is less well defined in other types of hypertension. The vasodilatory response to ACh in the afferent arteriole is attenuated in both the spontaneously hypertensive rat (SHR) and in Goldblatt hypertension [105, 162], although at least with SHR this does not appear to be due to NO deficiency [105]. In renal ablation-induced hypertension, increased intrarenal NO may cause the preglomerular vasodilation [163]; however, it has also recently been reported that L-arginine supplementation is protective [164]. Thus the role of NO in ablation induced injury remains unclear. Direct measurements of NO released by kidneys from hypertensive rats revealed that compared with kidneys from normal rats, renal NO synthesis/release was normal in kidneys from hypertensive SHR rats but it was markedly decreased in kidneys from Dahl-S rats and DOCA-salt rats [165]. This suggests that in the setting of hypertension, high dietary salt may have an independent negative effect upon NO synthesis/release or action, a phenomenon previously observed in studies of vascular responses in rats given high dietary salt [166].

Acute renal failure induced by renal ischemia is associated with a loss of responsiveness to the endothelium dependent vasodilators ACh and BK [167]. However, NOS activity is paradoxically increased in this model [168], a response that has also been reported in gentamicin-induced acute renal failure [169]. Deficient NO production has been implicated in glycerol-, uranyl nitrate- and cyclosporine-induced nephrotoxicity since L-arginine is protective in these models [170–172], although the mechanism of the protective effect of L-arginine remains to be determined.

Excess NO production may be pathogenic in some situations. For example, recent experimental studies have suggested that excess NO synthesis early in diabetes may be responsible, at least in part, for the glomerular hyperfiltration which characterizes this disease. Glomerular damage develops in diabetes and is preceded and possibly caused by falls in R_A and high P_{gc} [173] and an increase in NO has been implicated [174–176]. The rise in P_{gc} and consequent glomerular damage would be further aggravated in

the presence of a concomitant increase in systemic blood pressure. Poorly controlled diabetes results in increased glycosylation of proteins and formation of advanced glycosylation end-products (AGEs). AGEs have been shown to biologically inactivate NO, impairing NO stimulation of guanylate cyclase [177]. AGEs have also been suggested to participate in the genesis of the vascular disease which accompanies diabetes [177]. Therefore it is possible that the L-arginine/NO pathway is involved in diabetes in a bimodal fashion characterized by an early NO excess and followed by a functional deficiency when the disease advances [175–178]. Whether manipulation of the L-arginine/NO pathway can modify the natural history of diabetic nephropathy is at present unclear. The role of NO in endotoxic shock is discussed below.

NO and the sepsis syndrome

Nitric oxide inhibits platelet aggregation and adhesion to collagen [5, 41, 178]. $PG1_2$ synergizes with NO in inhibiting platelet aggregation but has no effect on platelet adhesion [41]. However, platelets can generate their own NO when stimulated to aggregate with collagen, ADP or arachidonic acid [5]. *In vitro*, L-arginine inhibits platelet aggregation induced by these agents, and these effects of L-arginine can be inhibited by a substituted L-arginine analog such as L-NMMA which inhibits NO synthesis [5]. The platelet NOS, similar to that present in the endothelium, is calcium dependent and may play an important autocrine role synthesizing NO and increasing platelet cGMP in response to many stimuli which foster platelet aggregation. However, strong platelet aggregating substances such as thrombin cannot be inhibited by L-arginine supplementation during the aggregating process, but can be inhibited *in vitro* by addition of PGI_2. *In vivo* inhibition of NO synthesis with L-arginine analogs does not result in platelet aggregation and thrombosis in the absence of other stimuli [179].

Fibrin deposition is a variable component of most forms of glomerular injury [180, 181]. Platelet adhesion and fibrin deposition has been observed in most forms of immune- as well as in hemodynamically-mediated glomerular injury. Moreover, in diseases in which intravascular coagulation is a predominant feature, such as uremic hemolytic syndrome, post-partum renal failure, and in certain cases of gram negative sepsis, diffuse glomerular thrombosis is common [180–182]. Given the particular anatomy of the glomerulus, the anti-thrombogenic action of NO may be important, particularly its synergistic effect with PGI_2 which is also synthesized by both endothelial cells and mesangial cells.

Induction of NOS in rat mesangial cells has been shown recently by several laboratories [24–26]. Incubation of mesangial cells with lipopolysacchride (LPS) of gram negative bacteria and/or several cytokines, such as tumor necrosis factor (TNF), γ interferon and IL-1 results in increased mRNA for iNOS and in synthesis of NO, detectable by the cumulative increase in $N0_2/N0_3$ (oxidation products of NO), in the culture media [24]. In addition, synthesis of NO by mesangial iNOS is accompanied by increases in mesangial cGMP, therefore suggesting that within the glomerulus NO of mesangial origin may have autocrine as well as paracrine effects [24–26]. Rats given LPS *in vivo* have an increase in serum and urinary excretion of $N0_2/N0_3$ [179]. Glomeruli isolated from these rats continue to produce $N0_2/N0_3$ *ex vivo* in tissue culture. The *in vivo* and *ex vivo* synthesis of NO in response to LPS can be inhibited by L-NAME [179].

During gram negative sepsis, multiple biological systems are activated [182]. Endotoxin, the LPS component of the wall of gram negative bacteria is the triggering agent. Some of the biological responses observed during sepsis are mediated directly by LPS while others are mediated by the secondary synthesis and release of other mediators such as TNF, various interleukins, platelet activating factor (PAF), and components of the complement and the coagulation cascade [182]. Recent studies have suggested that the decrease in inotropic property of cardiac muscle, as well as the profound vasodilation (often resistant to vasopressors) observed during septic shock may be mediated by NO [5, 183–186]. Several studies *in vivo* and *in vitro* have found evidence of high levels of synthesis of NO by iNOS in vascular smooth muscle and mesangial cells [24, 27, 186]. *In vivo* the hypotension induced by either LPS or TNF can be reversed with L-NMMA, a NOS inhibitor [183, 184]. Although the demonstration of iNOS in humans has been more elusive, two lines of evidence suggest that NOS can be induced. (a) The vasopressor resistant hypotension of septic shock in humans can be improved with an intravenous administration of L-NMMA [185] and (b) recently two studies have shown increased NO synthesis in humans. One of the studies provided direct evidence of NO synthesis from L-arginine [187]. In this study patients were given N^{15} L-arginine and increased serum N^{15} $NO_2/NO_2/NOW_3$ was measured during IL-2 administration [187]. Similar increases in NO synthesis have been reported by Ochoa et al in septic patients [188].

Glomerular thrombosis occasionally severe enough to result in cortical necrosis has been observed in humans with sepsis. Studies by Shultz and Raij have shown, in rats, that LPS induces increased NO synthesis *in vivo* [179]. Inhibition of NO synthesis with L-NAME resulted in diffuse glomerular thrombosis after LPS administration, but inhibition of NO synthesis without LPS administration did not result in glomerular thrombosis [179]. In glomerular thrombosis induced by LPS, plus L-NAME can be prevented by concomitant administration of NO donnors such as GTN but not by other vasodilators [184].

These findings suggest that endogenous synthesis of NO in sepsis and sepsis related syndromes may have, in fact, a renoprotective role by maintaining renal vasodilation and by inhibiting platelet adhesion and aggregation [5, 179].

Within the glomerulus TNF, IL-1 and PAF can be released locally by either activated mesangial cells and/or blood borne macrophages [51, 189]. These same mediators induce endothelial synthesis of tissue factor and plasminogen inactivator, two substances which foster platelet adhesion and blood coagulation, respectively [57, 190]. Under these circumstances the local release of PGI_2 and NO would be important in preventing glomerular thrombosis. Moreover, plasminogen activator has been shown to potentiate NO synthesis by IL-1 induced NOS, while thrombin has been shown to have the opposite effect [191, 192].Taken together, these studies suggest that fibrin deposition during inflammatory processes affecting the glomeruli depends upon a delicate balance between locally produced procoagulants and anticoagulants, which include NO and $PG1_2$.

NO in pregnancy

Normal pregnancy is characterized by peripheral and renal vasodilation, falls in BP and increased GFR, the mechanisms of which are unknown [193, 194]. A gestational increase in cGMP production occurs in women and rats [195, 196], and elevations in

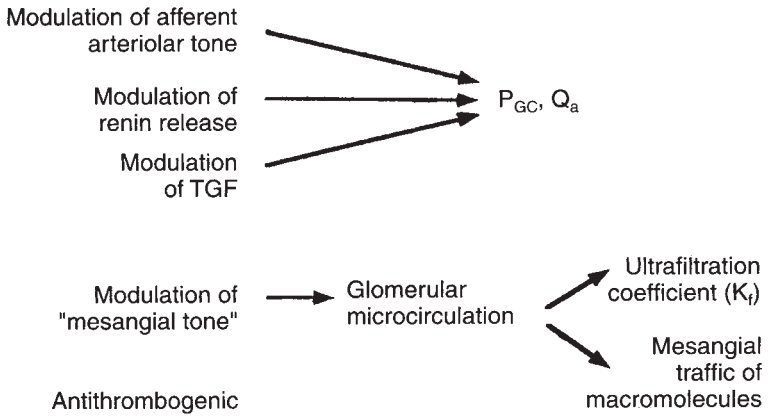

Fig. 3. *Schema depicting the physiological actions of NO at the glomerulus, these actions are mainly modulated by NO derived from cNOS.* Abbreviations are: TGF, tubuloglomerular feedback; P_{GC}, glomerular capillary pressure; Q_a, glomerular blood flow.

NO production have been reported in pregnant rats [181, 197, 198] which occur in phase with the increased cGMP [197]. Chronic NO blockade in pregnant rats prevents the renal and peripheral vasodilation and increase in GFR, and BP is elevated at term; proteinuria and compromise of maternal and fetal well-being are also evident [198]. Surprisingly, these pathological changes occur despite the fact that the late pregnant rat is relatively resistant to NO blockade with NAME [199]. A dose of NAME that produced only partial NO blockade in late pregnancy prevented the gestational rise in NO but left a level of NO production that is normal for an unblocked virgin, despite which BP rose [191]. This observation reinforces the concept that increased NO production is necessary to accomodate the altered hemodynamic status of pregnancy, particularly since in other models of chronic hypertension, pregnancy is antihypertensive, probably because of increased NO production [193, 199]. Recently, pregnancy in guinea pigs and rats has been shown to result in widespread increases in expression of cNOS [200, 201]. Also, studies in the conscious, chronically catheterized rat have suggested that the gestational renal vasodilation is NO dependent [202]. Thus, increased NO production certainly occurs during pregnancy in the rat and is probably associated with the gestational vasodilation.

Pregnancy is also a hypercoagulable state with an increased tendency to develop glomerular thrombosis in women and rats [193, 203]. Recent studies by Raij have shown that LPS provokes glomerular thrombosis in late pregnant rats, in a dose that has no effect in virgins [181]. A lower dose of LPS that has no effect alone in pregnancy provokes marked glomerular thrombosis when combined with L-NAME [181]. The glomerular thrombosis is prevented by L-arginine supplementation. Thus, the normal gestational increase in NO production to accomodate the hemodynamic changes may lead to a limited maternal reserve capability for NO synthesis, which may in part underlie the susceptibility for glomerular thrombosis in pregnancy. The disease of pregnancy, preeclampsia is characterized by hypertension, proteinuria, low GFR, glomerular thrombosis and maternal and fetal compromize, and this is clearly an endothelial cell disease [204]. The observations in the rat, discussed above, suggest that NO deficiency may play a primary role in the pathogenesis of preeclampsia. The role of NO in normal and pre-eclamptic pregnancy in women, has yet to be determined.

NO and glomerular inflammation

Several studies have shown that glomeruli from rats with immune-mediated glomerular inflammation have increased production of NO [205, 206]. Important questions regarding glomerular NO synthesis during inflammation are: (1) Which cells are the source of NO? (2) How is NO synthesis regulated? and (3) Are the effects of NO cytoprotective or cytotoxic? Cattell et al have provided evidence that in immune glomerular injury, blood borne glomerular macrophages are a major source of glomerular NO [206, 207]. However, the concomitant participation of intrinsic glomerular cells in the increased NO synthesis/release during this form of glomerular inflammation cannot be excluded [24, 207]. Moreover, the fact that induction of NOS in macrophages and in intrinsic glomerular cells is mediated by the interactions of cytokines such as TNF, IL-1 and γ interferon, acting in an autocrine and/or paracrine fashion, makes it difficult to establish the relative contribution of these cells to NO synthesis [5, 43, 60, 208]. For instance, early during inflammation primed macrophages may be the main source of NO. However, the release of cytokines by these cells within the glomerular environment, particularly within the mesangium, may induce mesangial cell synthesis of the same cytokines as well as induce NOS by autocrine and/or paracrine mechanisms [24–26, 35, 43, 59, 209]. MRL-*lpr/lpr* mice develop glomerulonephritis during the course of a spontaneous autoimmune disease which results in inflammatory injury of multiple organs. In these mice synthesis of NO is increased and inhibitors of NO synthesis attenuate the development of glomerulonephritis and arthritis [210]. The sequence of mechanisms involved in glomerular NO synthesis during inflammation may not only be regulated by agents which induce NOS, but also by those which inhibit its induction. The latter include PDGF, TGFβ, IL-4 and IL-10 [34–37]. Furthermore, NO synthesis may also be modulated, particularly in glomeruli, by arginase which metabolizes L-arginine to ornithine. Arginase may lead to insufficient substrate for NO synthesis [211]. The L-arginine NO pathway has also been implicated in the functional and histological changes which occur in the kidney in response to ureteral obstruction [212].

The question of whether or not NO synthesis during inflammation is always injurious is at present unclear (Fig. 3). In this context, several possibilities should be considered: (1) Generation

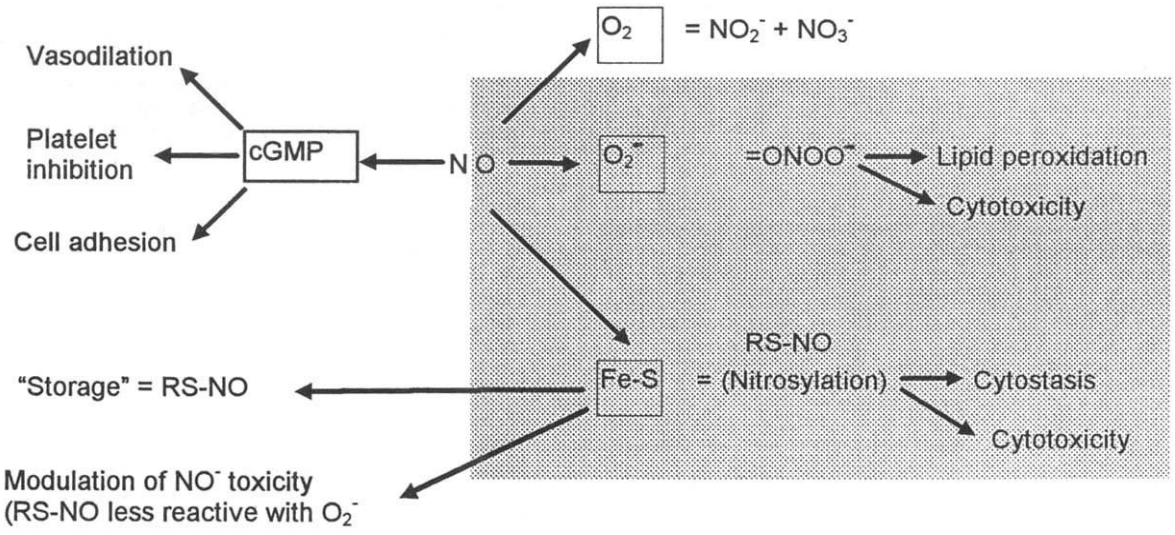

Fig. 4. *Schema summarizing the role of NO in glomerular inflammation.* The NO is mainly derived from iNOS. The area within the broken box indicates damaging actions of NO, whereas actions outside of the box are generally regarded as beneficial.

of peroxinitrite (OONO-) by interaction of NO with superoxide anion (O_2-) [45, 213] which could either directly or indirectly (due to its decomposition products NO and OH·) initiate lipid peroxidation and cytotoxicity. Glomeruli undergoing inflammation have multiple sources of O_2-, from macrophages, PMNs, mesangial cells and endothelial cells [214]. Superoxide dismutase (SOD) would prevent OONO- generation by acting upon O_2-. On the other hand, SH groups present in proteins may bind NO, forming S-nitrosothiols (RS-NO) [215]. Formation of RS-NO under appropriate conditions may have either salutory or pathologic consequences. The beneficial effect would come from "quenching" large amounts of NO, preventing generation of OONO-. By contrast, nitrosilation of critical free thiols may lead to inactivation of crucial enzymes resulting in inhibition of glycolysis, the respiratory chain and the citric acid cycle [43, 45, 215]. (2) NO has been shown to inhibit vascular smooth muscle and mesangial cell growth and may therefore affect mesangial cell proliferation [216] in proliferative glomerulonephritis. NO has been shown to modulate leukocyte adhesion to a variety of cells. These actions of NO may play an important role in local inflammation. (3) The vasodilatory and antithrombogenic effects of NO may also be beneficial in glomerular inflammation. Maintenance of patent glomerular capillary loops is crucial to prevent renal ischemia since the blood supply to the tubule is post-glomerular [38, 178].

From the above discussions it becomes clear that delineation of the time sequence of the generation of NO during glomerular inflammation as well as determination of the relative quantities of NO generated may be of importance for designing therapeutic interventions capable of modulating the L-arginine–NO pathway and prevent glomerular injury.

Summary

NO, a simple molecule synthesized from L-arginine by NO synthases, has been identified to play an important role in cell communication, cell defense and cell injury. The half life of NO is very short because NO either reacts with superoxide anion (O_2-), and/or binds to heme molecules or Fe-S groups present in proteins. The biological effects of NO depend on both the concentration of NO at the site of action as well as upon the specific location where NO is generated. Small quantities of NO are generated by cNOS such as that present in the vascular endothelium, while large quantities of nitric oxide are synthesized by iNOS in response to cytokines or bacterial products. Within the kidney NO generated by endothelial cNOS participates in the regulation of the glomerular microcirculation by modifying the tone of the afferent arteriole and mesangial cells (Fig. 4). In addition, NO generated by macula densa and the afferent arteriole control glomerular hemodynamics via TGF and by modulating renin release. Therefore NO is important in the physiologic regulation of glomerular capillary blood pressure, glomerular plasma flow and the glomerular ultrafiltration coefficient. Through its actions on glomerular pressures and flows, NO may also regulate the macro- and micromolecular traffic through the mesangium. Chronic NO insufficiency causes hypertension and glomerular damage and may be causally involved in the genesis of salt dependent hypertension. Increased NO production may be involved in the early pathogenic hemodynamic changes in diabetes and in the physiologic hemodynamic responses to normal pregnancy. Maintenance of the antithrombogenic properties of the endothelium is another important action of NO which inhibits platelet aggregation and adhesion. Large quantities of NO such as that synthesized by either glomerular cells or macrophages during glomerular inflammation may lead to glomerular injury. A better understanding of the physiology and pathophysiology of NO in the kidney will lead to the development of new therapeutic avenues.

Leopoldo Raij and Chris Baylis
Minneapolis, Minnesota and Morgantown, West Virginia, USA

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Reprint requests to Leopoldo Raij, M.D., Renal Section, VAMC, One Veterans Drive, Minneapolis, Minnesota 55417, USA.

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