Kidney International, Vol. 49 (1996), pp. 1727–1731

Importance of nitric oxide in the control of renal hemodynamics

CHRIS BAYLIS and CHANGBIN QIU[1]

Department of Physiology, West Virginia University, Morgantown, West Virginia, USA

Importance of nitric oxide in the control of renal hemodynamics. The kidney vasculature is under tonic control by nitric oxide (NO) and in cortex, NO controls R_A and K_f. Systemic NO inhibition leads to systemic hypertension, increases in R_E, mediated by Ang II and ET, and direct effects on R_A and K_f. The relationship between NO and other vasoconstrictor systems is variable. In the conscious relaxed animal, vasoconstrictor activity is low, yet acute NO inhibition leads to pressor and renal vasoconstrictor reponses. At physiologic levels, ET unexpectedly is a renal vasodilator, possibly via NO generation at R_A. When vasoconstrictor activity is high, NO is very important in maintenance of renal perfusion. Chronic L-NAME produces dose dependent systemic and glomerular capillary hypertension and eventual proteinuria and glomerular damage. NO deficiency is key in this process, although the hypertension becomes refractory to L-arginine administration and dependent on Ang II and the SNS, by mechanisms not yet defined. In contrast, the renal vasculature remains fully responsive to L-arginine, suggesting that pressor and renal vascular responses to chronic NO inhibition are separately regulated. NO generated from iNOS does not normally control BP or renal hemodynamics. The relative contributions of NO from bNOS and eNOS, and importance of NOS in different locations in the kidney, remain to be determined.

Nitric oxide (NO) is a simple messenger molecule, made from L-arginine by the enzymatic action of several nitric oxide synthases (NOS). The different isoforms of NOS are widely distributed. The brain type NOS, bNOS and the vascular endothelial, eNOS are constitutively expressed enzymes. The macrophage inducible NOS, iNOS, is induced in high quantities by immunological stimulation [1], although there may be a basal "constitutive" expression of iNOS in some locations [2]. Vascular tone is partly controlled by NO generated from eNOS, activated by shear stress [1]. The bNOS is more abundant and widely distributed than eNOS and both central and peripheral neural activity influences systemic and/or regional vascular tone [1, 3]. Under some pathological conditions, NO generated from vascular iNOS, can cause profound hypotension [1].

The production of NO is determined by the type and quantity of NOS present and by availability of co-factors and substrate [1]. Several L-arginine analogs inhibit NO synthase [1]. Drugs such as N monomethyl L-arginine (L-NMA), and nitro L-arginine methylester (L-NAME), are nonselective NOS inhibitors, whereas glucocorticoids and aminoguanidine preferentially inhibit iNOS [1, 4]. Much of our insight into the physiologic role of NO in control of renal function has been obtained using inhibitors of NO synthesis, and most of the data discussed below deal with studies employing this approach.

Distribution of NOS in the kidney

In the kidney, as elsewhere, the most abundant NOS identified is the bNOS, found in glomeruli and vasculature as well as the macula densa, collecting duct and inner medullary thin limb [5]. Detection of eNOS has been more difficult, although recently eNOS was found in the arcuate and interlobular arteries, afferent arterioles and the glomerulus using RT-PCR [6]. Presumably eNOS is also present throughout the vascular endothelium of the renal circulation, although functional evidence, discussed below, suggests that the efferent arteriolar resistance (R_E) is not under tonic NO dependent control [7]. In addition, two structurally distinct iNOS occur constitutively in the rat kidney with a wide distribution, which includes vascular smooth muscle at the juxtaglomerular apparatus and tubule epithelium in various segments [1, 2]. In response to immunological stimuli, iNOS have been reported throughout the tubule, as well as in mesangial cells, vascular endothelial cells, and vascular smooth muscle cells [1].

NO and renal hemodynamics

Acute studies

Systemic NO inhibition. In several species systemic administration of the non-specific NO inhibitors produces dose dependent increases in BP and RVR with falls in RPF and smaller declines in GFR [1, 8, 9]. As shown in Figure 1, NOS inhibition in the conscious chronically catheterized rat, produces ~35% increase in BP and ~100% increase in RVR, leading to a fall in RPF and a smaller fall in GFR due to an increase in filtration fraction [9]. These effects persist for the duration of NO synthesis inhibition, which is particularly impressive since all buffer mechanisms (which should serve to blunt the effect of loss of one vasoactive control system) are operative in the conscious animal. There are regional differences in the extent to which NO controls the circulation, and the renal vasculature appears to be particularly sensitive since systemic infusion of low doses of NOS inhibitors, which have no effect on BP, and intrarenal administration of NOS inhibitors, produce increased RVR with reductions in RPF [1, 7, 8, 10].

In vivo glomerular micropuncture studies have shown that systemic NO inhibition causes marked increases in both preglomerular (R_A) and efferent arteriolar (R_E) resistances, Figure 2 [7, 11]. As a result, glomerular plasma flow falls but SNGFR is relatively protected due to the large rise in glomerular blood pressure (P_{GC}) resulting from the increased BP and R_E. In addition, the glomerular capillary ultrafiltration coefficient (K_f) is

[1] Present address: Gladstone Institute of Cardiovascular Disease, UCSF, San Francisco, CA 94141, USA.

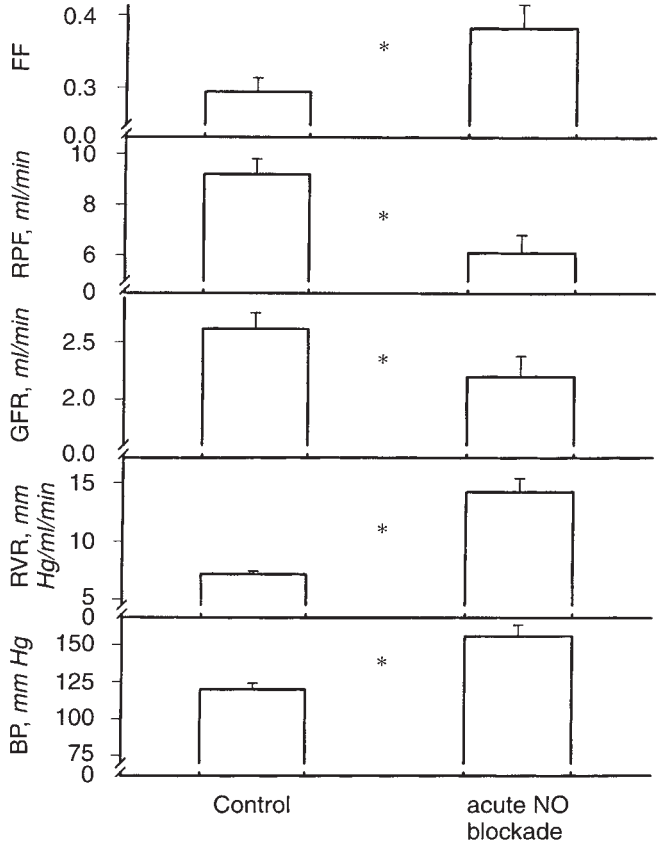

Fig. 1. *The effect of acute NO blockade (10 mg/kg, L-NAME i.v.) on mean arterial blood pressure (BP), renal vascular resistance (RVR), GFR, renal plasma flow (RPF), and filtration fraction (FF) in the conscious chronically catheterized rat.* Data shown as mean ± 1 SE, *Significant difference from the control value. Data are obtained from [9].

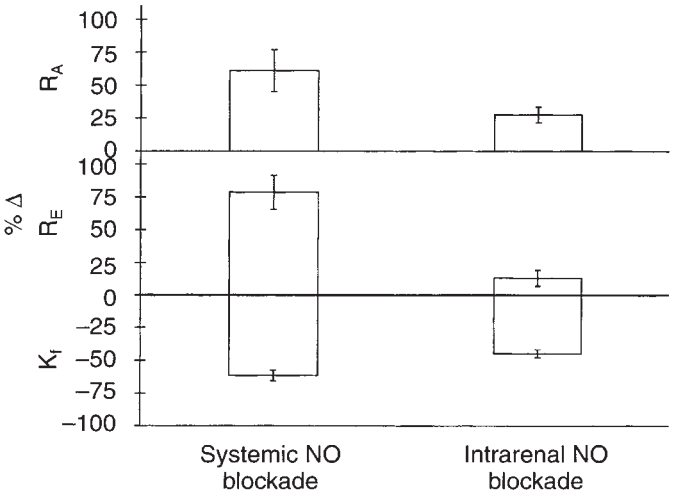

Fig. 2. *Effect of systemic NO blockade (NMA, 30 mg/kg bolus, 2 mg/kg/min, i.v.) and intrarenal NO blockade (NMA, 3 mg/kg bolus, 0.2 mg/kg/min, intrarenal artery) on preglomerular resistance (R_A), efferent arteriolar resistance (R_E), and the ultrafiltration coefficient (K_f).* The data are shown as percent change (%Δ) from control, and are taken from [7].

reduced [7, 11], probably mediated by mesangial cell contraction, since *in vitro* NO relaxes the glomerular mesangial cell [1].

Local, intrarenal NO inhibition. Since systemic NO inhibition produces widespread inhibition of NOS and increases in BP, it is difficult to discriminate between direct intrarenal versus indirect effects of NOS inhibition. Local intrarenal inhibition of NO generation causes smaller increases in RVR than are seen during systemic NO inhibition [7, 8]. As shown in Figure 2, intrarenal NO inhibition increases R_A, but has no effect on R_E while exhibiting the similar K_f reducing effect seen with systemic NOS inhibition [7]. *In vitro* studies on isolated microperfused cortical arterioles have supported our *in vivo* observation that intrarenal generation of NO control R_A but not R_E in cortical vessels, although in contrast, NOS inhibition constricts both R_A and R_E of the *in vitro* juxtamedullary nephron preparation [1]. In some situations, the cortical efferent arteriole can make and respond to NO, and NOS has been localized in R_E as well as R_A [1, 5]. The increased R_E, seen with systemic NO inhibition when blood pressure rises, is therefore not apparently due to inhibition of locally generated NO, but reflects some secondary phenomena (see below).

NOS is abundant at the juxtaglomerular apparatus and NO generated within the macula densa controls glomerular hemodynamics via the tubuloglomerular feedback (TGF) system, providing a vasodilatory arm of the autoregulatory response by blunting the increase in R_A to an increase in systemic BP [12]. NO may also influence the myogenic component of autoregulation, but although there is a suggestion that NO contributes to low pressure dilation of R_A, renal autoregulatory ability is relatively intact during NO inhibition, although RVR is reset to a higher value [1]. Furthermore, acute NO inhibition reduces inner medullary blood flow and interferes with the pressure natriuresis [13].

Interactions with other vasoconstrictor systems. As discussed above, acute NO inhibition leads to significant renal vasoconstriction. This vasoconstriction could result either from withdrawal of an active NO vasodilatory stimulus and/or from amplification of underlying vasoconstrictor systems. Below we consider the interactions between NO and other vasoconstrictor control systems.

(a) Angiotensin II. The response to systemic NO inhibition closely resembles the response to angiotensin II (Ang II) infusion [1]. However, blockade of the endogenous Ang II system has no effect on either the pressor or the renal vasoconstrictor response to systemic NO inhibition in the conscious chronically catheterized rat [14], a preparation in which endogenous levels of Ang II are low, and are not tonically controlling renal hemodynamics. When the Ang II system is acutely activated (volume depletion, surgical stress), or when exogenous Ang II levels are raised by infusion, the renal vasoconstrictor response to acute NOS inhibition is greatly amplified by the high level of Ang II [1, 15]. The mechanism(s) by which NO and Ang II interact when Ang II levels are high, is unclear and may involve interactions at the receptor level as well as NO dependent control of Ang II levels via control of renin release [1].

In the anesthetized animal acutely prepared for micropuncture, some activation of the renin-angiotensin system is inevitable, and we have preliminary micropuncture data that suggest that this activated Ang II does contribute to the glomerular microcirculatory changes seen with systemic NO inhibition [16]. Concomitant Ang II blockade with losartan attenuates the increases in BP, R_A, and particularly R_E, and the reduction in K_f seen with systemic NO inhibition (with NMA) alone. Earlier studies by DeNicola,

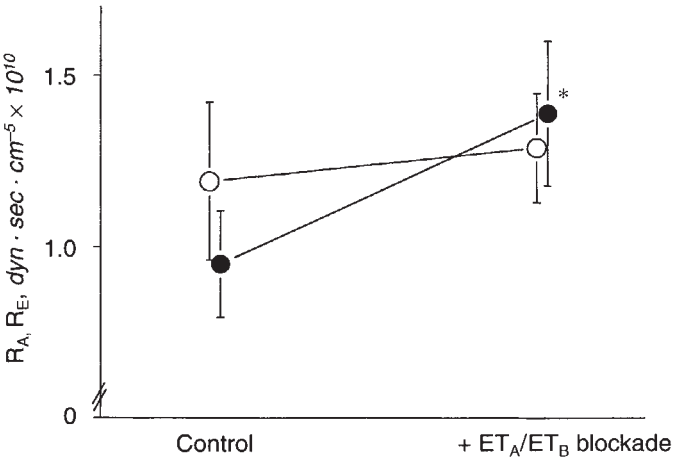

Fig. 3. *The effect of acute systemic endothelin (ET) blockade using the nonselective receptor antagonist, bosentan (10 mg/kg, i.v.), on preglomerular resistance (R_A, ●) and efferent arteriolar resistance (R_E, ○) in the normal euvolemic rat.* These data are taken from [21].

Blantz and Gabbai also suggested that endogenous Ang II mediates some of the glomerular hemodynamic responses to acute systemic NO inhibition in the anesthetized animal [17].

(b) Endothelin. Endothelin (ET) receptors are widely distributed throughout the vasculature, and while there are both ET_A and ET_B receptors in the kidney, recent evidence suggests that ET induced renal vasoconstriction in the normal kidney is via ET_B stimulation [18]. Acute systemic NO inhibition both potentiates the vasoconstrictor actions of ET and also enhances the synthesis and release of ET [19]. In the conscious chronically catheterized rat we found that the increases in BP and RVR seen with acute systemic NO synthesis inhibition were attenuated by concomitant inhibition of ET using either the ET converting enzyme inhibitor phosphoramidon or the mixed ET receptor antagonist, bosentan (which blocks both ET_A, and ET_B receptor subtypes; Fig. 3). The falls in RPF and GFR due to acute NO inhibition were not blunted by ET inhibition, suggesting that in the conscious rat, ET inhibition modifies renal hemodynamics secondary to the blunted pressor effect [20]. We also have preliminary data in the anesthetized micropunctured rat, where the pressor, renal vasoconstrictor, and K_f lowering effects of acute systemic NO inhibition (+NMA) are attenuated by ET blockade. Of particular note, the increase in R_E is particularly attenuated by ET inhibition [16]. These studies together with the observations with acute Ang II receptor inhibition (see above) suggest that the increase in R_E with systemic but not local intrarenal NO inhibition, is the result of secondary effects of ET and Ang II [16].

In the course of these studies we conducted control experiments investigating the effect of ET_A and ET_B receptor blockade on the renal vasculature in the normal baseline state. As shown in Figure 3, unexpectedly, blockade of ET_A and ET_B receptors produced a paradoxical constriction of the preglomerular resistance vessels, suggesting that the physiologic action of ET on the glomerular microcirculation is as a vasodilatory agent [21]. Since selective ET_A blockade (with BQ123) has no effect on R_A, [21] this atypical vasodilatory response to ET is mediated via the ET_B receptor and presumably reflects ET_B mediated release of NO and/or PGI_2.

(c) Sympathetic nervous system (SNS). The role of the SNS in the vasoconstrictor responses to acute NO inhibition is controversial. Some workers report that SNS inhibition (ganglion blockade, pithing, or adrenergic receptor inhibition) has little effect on the increase in BP and RVR seen with acute NO inhibition. In contrast, others report that the hypertension and renal vasoconstriction is at least partly due to both central and peripheral sympathetic activation [1]. Recent evidence suggests that the renal vasoconstriction seen during acute systemic NO inhibition is partially the result of increased renal nerve activity [22]. We have recently investigated the effect of chronic bilateral renal denervation on the renal responses to acute systemic NO inhibition and to stimulation of renal NO synthesis with L-arginine infusion [23]. In the conscious unstressed preparation where efferent renal sympathetic nerve activity is low, we found that renal denervation had no impact on the renal hemodynamic responses to either NO inhibition or NO stimulation.

Overall, withdrawal of NO amplifies any vasoconstrictor systems that are currently active. However, in the basal relaxed state, when vasoconstrictor systems are dormant we still see marked renal vasoconstricor responses to acute NO inhibition, suggesting that tonically, NO exerts a direct vasodilatory effect on the renal microcirculation.

Chronic studies

Hemodynamic and structural effects of chronic NO inhibition. It is possible to produce a sustained hypertension by chronic administration of NO inhibitors such as L-NAME. In studies by us, partial NO inhibition for eight weeks in the rat produced moderate, stable hypertension, marked renal vasoconstriction, with constriction of both preglomerular and efferent resistance vessels, as well as reductions in K_f. Because of the sustained systemic hypertension and increase in R_E, glomerular blood pressure is chronically elevated and these rats display moderate proteinuria and histologic evidence of structural damage with a mild increase in focal and segmental glomerular sclerosis [24]. In this model only slight falls in GFR are seen. Ribeiro and colleagues used a higher dose of L-NAME in the drinking water, to produce near complete NO inhibition in rats for four to six weeks [25]. This produced severe and sometimes malignant hypertension with widespread structural damage and large falls in GFR. More complete NO inhibition leads to further elevations in P_{GC}, which probably contributes to the increased glomerular injury in the more severe models [1, 24], although withdrawal of the growth inhibitory actions of NO [26] may also contribute to the development of glomerular injury.

Mechanisms of the hypertension. (a) Role of NO deficiency. The basis for this hypertension, produced by chronic administration of L-arginine analogs, is clearly NO deficiency and as expected, 24-hour urinary nitrite plus nitrate excretion ($U_{NOX}V$; indicative of NO production) is markedly depressed in chronically NO blocked animals [27]. The 24-hour $U_{NOX}V$ do not correlate quantitatively and inversely with the level of hypertension, however, since we have found that administration of very high dose L-NAME produces further increments in BP without further depressing 24-hour $U_{NOX}V$ [28 and unpublished data].

The response to L-arginine administration alters as the chronic NO inhibition induced hypertension evolves, suggesting that the factors responsible for the maintenance of the hypertension change. L-arginine is the native substrate for NO and competitively inhibits the NO blocking actions of L-NAME. Chronic

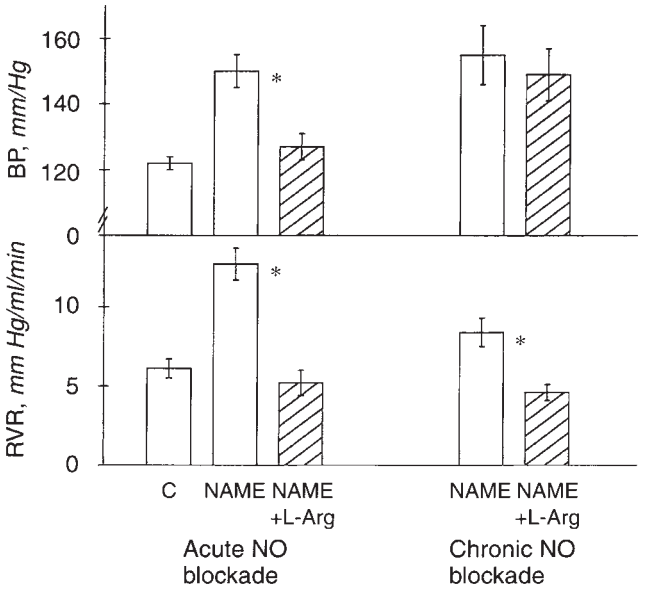

Fig. 4. *The effect on blood pressure (BP) and renal vascular resistance (RVR), in the conscious chronically catheterized rat, in response to acute NO blockade (left panel, 10 mg/kg, i.v. L-NAME) and chronic NO blockade (right panel, daily oral NAME, 10 mg/kg per 24 hr for 4 to 5 weeks).* The effect of acute L-arginine infusion (L-Arg, bolus 300 mg/kg, 50 mg/kg per min) on acute and chronic NO blockade, is shown by the hatched columns. Data are taken from [9, 30].

administration of L-arginine, together with the L-arginine analog, L-NAME, prevents any increase in BP [29], but after one week of chronic L-NAME administration in rats acute L-arginine infusion is only capable of partially reversing the increased BP [25]. As shown in Figure 4, we have recently reported that after four to five weeks of chronic L-NAME, acute L-arginine has little effect on BP [30], although remarkably, the kidney vasodilates normally to the NO substrate, with RVR returning to control values.

Thus, although there is clearly a major role for NO deficiency in L-NAME induced hypertension, the diminishing ability to reverse the hypertension with L-arginine suggests that simple competitive inhibition of NO production is not the only mechanism. Structural vascular changes (hypertrophy of resistance vessels) may also be involved although other functional hypertensive mechanisms are also apparently activated [31].

(b) Role of other vasoconstrictor systems. A number of studies have provided clear evidence that Ang II plays a primary role in the pathogenesis of chronic NO inhibition-induced hypertension. Chronic Ang II inhibition with either receptor antagonists, or converting enzyme inhibitors, ameliorates the hypertension and renal dysfunction and blunts or prevents the arteriolar and glomerular injury seen with chronic NO inhibition [25, 31, 32].

Despite these findings, acute Ang II blockade alone has little effect on BP or RVR in anesthetized or awake rats with chronic NO inhibition-induced hypertension [33, 34]. However, when acute Ang II blockade is combined with $\alpha 1$ adrenergic blockade in the conscious rat, the BP is almost normalized, whereas RVR remains elevated [34]. There is other evidence that alterations in both the central and peripheral sympathetic nervous system are involved in initiation and maintenance of the chronic L-NAME induced hypertension [1, 22, 35], although the way in which Ang II and the SNS interact is not yet clear. Based on our findings with L-arginine and combined Ang II and $\alpha 1$ adrenoceptor blockade, however, it does seem that that the pressor and the renal hemodynamic responses to chronic L-NAME are separately regulated [34].

Role of the various NOS isoforms. It is generally anticipated that NO generated from the constitutive endothelial and possible neuronal NOS plays a major role in control of BP and renal hemodynamics. Unfortunately, the L-arginine analogs most widely used to study the effect of chronic NO inhibition are relatively nonspecific and block all NOS isoforms when administered in high doses. We have conducted preliminary studies in which chronic iNOS inhibition has been produced in the normal, conscious chronically catheterized rat, using daily oral aminoguanidine [36]. There are no effects on BP or renal hemodynamics with two weeks of continual iNOS inhibition, suggesting that at least in rats on a normal dietary salt intake, iNOS, wherever located, have little role or control of blood pressure. Studies are currently underway in a number of laboratories, using the selective bNOS inhibitors in order to describe the roles of this isoform in the control of renal hemodynamics.

Acknowledgments

This work was partly supported by NIH grants # DK 45517 and HL 31933. The secretarial assistance of Kim Moccio is gratefully acknowledged.

Reprint requests to Chris Baylis, Ph.D., Department of Physiology, West Virginia University, Morgantown, West Virginia 26506-9229, USA.

References

1. Raij L, Baylis C: Nitric oxide and the glomerulus. (Editorial review) *Kidney Int* 48:20–32, 1995
2. Mohaupt MG, Elzie JL, Ahn KY, Clapp WL, Wilcox CS, Kone BC: Differential expression and induction of mRNA's encoding two iNOS in rat kidney. *Kidney Int* 46:653–665, 1994
3. Cabrera C, Bohr D: The role of NO in the central control of BP. *BBRC* 194:654–658, 1995
4. Tilton RG, Chang K, Hasan KS, Smith SR, Petrash JM, Misko TP, Moore WM, Currie MG, Corbett JA, McDaniel ML, Williamson JR: Prevention of diabetic vascular dysfunction by guanidines. Inhibition of NOS versus advanced glycation end-product formation. *Diabetes* 42:221–231, 1993
5. Bachmann S, Mundel P: NO in the kidney: Synthesis, localization and function. *Am J Kid Dis* 24:112–129, 1994
6. Ujiie K, Yuen J, Danzinger R, Star RA: Localization and regulation of endothelial NO synthase mRNA expression in rat kidney. *Am J Physiol* 267:F296–F302, 1994
7. Deng A, Baylis C: Locally produced EDRF control preglomerular resistance and the ultrafiltration coefficient. *Am J Physiol* 264:F212–F215, 1993
8. Granger JP, Alberola AM, Salazar FJ, Nakamura T: Control of renal hemodynamics during intrarenal and systemic blockade of NO synthesis in conscious dogs. *J Cardiovas Pharmacol* 20:S160–S162, 1992
9. Baylis C, Harton P, Engels K: Endothelial derived relaxing factor (EDRF) controls renal hemodynamics in the normal rat kidney. *J Am Soc Nephrol* 1:875–881, 1990
10. Slangen B, Weaver C, Baylis C: Renal effects of low dose NO inhibition in the rat. (abstract) *J Am Soc Nephrol* 4:569, 1993
11. Zatz R, de Nucci G: Effects of acute nitric oxide inhibition on rat glomerular microcirculation. *Am J Physiol* 261(2 Pt 2):F360–F363, 1991

12. ITO S, REN Y: Evidence for the role of nitric oxide in macula densa control of glomerular hemodynamics. *J Clin Invest* 92:1093–1098, 1993
13. COWLEY AW, ROMAN RJ, FENOY FJ, MATTSON DL: Effect of renal medullary circulation on arterial pressure. *J Hypertens* 10:S187–S193, 1992
14. BAYLIS C, ENGELS K, SAMSELL L, HARTON P: Renal effects of acute endothelial-derived relaxing factor blockade are not mediated by angiotensin II. *Am J Physiol* 264:F74–F78, 1993
15. BAYLIS C, HARVEY J, ENGELS K: Acute nitric oxide inhibition amplifies the renal vasoconstrictor actions of angiotensin II. *J Am Soc Nephrol* 5:211–214, 1994
16. QIU C, SAMSELL L, BAYLIS C: Endothelin (ET) and angiotensin II (AII) modulate glomerular hemodynamic responses to acute NO blockade (NOB). (abstract) *J Am Soc Nephrol* (in press)
17. DE NICOLA L, BLANTZ RC, GABBAI FB: Nitric oxide and angiotensin II. Glomerular and tubular interaction in the rat. *J Clin Invest* 89:1248–1256, 1992
18. POLLOCK DM, OPGENORTH TJ: Evidence for endothelin-induced renal vasoconstriction independent of ET_A receptor activation. *Am J Physiol* 264:R222–R226, 1993
19. KOUREMBANAS S, MCQUILLAN LP, LEUNG GK, FALLER DV: Nitric oxide regulates the expression of vasoconstrictors and growth factors by vascular endothelium under both normoxia and hypoxia. *J Clin Invest* 92:99–104, 1993
20. QIU C, ENGELS K, BAYLIS C: Endothelin modulates the vasoconstrictor response to acute systemic NO blockade. *J Am Soc Nephrol* (in press)
21. QIU C, SAMSELL L, BAYLIS C: Actions of endogenous endothelin on glomerular hemodynamics in the rat. *Am J Physiol* 269:R469–R473, 1995
22. KUMAGAI K, SUZUKI H, ICHIKAWA M, JIMBO M, MURAKAMI M, RYUZAKI M, SARUTA T: NO increases renal blood flow by interacting with the sympathetic nervous system. *Hypertension* 24:220–226, 1994
23. BRAITH R, ENGELS K, SANTMYIRE B, QIU C, BAYLIS C: Effect of chronic bilateral renal denervation (DNX) on renal responses to acute nitric oxide blockade (NOB) and L-arginine infusion. (abstract) *J Am Soc Nephrol* 6:655, 1995
24. BAYLIS C, MITRUKA B, DENG A: Chronic blockade of nitric oxide synthesis in the rat produces systemic hypertension and glomerular damage. *J Clin Invest* 90:278–281, 1992
25. RIBEIRO M, ANTUNES E, DE NUCCI G, LOVISOLO SM, ZATZ R: Chronic inhibition of nitric oxide synthesis: A new model of arterial hypertension. *Hypertension* 20:298–303, 1992
26. GARG UC, HASSID A: Inhibition of rat mesangial cell mitogenesis by nitric oxide-generating vasodilators. *Am J Physiol* 257:F60–F66, 1989
27. QIU CB, ENGELS K, BAYLIS C: Evolution of chronic endothelial derived relaxing factor (EDRF) blockade induced hypertension (EB-HT). (abstract) *J Am Soc Nephrol* 3:550, 1992
28. ENGELS K, DENG A, SAMSELL L, HILL C, BAYLIS C: Increased nitric oxide (NO) production in normal pregnancy is resistant to inhibition. (abstract) *J Am Soc Nephrol* 4:548, 1993
29. HU L, MANNING D, BRANDS MW: Long-term cardiovascular role of nitric oxide in conscious rats. *Hypertension* 23:185–194, 1994
30. QIU C, ENGELS K, SAMSELL L, BAYLIS C: Renal effects of amino acid infusion in hypertension induced by chronic nitric oxide blockade. *Hypertension* 25:61–66, 1995
31. MORTON J, BEATTIE ECSPEIRS A, GULLIVER F: Persistent hypertension following inhibition of nitric oxide formation in the young Wistar rat: Role of renin and vascular hypertrophy. *J Hypertens* 11:1083–1088, 1993
32. POLLOCK DM, POLAKOWSKI JS, DIVISH BJ, OPGENORTH TJ: Angiotensin blockade reverses hypertension during long-term nitric oxide synthase inhibition. *Hypertension* 21:660–666, 1993
33. BANK N, AYNEDJIAN HS, KHAN GA: Mechanism of vasoconstriction induced by chronic inhibition of nitric oxide in rats. *Hypertension* 24:332–328, 1994
34. QIU C, ENGELS K, BAYLIS C: Importance of angiotensin II and α_1-adrenergic tone in chronic nitric oxide blockade-induced hypertension in conscious rats. *Am J Physiol* 266:R1470–R1476, 1994
35. SCROGIN KE, VEELKEN R, LUFT FC: Sympathetic baroreceptor responses after chronic N^G-Nitro-L-Arginine methyl ester treatment in conscious rats. *Hypertension* 23:982–986, 1994
36. QIU C, BAYLIS C: Chronic inhibition of inducible nitric oxide synthase (iNOS) has no effect on blood pressure (BP) or renal hemodynamics in the normal rat. (abstract) *J Am Soc Nephrol* 5:589, 1994