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Forum Review

Acute Renal Failure: Is Nitric Oxide the Bad Guy?

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ABSTRACT

Nephrotoxicity is a major side effect in clinical practice, frequently leading to acute renal failure (ARF). Many physiological mechanisms have been implicated in drug-induced renal injury. Currently, nitric oxide (NO) is considered to be an important regulator of renal vascular tone and a modulator of glomerular function under both basal and physiopathological conditions. Historically, NO has been implicated in ARF and, after its discovery, several publications have suggested that changes in NO production could play an important role in the hemodynamic alterations observed in ARF. In this review, we evaluate the participation of NO in ARF and summarize many of the findings in this research area in an attempt to elucidate the role of NO in ARF. *Antioxid. Redox Signal.* 4, 925–934.

INTRODUCTION

THE KIDNEY is particularly vulnerable to the effect of many toxic drugs owing to its rich blood supply and its ability to concentrate toxins within the medullary interstitium and renal epithelial cells (66). In addition, the kidney is also an important site for xenobiotic metabolism and may transform relatively harmless parent compounds into toxic metabolites (48, 66). Furthermore, the dependence of proximal tubular cells on aerobic metabolism makes the kidney very sensitive to relatively short periods of ischemia (17).

Both ischemic and toxic acute renal failure (ARF) are characterized by a reduction in renal blood flow (RBF). The mediators of reduced RBF in ARF remain controversial, especially if the different pathogenic factors on which the experimental model is based and the stage are considered (45). Increased production of endothelial vasoconstrictor factors such as endothelin and adenosine has been suggested as contributors to the reductions in RBF associated with ARF (58, 90).

Nitric oxide (NO) is one of the smallest biologically active messenger molecules (5). NO regulates RBF (by contributing to renal vasodilatation), glomerular hemodynamics, the contractility of mesangial cells, and K_f (69). Hill-Kapturczak *et al.* (44) reported that both constitutive nitric oxide synthase (cNOS) and inducible NOS (iNOS) are present in all vascular segments, including all large vessels and arterioles, the juxtaglomerular apparatus, and renal tubular segments (especially the inner medullary collecting duct). Other authors have also reported the expression of iNOS in mesangial cells (82). These findings are compatible with a role for NO in the regulation of renal hemodynamics, glomerular filtration rate (GFR), pressure-natriuresis, and tubuloglomerular feedback (69). Owing to the diversity of functions identified, NO has been implicated in many renal diseases (59), including nephrotoxicity (3, 34, 51, 69, 72, 84, 85, 93).

NO has been implicated in the regulation of other endothelium-derived mediators, such as endothelin-1, prostaglandins, and angiotensin II (69). It has been reported that in nephrotoxic conditions in which NO levels are reduced, one or more of the above mediators are elevated (2, 84).

In a recent review, Gordge (39) focused on the duality of the actions of NO. In the words of Gordge: "NO shows an unusual divergence of action, being utilized both as a physiological signaling molecule, and as a toxic mediator." As a "bad" molecule, NO can disrupt mitochondrial respiration (18), inhibit many essential enzymes (50), damage membranes (68), damage DNA (61), and also release iron from FeS complexes (98). All these actions are potentially toxic to cells and can produce serious consequences. On the other hand, the beneficial effects of NO include protection against H_2O_2-mediated

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injury (23) and termination of lipid peroxidation (reacting with alkoxyl and peroxyl radicals to form nonradical nitroso derivatives) (77) and suppression of cell proliferation (inhibiting ornithine decarboxylase, the enzyme producing polyamines) (81). NO also plays an important role in the prevention of oxidative injury (107). Furthermore, adhesion of polymorphonuclear leukocytes to the endothelium accentuates kidney injury in ARF, and NO is a potent antiadhesion molecule (53).

Recent studies have clearly demonstrated that NO participates in the pathogenesis of ARF and the issue of whether NO is a "good" or "bad" molecule in ARF is currently under extensive investigation (see Fig. 1 for potential effects of increased NO in ARF). Thus, the aim of this review is to gather together the most relevant information about these issues in the hope that it will stimulate further investigation in this area.

TOXIC ARF

Antibiotics–antifungals

All members of the aminoglycoside group of antibiotics exert at least some nephrotoxic effects. Gentamicin is presently the most widely used aminoglycoside and is a first choice drug in the therapy of serious gram-negative infections and, indeed, often the only effective drug for resistant organisms (25).

In 1994, Rivas-Cabañero *et al.* (72) demonstrated that in glomeruli from gentamicin-treated rats (100 mg/kg/day for 6 days) NO-dependent cyclic GMP (cGMP) production is significantly increased in comparison with that in glomeruli from control animals. In later reports, they also demonstrated an increase in nitrite production (related to the severity of renal failure) and in NADPH diaphorase activity in glomeruli from gentamicin-treated rats (74). This overproduction of NO was blocked by N^{ω}-nitro-L-arginine methyl ester (L-NAME) and enhanced by desferrioxamine and superoxide dismutase (75).

The isoform of NOS responsible for this increase in NO synthesis is not clear. Although iNOS could not be detected either by western blot or by immunohistochemistry in glomeruli from gentamicin-treated rats (74), in cultured mesangial cells treated with gentamicin, iNOS was observed by immunocytochemistry and iNOS mRNA was also detected by northern blot (75).

Increased NO synthesis in gentamicin-induced ARF appears to play a protective role in renal function. Inhibition of NO production with L-NAME in gentamicin-treated rats leads to increased plasma creatinine levels and decreased creatinine clearance in comparison with animals treated with gentamicin alone (20, 73). Also, treatment with L-arginine (given in the drinking water) improved renal function in gentamicin-treated rats (20, 104).

The protective role of NO in gentamicin-induced ARF may be based upon several mechanisms. As previously summarized, NO plays an important role in glomerular hemodynamics, and increased NO formation can counteract the vasoconstriction observed in gentamicin-induced ARF. Also, the increase in NO production observed in mesangial cells treated with gentamicin reverses the contractile and proliferative effects induced in mesangial cells incubated with gentamicin (76) and hence could ameliorate the decrease in K_f observed in gentamicin-induced nephrotoxicity.

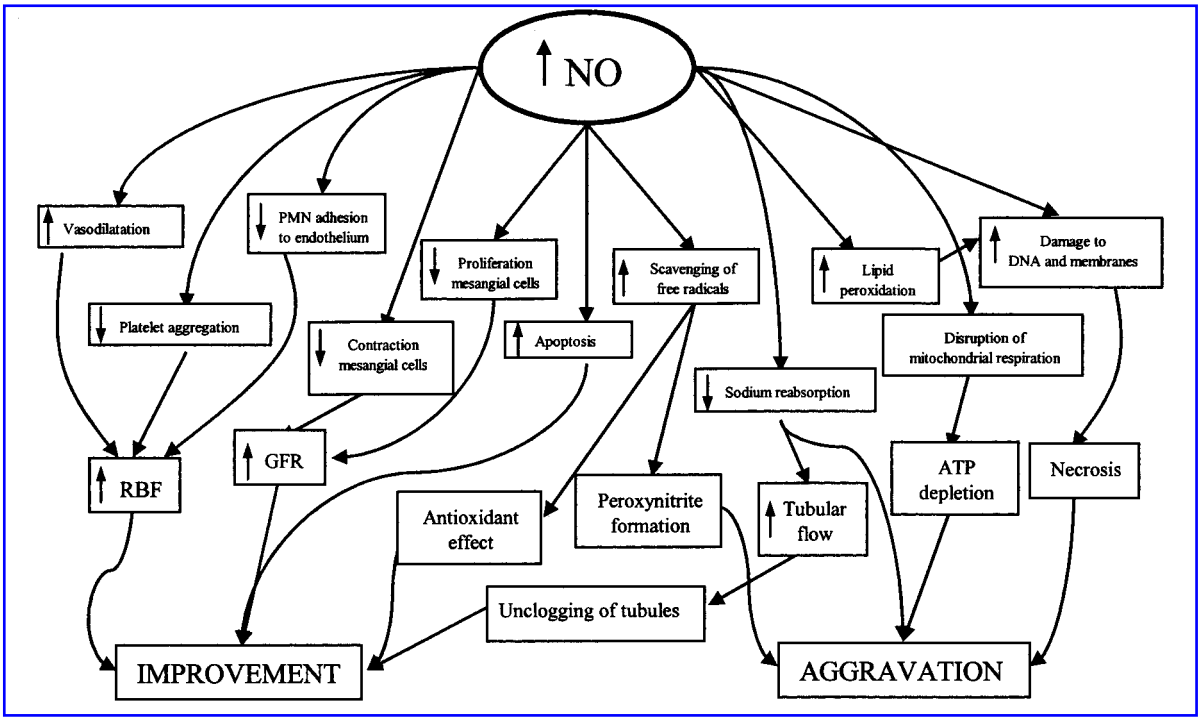

FIG. 1. Potential effects of increases in NO levels in the progression of ARF.

Amphotericin B (AmB) is the predominant antifungal drug utilized today (37). In parallel with its therapeutic efficacy, serious toxicities are observed among which nephrotoxicity is the major limiting factor in its use. A recent work from Suschek *et al.* (97) demonstrated a direct effect of AmB on renal NOS activity. In this article, the authors demonstrated that AmB exerts biphasic effects on endothelial NOS (eNOS) in endothelial cells. Low doses of the antifungal drug (in the clinically relevant range of peak serum levels) lead to increases in eNOS mRNA and protein with no changes in iNOS expression. Alternatively, high doses of the same compound (similar to the levels accumulating in the kidney) lead to a decrease in eNOS mRNA and protein content. This effect is not related to an effect of the drug on promoter activity and is due to the modulating effects of the drug on the stability of eNOS mRNA.

Radiocontrast

Radiocontrast-induced nephropathy remains one of the most serious and frequent complications of contrast imaging. ARF following the administration of radiocontrast agents may range in severity from nonoliguric, asymptomatic, and transient renal dysfunction to oliguric, severe, and protracted renal failure requiring dialysis.

The role of NO in radiocontrast-induced ARF has not been fully elucidated. In a study by Agmon *et al.* (1), rats pretreated with L-NAME, indomethacin, or both showed greater morphological and functional damage in response to contrast media (iothalamate). Furthermore, hemodynamic studies using laser-Doppler probes have shown that, when injected alone, contrast doses of iothalamate increase outer medullary blood flow. Pretreatment with L-NAME, indomethacin, or both reduces basal medullary blood flow and transforms the medullary vasodilator response to radiocontrast into vasoconstriction. These results suggest that prostanoids and NO play important protective roles in the renal responses to contrast substances.

In a more recent work by Heyman *et al.* (43), differing effects in cortical and medullary NOS activity were reported. Whereas cortical NOS activity was decreased 30 min after contrast media administration, outer medullary NOS activity remained unchanged. The decrease in cortical NOS activity was exacerbated by pretreatment with an endothelin-1 antagonist. NO levels, measured with an electrode, were decreased in cortical tissue, but were increased in the outer medullary area, despite the absence of changes in NOS activity. The authors explained this paradox as an effect of increased NO bioavailability in a region of reduced O_2 tension. It has been described that in a solution containing a NO donor, NO concentration increased with the reduction of O_2 content (42). As the infusion of contrast media reduced outer medullary oxygenation, they proposed that contrast agent-induced hypoxia enhances NO bioavailability that leads to regional vasodilatation.

Schwartz *et al.* (85) induced ARF with radiocontrast in normal and salt-depleted rats. L-Arginine administration before ARF abolished the decrease in renal plasma flow (RPF) and improved GFR. Administration of a NOS inhibitor did not modify the effect of contrast media on GFR. Andrade *et al.* (7) induced ARF with contrast media in hypercholesterolemic salt-depleted rats. In this model, endothelium-dependent relaxation is reduced and vasoconstriction is increased, and NO has been implicated in its pathophysiology. Under these circumstances, L-arginine, but not D-arginine, restored renal function completely.

The effect of hypo- and hyperosmotic contrast media in cultured mesangial cells has also been examined (113). Both types of radiocontrast media reduced basal and lipopolysaccharide-stimulated (LPS) NO production by these cells.

Cisplatin

Cisplatin is an effective chemotherapeutic agent for a number of cancers. However, it exerts significant nephrotoxic effects (28), and the exact mechanism of cisplatin-induced renal injury is unclear.

Although few publications have addressed the role of NO in cisplatin nephrotoxicity, it has been suggested that cisplatin-induced tubular and glomerular injury might be modulated by NO production. Srivastava *et al.* (94) showed that cisplatin treatment in rats increased the activity of calcium-independent NOS in kidneys. The administration of L-NAME decreased renal toxicity and levels of blood urea nitrogen and creatinine. In a previous report, Son and Kim (91) showed that macrophages exposed *in vivo* to cisplatin express iNOS.

Alternatively, in cisplatin-treated rats, the infusion of glycine increases GFR and RBF (41, 51) in a NO-dependent manner (22). The administration of L-NAME abolishes the improvement in RBF induced by glycine in these animals (51).

Cyclosporine

Although cyclosporine A (CsA) and tacrolimus (FK506) do not share similar chemical structures and react with different biochemical targets, they produce similar signal transduction effects in T lymphocytes, resulting in the desired immunosuppressive effect (22). Their toxicity spectra are similar, and indeed the main problem with both drugs is nephrotoxicity (12, 35, 109).

It is currently believed that in CsA nephrotoxicity there is an alteration of the L-arginine–NO pathway in blood vessels. It is well known that CsA administration causes hypertension both in humans and in laboratory animals (40, 102). A number of explanations for this phenomenon have been proposed, but none of them definite. Data have been presented suggesting that CsA produces endothelial damage, which is both time- and dose-dependent (117). CsA impairs endothelium-dependent relaxation in response to acetylcholine (ACh) in rat arteries and isolated resistance vessels from humans (71). Also, aortic rings isolated from rats treated with CsA demonstrated impaired endothelial-dependent relaxation, achieving levels similar to that observed in endothelium-denuded rings (63). Nitrite/nitrate levels were also similar. The ability of the CsA-treated rat aortic rings to relax after addition of a NO donor was preserved and was not suppressed by addition of CsA (63). When CsA was added acutely to intact aortic rings from normal rats, tension increased and nitrite/nitrate and cGMP production decreased, suggesting a decrease in NO production. However, in a different publication by Navarro-Antolin *et al.* (60), 24-h incubation of bovine aortic endothelial cells with CsA produced an increase in eNOS mRNA,

probably due to an increase in the transcription rate. Stroes *et al.* (96) also found an increase in eNOS in human endothelial cells incubated with CsA. This effect appears mediated by an increase in reactive oxygen species. Additional evidence for the involvement of the NO pathway in CsA-induced nephropathy was generated by Potier *et al.* (67). In this publication, incubation of normal glomeruli or mesangial cells with CsA induced an increase in contractility, which was blunted by coincubation with a NO donor.

Wu *et al.,* in 1998 (114) demonstrated that incubation of medullary thick ascending limb cells with CsA decreased LPS-stimulated NO production. Protein kinase C is involved in this process. In two different studies, Amore *et al.* (4) and Esposito *et al.* (36) demonstrated that CsA induces apoptosis in various cultured renal cells (endothelial, epithelial, and tubular). This effect is mediated by increases in iNOS-derived NO, because CsA induces an increase in iNOS mRNA, and apoptosis can be inhibited by L-NAME and enhanced by NO donors.

Analysis of NOS expression in kidneys of animals treated with CsA produces controversial results. Whereas Gonzalez-Santiago *et al.* (38) found a decrease in eNOS mRNA in aorta and renal cortex of animals treated for 30 days with CsA, and Vaziri *et al.* (108) found decreases in iNOS mRNA and protein and no changes in eNOS, Sanchez-Lozada *et al.* (79) observed an increase of eNOS mRNA in cortex and reductions in iNOS and neuronal NOS (nNOS) in the medulla of 7 day-treated animals. The increase in eNOS, in this case, was related to an increase in shear stress due to vasoconstriction. In a different study, Bobadilla *et al.* (15) also showed an increase in eNOS in cortex and also in the medulla, with decreases in nNOS and iNOS in medulla after 7 days of treatment. Rao *et al.* (70) found an increase in NOS activity in animals treated with CsA. Tack *et al.* (99) did not find any changes in glomerular eNOS mRNA 6–9 h after a single dose of CsA, despite the fact that those glomeruli produced higher amounts of cGMP. *In vivo* L-NAME treatment and *in vitro* calcium depletion blunted this increase in cGMP.

In isolated perfused kidneys, CsA has been shown to reduce the vasodilator response to ACh and nitroprusside (19) and L-arginine reverses cyclosporine-induced vasoconstriction, whereas L-NAME has no additional effect (13). However, in another study, Stephan *et al.* (95) showed that in isolated kidneys of rats treated with subacute doses of CsA, ACh-induced relaxation was blunted (with a defect in NO-mediated relaxation), whereas endothelium-related relaxation (after addition of nitroprusside or fenoldopam) was totally preserved. In micropuncture studies performed by De Nicola *et al.* (34), CsA decreased NO-dependent glycine vasodilatation, suggesting a decrease in NO production.

Administration of CsA to animals *in vivo* has been reported to increase urinary nitrite excretion in one case (9), to decrease nitrite and cGMP excretion in some others (63, 108), and to produce no changes in another (14). The renal dysfunction induced by CsA has been improved by dietary supplementation with L-arginine (3, 6, 9, 34, 87, 115). Administration of L-arginine causes an increase in urinary nitrite excretion (6, 9, 14); therefore, an increase in NO production appears involved in the improvement in renal function, probably by decreasing renal vascular resistances and increasing glomerular plasma flow (14, 34). These results agree with those from Andrés *et al.* (8) in renal transplant patients, in which administration of L-arginine increases RPF, GFR, and natriuresis.

In other studies, administration of L-NAME to CsA-treated animals has produced a worsening of renal function (3, 6, 14, 15, 87). This effect of L-NAME in CsA-treated animals is a consequence of an increase in afferent arteriolar resistance and a decrease in glomerular capillary pressure (14, 15). Furthermore, administration of L-NAME to CsA-treated rats worsened tubulo-interstitial fibrosis (6, 87).

Little is known about the relationship between FK506 and NO. Two studies have been published concluding that FK506 induces a decrease in both eNOS mRNA and activity in endothelial cells (101), possibly due to an inhibition in NOS phosphorylation (32).

ISCHEMIC ARF

The involvement of NO in ischemic ARF has been established since 1988 (27, 52). However, the controversial issue is whether the production of NO is increased or decreased in this model of ARF and whether this increase is beneficial or deleterious. Several models of ischemic ARF indicate that NOS activity increases. This increase has been reported as glomerular nitrite production (73, 105), renal nitrite content (111, 112), urinary nitrite excretion (65), electron paramagnetic resonance in renal tissue (56), arginine–citrulline conversion rates (88), cGMP production (105), NADPH diaphorase activity (105), and direct electrode measurements of NO in renal cortex (78).

The source of the increased NO is still a controversial issue. Several authors have described an increase in eNOS protein content in glomerular tuft (78, 88, 105), and also an increase in iNOS activity has been described in tubular cells (62, 105). Furthermore, Yu *et al.* in 1994 (116) demonstrated that freshly isolated proximal tubules responded to hypoxic periods with increases in Ca^{2+}-independent NO release.

The nonselective inhibition of NO synthesis in rats with ischemic ARF leads to a worsening in renal function. Several groups have reported that the inhibition of NO synthesis worsens GFR after ischemic ARF (24, 57, 105, 112). Cristol *et al.* (29) found that L-NAME decreased RPF in rats with ischemic ARF. This issue has been addressed also by several others (26, 57, 78). Jerkic *et al.* (46) also showed a further decrease in RBF of ischemic rats treated with L-NAME, which was reversed with L-arginine coadministration. Atanasova and his group (10) reported that, in anesthetized rats, L-NAME combined with renal ischemia not only induces a deleterious renal effect, but also leads to a pronounced cardiac depression and a major increase in systemic vascular resistance and pulmonary vascular resistance, associated with high mortality. Also, inhibition of NO synthesis with L-NAME during the reperfusion period increases morphological damage (46, 47, 62, 105).

The application of iNOS specific inhibitors has been reported to be beneficial *in vivo* reducing plasma creatinine concentration and tubular damage (110). Also, various strategies utilized to reduce iNOS-derived NO have been reported

to be beneficial. Ling *et al.* (54) induced renal ischemia in the iNOS knockout mouse and observed both less reduction in renal function and morphological damage than in wild-type animals. Noiri *et al.* (62), using a different approach, also observed an improvement in renal function and morphological structure in rats treated with antisense oligodesoxynucleotides against iNOS. Weight *et al.* (112) found that administration of aminoguanidine, a purported iNOS inhibitor, exerts a protective effect on renal function at day 2 after ischemia, but had no beneficial effect by day 7.

In contrast, attempts to stimulate NO synthesis with L-arginine infusion have provided controversial results. Whereas some authors have found that L-arginine administration exerts beneficial effects (24, 46, 57, 83, 88, 103), others report no response (30, 47) or detrimental to variable effects, depending on the dose, time, and the presence of superoxide dismutase (21, 112). Also, Dagher and co-workers (31) observed a beneficial effect of L-arginine infusion when given before the ischemic insult.

Studies in isolated tubules have led to more consistent results. Ischemia does stimulate iNOS (116), and this NO generated seems to exert a deleterious effect. Addition of L-NAME to tubules decreases the degree of damage induced by ischemia (64, 103, 116) and L-arginine (103, 116) or NO donors (116) increase injury.

ARF DUE TO SEPSIS

It is clear that sepsis, either bacterial sepsis or the sepsis syndrome, is one of the major contributing factors to ARF in the intensive care unit (16). Sepsis is produced experimentally by the administration of bacterial LPS, and cytokines are generated that perform several functions. These functions include (a) increased uptake of arginine by a variety of cells that normally do not take up arginine avidly, (b) the induction of a variety of enzymes in nonkidney, nonhepatic cells, which leads to the synthesis of arginine within the cell, and (c) induction of NOS, which in turn produces NO (55, 99, 106). The generation of NO leads to multiple systemic hemodynamic events, which include reductions in systemic vascular resistance, a secondary increase in cardiac output, and, eventually, systemic hypotension. Reductions in GFR after the administration of LPS occur within a very short period of time (11, 49, 89, 92). NO generation increases probably within 30 min (as measured by plasma values) (55). The increase in NO occurs somewhat before there is evidence of new transcription of iNOS as evidenced by mRNA and well before increased iNOS can be demonstrated by immunohistochemistry or western blots. These results imply that arginine uptake by cytokine-induced expression of Y^+ arginine transporters leads to the generation of NO before iNOS is generated, implying a level of constitutive iNOS activity in certain cells.

Plasma arginine levels decrease within 30 min of LPS administration. NO levels increase clearly within 60 min. The reduction of GFR, however, occurs well before there is any evidence of reduction to systemic blood pressure, implying that there are other mechanisms contributing to vasoconstriction within the kidney (86). The early phases of renal failure are prerenal in type, but with severe sepsis, acute tubular necrosis can certainly occur. There are several excellent studies documenting the critical role of NO generation in the generation of ARF.

However, it does seem somewhat peculiar that NO contributes to the reduction of systemic vascular resistance while blood flow is decreasing in certain vascular beds due to increases in vascular resistance. Notably these vascular beds include the renal and mesenteric vasculature.

Earlier studies by Shultz and Raij (89) have demonstrated that NO is a critical factor in the generation and prevention of ARF in sepsis. It has been demonstrated that after administration of large doses of LPS, GFR was significantly reduced. When animals treated with LPS were also treated with L-NAME, GFR was further reduced. This reduction was due to an increase in glomerular thrombosis. These studies had suggested that NO is protective against ARF in an experimental model of sepsis.

The later studies from our laboratories duplicated these findings and demonstrated that nonselective NOS inhibitors did decrease GFR while maintaining systemic blood pressure, whereas administration of selective iNOS inhibitors restored GFR, as well as systemic blood pressure to normal levels (86). In addition, we demonstrated that this observation was not the result of hypotension because animals that were awake did not demonstrate hypotension after LPS, but also decreased GFR. This event was prevented by selective inhibition of the iNOS enzyme. *In vitro* studies in isolated glomeruli also demonstrated that excess NO generation from the iNOS enzyme appeared to autoinhibit NOS, resulting in renal vasoconstriction and further reductions in GFR. There were no alterations in transcription or steady-state mRNA for eNOS. The presence of high concentrations of NO generated from iNOS autoinhibited eNOS, and administration of iNOS inhibitors restored agonist-stimulated eNOS responses and GFR.

Previous studies from our laboratory and others have demonstrated that eNOS or NO generated from eNOS plays an important and reasonably unique role in the kidney by acting as a buffer or inhibitor of vasoconstrictors system, such as angiotensin II (33). Glomerular hemodynamic events following nonselective blockade of NOS enzymes can be largely reversed by the administration of angiotenisin-AT1 receptor blockers.

There is also considerable variability within humans and experimental animals in the systemic hemodynamic responses to LPS administration. Cytokine stimulation does increase cellular arginine uptake and the generation of arginine metabolites. Selective inhibition of iNOS activity induced experimentally does result in the generation of increased quantities of other arginine metabolites including agmatine, or decarboxylated arginine generated from arginine decarboxylase, and polyamines that result from the activity of arginase and ornithine decarboxylase (55). There appears to be no feedback regulation of arginine uptake in nonrenal cells by the NO generated after cytokine induced iNOS. Clearly, these studies suggest that patients who are incapable of activating iNOS have less systemic hypotension and renal failure. However, this may not alter their short- or long-term morbidity or mortality. It is also interesting to speculate that low iNOS responders may, in fact, divert arginine into metabolic pathways that may not be beneficial for the individual in terms of cell

proliferation, matrix deposition, or the regulation of duration and intensity of inflammatory responses (80).

Therefore, sepsis induced by cytokines does result in renal failure that is initially a consequence of renal vasoconstriction; this event results from the capacity of excess NO to autoinhibit normal buffering pathways through eNOS that limit the action of vasoconstrictors. Undoubtedly, the volume status of the patient contributes to this renal effect, and reductions in vasoconstrictor impacts may ameliorate some of these effects on GFR.

CONCLUDING REMARKS

NO is critically involved in the functional and morphological alterations observed in experimental models of drug-induced nephrotoxicity and ischemic renal failure. In the majority of models, NO synthesis appears elevated. In all the cases, increased NO synthesis appears primarily protective to the remaining renal function. This increase in NO synthesis and release does not lead to renal vasodilatation, probably due to the simultaneous increase in the release of vasoconstrictors. Thus, the contribution of NO to arterial tone is more important in cases in which vasoconstrictor influences are magnified. In these circumstances, NO inhibition leads to a worsening in renal function that is more important than in normal conditions.

The enzymatic source of increased NO synthesis, in cases in which it has been studied, is the constitutive isoform of NOS. These results on ARF agree with the notion that there are two different types of NO production: the "bad" and the "good." This consequence to renal function is often based on the quantities of NO generated. cNOS produces lower levels of NO than the inducible form. It is now accepted that at physiological concentrations generated by cNOS, NO is not toxic and that problems may only arise when supraphysiological NO production occurs due to the presence of iNOS. When sustained, increased NO synthesis occurs, significant amounts of NO become available to interact with oxygen and to compete with superoxide dismutase for superoxide. The result of these reactions is an increase in N_2O_3 and peroxynitrite, leading to toxic effects.

In conclusion, studies performed to date on this topic primarily suggest that NO plays a protective role in ARF. Although ARF may be characterized by considerable renal vasoconstriction, in most cases NO synthesis is increased. This increase in NO production could counteract the negative influence of vasoconstrictors in ARF. Therefore, in this particular case, NO does not appear to be the "bad guy" of the film.

ABBREVIATIONS

ACh, acetylcholine; AmB, amphotericin B; ARF, acute renal failure; cGMP, cyclic GMP; cNOS, constitutive nitric oxide synthase; CsA, Cyclosporine A; eNOS, endothelial nitric oxide synthase; GFR, glomerular filtration rate; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; L-NAME, N^{ω}-nitro-L-arginine methyl ester; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; RBF, renal blood flow; RPF, renal plasma flow.

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