The discovery in 1987 that endothelium-derived nitric oxide (NO) mediates the vasodilatory effect of certain endothelium-dependent agonists \(^1,\,^2\) inaugurated the current huge field of NO biology. It is now recognized that NO plays essential roles in many diverse physiological processes and in some pathophysiologic events. Development of these concepts has been based largely on evidence obtained by limiting NO biosynthesis. This review is centered on the cardiovascular and particularly the renal functional and structural consequences of chronic pharmacologic NO inhibition by \(\text{L-arginine analogues}\). We devoted special attention to the mechanisms of hypertension and organ injury that occur under these circumstances, while appreciating the inherent limitations surrounding interpretation of this data.

### Ubiquity and Heterogeneity of NO Biosynthesis

NO is made by the enzymatic action of several widely distributed NO synthases (NOS). In the presence of the substrates \(\text{L-arginine and oxygen}\), as well as a number of essential cofactors, NO is produced in response to appropriate stimuli. The constitutively expressed NOS play a major role in the physiological control of vascular tone and kidney function.\(^3,\,^4\) Vascular endothelial NOS (eNOS) and brain-type NOS (bNOS) are widely distributed throughout the kidney\(^5\) as well as the cardiovascular system and in strategic locations in the peripheral and central nervous system (CNS).\(^6,\,^7\)

Both eNOS and particularly bNOS are abundant in the kidney, glomeruli, and vasculature as well as in most segments of the tubule,\(^3,\,^5\) and NOS activity in medulla is considerably greater than in cortex.\(^8\) NO generated within the kidney controls the glomerular filtration rate (GFR), total renal and medullary blood flow, pressure natriuresis, epithelial sodium transport, and production of various vasoactive factors including renin.\(^3,\,^5\) eNOS is distributed throughout most parts of the arterial and venous circulation, although there is considerable heterogeneity in the extent to which NO controls tone in regional circulations.\(^9\) Although there is some basal NO release from eNOS, shear stress is the physiologically important regulator of vascular NO production.\(^3\) In the CNS, NO is made in the nucleus tractus solitarius, the paraventricular nucleus, and the ventral medulla and can control sympathetic outflow.\(^6,\,^{10}\) In addition to central regulation of effenter renal sympathetic nerve activity, there is direct nitrergic innervation to several locations including the renal vasculature.\(^7\)

Inducible NOS (iNOS) can be activated in many cell types in response to immunologic challenge, but there is some localized low-level constitutive iNOS expression in kidney and vascular smooth muscle. Whether this influences blood pressure (BP) and/or kidney function is unclear.\(^3\) Recent evidence has implicated iNOS-derived NO in the pathogenesis of tissue injury in a variety of processes, although a detailed analysis of this hypothetical “dark side” of NO is beyond the scope of this review.

### Renal and Hemodynamic Effects of Acute NOS Inhibition

Determination of the biosynthetic pathways leading to NO formation set the scene for investigation of the regulatory roles of endogenous NO. In 1989, Rees et al\(^1^1\) showed that the abrupt interruption of NO synthesis with the \(\text{N}^\text{G}\)-substituted \(\text{L-arginine analogue}\) \(\text{N}^\text{G}\)-monomethyl-\(\text{L-arginine (L-NMMA)}\) markedly elevated BP in rabbits, an effect that was abrogated by administration of excess \(\text{L-arginine}\). Other investigators confirmed this finding in several species including humans.\(^1^2,\,^1^3\) which demonstrated that by promoting a constant vasorelaxing effect, NO was an important modulator of the circulatory function.

The role of NO in the regulation of kidney function was soon investigated. Acute systemic NOS inhibition with several \(\text{L-arginine analogues}\) produced intense renal vasoconstriction with marked reduction of renal plasma flow and a smaller reduction in GFR. These effects were seen in several species and were apparent in the awake and the anesthetized animal.\(^3,\,^4\) Because of the pressor effect of acute systemic NO inhibition, some of the increased renal vascular resistance was autoregulatory; however, intrarenal local and low-dose systemic NO inhibition produced renal vasoconstriction in the absence of increased BP.\(^3,\,^1^4\) Thus, NO tonically generated within the kidney lowers renal vascular resistance. Zatz and De Nucci,\(^1^5\) using glomerular micropuncture, showed that acute systemic NOS inhibition led to both afferent and effenter arteriolar vasoconstriction, which together with the rise in BP resulted in large increases in glomerular BP; these findings were subsequently confirmed by others.\(^1^6,\,^1^7\) In addition, the glomerular capillary ultrafiltration coefficient \((K_f)\) fell,\(^1^5,\,^1^7\) probably due to mesangial cell contraction.\(^1^8\) In contrast, local intrarenal NOS inhibition, without a rise in systemic BP, led to a smaller increase in...
afferent arteriolar resistance \( (R_a) \) but unexpectedly had no effect on the efferent arteriolar resistance \( (R_e) \), although the \( K_r \)-reducing effect was preserved.\(^{16} \)

Control of glomerular microcirculation by NO is complex, involving direct regulation of tone by locally derived NO from eNOS, tubuloglomerular feedback control (via macula densa bNOS), and possible regulation via nitrergic renal nerves.\(^1 \) as well as by indirect actions mediated via other vasoactive control systems.\(^3 \) In addition, NO regulates sodium excretion.\(^3 \) NO was shown to act directly on tubular epithelium to inhibit reabsorption,\(^19,20 \) to be activated by sodium loading,\(^21 \) at least in the kidney and the CNS,\(^22-24 \) and to be involved in the pressure natriuresis.\(^25 \) Despite these natriuretic actions of NO, sodium excretion was markedly increased with a pressor dose of NOS inhibitor,\(^26 \) possibly secondary to the increased BP, although other unknown factors may also be involved.\(^3 \)

**Development of the Chronic NOS Inhibition Model**

The fact that abrupt interruption of NO synthesis leads to hypertension and renal vasoconstriction does not necessarily imply that NO is indispensable in the control of circulation on a chronic basis, since other vasodilating systems might be recruited in the long run to compensate for NO deficiency. However, it was soon proven that NO does play an essential role in the long-term regulation of BP. In 1992, both of our research groups, working independently, showed that chronic administration of an orally active inhibitor of NO synthesis, \( N^\bullet - \text{nitro-L-arginine methyl ester (L-NAME),} \) promoted persistent hypertension and renal damage. Baylis et al\(^{27} \) showed that administration of L-NAME for 8 weeks led to the development of stable hypertension and glomerulosclerosis. By use of a much higher dose of L-NAME, Ribeiro et al\(^{28} \) obtained a severe and progressive form of hypertension associated with glomerular ischemia, glomerulosclerosis, and renal interstitial expansion. Two other groups reported simultaneously or soon thereafter the development of hypertension associated with chronic L-NAME treatment.\(^{29,30} \) These findings, subsequently confirmed by other researchers, indicated that NO is a fundamental and irreplaceable element in the regulation of BP and gave birth to a new model of arterial hypertension.

It was later shown that knockout mice lacking the gene for the endothelial isoform of NOS developed systemic and pulmonary hypertension,\(^{31,32} \) whereas deletion of the genes encoding the neuronal and inducible isoforms, respectively, led to no detectable circulatory changes.\(^{33,34} \) Although these observations initially suggested that NO derived from eNOS, but not from bNOS or iNOS, is crucial to the maintenance of normal circulatory function, human studies indicated no genetic linkage between eNOS and essential hypertension,\(^{35,36} \) whereas more recent experimental evidence has strongly implicated an important role for NO derived from bNOS in influencing the tubuloglomerular feedback\(^{37} \) and/or the sympathetic nervous system (SNS).\(^{6,38,39} \)

The following sections discuss the mechanisms involved in sustaining high BP during chronic nonselective NOS inhibition, revealing that in fact this is a very complex model of hypertension.

**Mechanisms of Hypertension in the Chronic NOS Inhibition Model**

Sustained BP elevation requires the persistence of at least 1 of the following abnormalities: (1) increased cardiac output, (2) increased peripheral resistance, or (3) impaired renal ability to excrete sodium (Guyton’s hypothesis).\(^{40} \) Because the available evidence suggests that cardiac output is actually decreased in chronic NOS inhibition,\(^41 \) we will consider the possible factors leading to systemic vasoconstriction and/or salt retention in the chronic NOS inhibition model.

**Lack of Tonic Vasodilation**

Since the first experiments with acute inhibition of NOS, the concept has emerged that the hemodynamic changes thus obtained reflect the abrupt withdrawal of a tonic vasodilator effect, leaving unopposed an equally tonic action of endogenous vasoconstrictors. This notion was supported by the observation that under certain conditions the effects of acute NO inhibition could be at least partly reversed by inhibition of vasoconstrictors such as angiotensin II (Ang II),\(^{42} \) vasopressin,\(^43,44 \) or endothelin\(^44 \) and that the renal vasoconstrictor response to Ang II was augmented by acute NO inhibition.\(^45 \) If persistent unmodulated vasoconstriction is indeed responsible for the maintenance of hypertension in the chronic NOS inhibition model, then either acute or chronic inhibition of the vasoactive principle(s) underlying peripheral vasoconstriction in this model should completely reverse hypertension. There is now considerable evidence that both Ang II and the SNS contribute to the hypertension of chronic NOS inhibition, as discussed in detail below.

Data are inconsistent regarding the effect of administration of excess exogenous L-arginine, which in principle would be expected to competitively reverse NOS inhibition and therefore abrogate L-NAME–induced hypertension. This did occur when L-arginine treatment was begun simultaneously with NO inhibition.\(^46 \) After NO inhibition had been maintained for 1 week, however, correction of hypertension with acute L-arginine was only partial,\(^28 \) and an even smaller effect was obtained in rats that had been treated for 4 to 6 weeks.\(^7,46 \) Of interest, although Ribeiro et al\(^{29} \) showed that hypertension regressed when the NO inhibitor was withdrawn after 4 weeks of treatment, Morton et al\(^{47} \) observed persistent hypertension even after NO inhibition was discontinued after 14 weeks of treatment. These observations suggest that once NO has been inhibited for more than a few days, the hypertension no longer depends exclusively on inactivation of the L-arginine/NO pathway. The pathogenic mechanisms attending this late autonomous phase of the model are unclear and may involve structural alteration of the vascular walls,\(^49,50 \) as well as renal parenchymal injury such as glomerulosclerosis, glomerular collapse, and interstitial fibrosis.\(^27,28,51 \) In addition, abnormal activation of the renin-angiotensin system (RAS), initiated during L-NAME treatment, may fail to subside after NO inhibition is discontinued (see below).

**Role of the RAS**

Studies of acute inhibition of Ang II in the chronic NOS inhibition model have yielded inconclusive results. Zanchi et al\(^52 \) obtained a large BP reduction with angiotensin type 1 (AT\(_1\)) receptor blockade, whereas Bank et al\(^53 \) and Baylis et
al observed little effect of Ang II blockade on BP or renal hemodynamics in rats with chronic NOS inhibition. However, combined acute inhibition of both Ang II and α-adrenergic receptors reversed L-NAME–associated hypertension almost completely, raising the possibility that the state of generalized vasoconstriction characteristic of the chronic NOS inhibition model is maintained by an interaction between the SNS (see below) and the RAS.

Ribeiro et al showed that concomitant chronic administration of the Ang II receptor antagonist losartan to rats chronically treated with L-NAME prevented both the hypertension and the renal injury associated with this model, suggesting a key participation of the RAS in these events. These findings have been corroborated in several subsequent studies that involved chronic administration of either Ang II receptor antagonists or angiotensin-converting enzyme inhibitors. In addition, chronic Ang II blockade reversed established hypertension and reduced persistent hypertension after discontinuation of NOS inhibition, raising the interesting possibility that the RAS plays a causative or permissive role in L-NAME hypertension even after NO inhibition is interrupted.

Beside modulating the effects of chronic NO inhibition, the RAS in turn may be influenced by this treatment, although the very direction of this relationship is still a matter of controversy. Plasma renin activity (PRA) was reported to be increased, unchanged, or decreased in this model of hypertension. Several in vitro studies provided evidence that NO might act as an inhibitor of renin release. However, other in vitro observations and experiments in isolated perfused kidneys suggested that NO stimulates the synthesis and/or secretion of renin. In addition, several investigators reported decreased circulating renin in the chronic NOS inhibition model, even in animals in which PRA was initially elevated by restricted dietary sodium intake or reduction of renal perfusion pressure. Only when L-NAME treatment lasted long enough to result in significant renal structural injury did renin levels rise as an epiphenomenon, although recent evidence obtained by Baylis et al suggested that even this late rise in PRA may be only transient. Thus, circulating PRA is unpredictable and bears no consistent relationship with the protective action of chronic Ang II blockade. Perhaps the Ang II dependence of chronic NOS inhibition hypertension is associated with normal or increased tissue Ang II levels, increased sensitivity to Ang II, and/or an interaction between Ang II and the SNS.

An anatomic basis for the complex interaction between NO and the RAS is provided by the observation that neuronal NOS (nNOS) is particularly abundant in the macula densa, consistent with a mediatory or permissive role of NO in the process of renin release from the juxtaglomerular apparatus. Indeed, selective bNOS inhibition blunted the increase in renin secretion induced by furosemide treatment, which is likely to originate from macula densa signaling, but failed to prevent hyperreninemia associated with lowering renal perfusion pressure, which is linked to baroreceptor stimulation. Likewise, acute bNOS inhibition limited the increase in renin secretion observed in salt-depleted rats.

Role of the CNS and the SNS
As with Ang II, acute inhibition of the SNS in the chronic NOS inhibition model has produced variable results, with both a substantial fall and little change in BP being reported during acute α-adrenergic receptor blockade. Acute ganglionic blockade, however, produced a large fall in BP in rats with chronic NOS inhibition, which was exacerbated compared with the depressor response of controls. Also, chronic sympathectomy by daily injections of ganglionic blockers attenuated the hypertension that resulted from 1 week of chronic L-NAME administration, suggesting that increased central sympathetic drive may be involved in chronic NOS inhibition hypertension. Indeed, NOS inhibitors that are given systemically cross the blood-brain barrier and produce local NOS inhibition in the CNS as well as in the circulation. Because acutely administered NOS inhibitors given directly into some areas of the CNS produce hypertension, some of the pressor response to systemic NOS inhibition may result from NOS blockade in strategic areas of the CNS. Part of this involvement of the SNS in chronic NOS inhibition may result from an increased sensitivity of vascular smooth muscle to α-adrenoceptor stimulation. Elegant studies in the conscious rat have recently demonstrated that the role of the SNS varies with the duration of NOS inhibition, which may explain some of the variable findings with acute inhibition of the α-adrenoceptor.

There is some evidence for a specific involvement of the renal nerves, since chronic bilateral renal denervation delayed and attenuated hypertension in rats with chronic NOS inhibition. These effects may be partly mediated via a reduction in sensitivity of the baroreceptor reflex, which contributes permissively to L-NAME hypertension. In contrast, other investigators have reported evidence that renal nerve traffic plays little or no role in the hypertension of chronic NOS inhibition. The relationship between NO and the SNS is likely to be highly complex, with direct interactions at the various adrenergic receptor subtypes and indirect interactions through baroreceptor control of BP, for example, providing numerous and sometimes opposing influences. The variability in the literature presumably is related to this complexity.

Role of Endothelin
Unlike the results obtained with Ang II inhibition, neither acute nor chronic endothelin (ET) inhibition with either a specific ET of a combined ET /ET antagonist had any effect on either hypertension or renal injury in rats given chronic L-NAME treatment. In a recent study, the alternative NOS inhibitor N^−-nitro-L-arginine (L-NNA) was given in high doses for 3 weeks; here, concomitant chronic ET receptor blockade attenuated the hypertension and vascular damage and prevented the glomerular ischemia and proteinuria. Possible reasons for differences between L-NNA– and L-NNAME–induced chronic hypertension are discussed below. At present, the role played by ET in the pathogenesis of hypertension in this model remains uncertain.

Role of Calcium Channels
There is abundant evidence that NO modulates the activity of both L-type calcium channels and calcium release channels (ryanodine receptor channels), thus profoundly influencing cell metabolism, especially in excitable tissue. Therefore, the dramatic changes observed in the chronic NOS inhibition
model may reflect at least in part defective intracellular calcium metabolism. Consistent with this view, several studies showed a marked effect of calcium channel inhibitors in this model. Acute blockade of voltage-dependent calcium channels with verapamil in rats that had received L-NAME for 3 weeks reversed the hypertension, whereas concomitant chronic treatment with verapamil prevented hypertension in rats subjected to chronic NOS inhibition for 6 weeks. Similarly, Ribeiro et al showed that chronic treatment with nifedipine attenuated hypertension and prevented renal injury in rats receiving L-NAME for 4 weeks, whereas Erley et al showed attenuation of hypertension but not renal functional amelioration with the simultaneous use of felodipine in rats receiving L-NAME for 12 weeks. Together, these observations suggest that the presence of endogenous vasoconstrictors, especially Ang II, and an adequate operation of voltage-gated calcium channels are necessary for the hemodynamic and cellular actions caused by chronic L-NAME treatment to take place.

Role of Salt Retention
According to Guyton, arterial hypertension results from an impaired renal ability to excrete sodium. Because of this primary defect, BP will rise until renal sodium excretion is increased (by pressure natriuresis) to again equal sodium intake. NO may play a key role in this process of pressure natriuresis. Mattson and Higgins showed that sodium overload induces a large increase in medullary NO generation. In a related study, these investigators performed a chronic infusion of L-NAME in the rat renal medullary area and observed the development of sustained hypertension, which regressed on discontinuation of the infusion. Furthermore, although renal NO production is increased in response to dietary salt overload in the Dahl salt-resistant rat, this response is greatly attenuated in Dahl salt-sensitive rats. L-Arginine administration restores NO production and prevents salt-induced hypertension in Dahl salt-sensitive rats.

From the evidence discussed above, it might be inferred that the level of salt intake would profoundly influence the development of hypertension in the chronic NOS inhibition model. Indeed, Fujihara et al and Tolins and Schultz showed that administration of a high salt diet aggravated hypertension and renal injury in rats given chronic treatment with L-NAME. Conversely, Romero et al showed that dietary salt restriction completely prevented development of hypertension in this model. Nevertheless, other investigators observed no impact of varying salt intake on L-NAME-induced hypertension. Of note, the doses of NOS inhibitor used in these studies varied considerably. Even in the original studies 6 years ago, Ribeiro et al and Baylis et al used widely differing doses of L-NAME (70 mg·kg⁻¹·d⁻¹ and 5 mg·kg⁻¹·d⁻¹, respectively). A range of intermediary doses has been used since then. To investigate whether the extent of NO inhibition could influence salt sensitivity, Yamada et al compared the effects of salt intake in rats receiving 2 different doses of L-NAME. They confirmed previous observations that the pattern of salt sensitivity observed in Dahl rats can be reproduced by chronic treatment with a low nonpressor dose of L-NAME. The slope of the pressure-natriuresis line was significantly reduced in these animals, indicating limited renal ability to excrete sodium. In rats treated with a much higher pressor dose of L-NAME, however, hypertension persisted even after severe dietary salt restriction. In these rats, the pressure-natriuresis line and the x intercept were shifted to the right, but the slope of the line was unchanged compared with normal animals, predicting low salt sensitivity and persistence of hypertension even with no salt intake. In fact, this high-dose L-NAME model is associated with immediate and persistent volume depletion during the evolution of hypertension.

Taken as a whole, these data indicate that the chronic NOS inhibition model may actually follow 3 different patterns, depending on the extent of NO inhibition. (1) Very low doses of NOS inhibitor do not directly raise systemic vascular resistance and produce a purely volume-dependent hypertension. (2) An intermediate dose, which causes widespread partial NOS inhibition, elicits a hypertension that is substantial but stable and that does not progress over a 2-month period. (3) High-grade, near-complete NOS inhibition promotes renal and systemic vasoconstriction to such a degree as to obscure any beneficial effect of salt restriction. This hypertension is progressive despite administration of a constant dose of inhibitor throughout. These animals develop rapidly progressive and malignant hypertension with severe vascular and parenchymal damage, particularly at the kidneys. The original study reported by Ribeiro et al represents an archetype of this third modality of L-NAME hypertension.

Role of Arachidonic Acid Derivatives
There is a considerable amount of cross-talk between the NO system and the various arachidonic acid derivative pathways. There is clearly stimulation of prostanooids from the inducible cyclooxygenase isofom (COX-2) by iNOS-derived NO, but the relationship between constitutively derived NO and cyclooxygenase products is less clear. Prostacyclin (PGI₂) inhibits NO release from cultured endothelial cells, possibly via a cAMP-mediated action. In the dog kidney, the full renal vasodilatory potential of NO (or PGI₂) is expressed only in the presence of prostaglandin (or NO) inhibition, suggesting that these autacoids are mutually antagonistic on each other’s synthesis/release. Nevertheless, acute cyclooxygenase inhibition does not aggravate hypertension in rats treated chronically with L-NAME, although additional renal vasoconstriction does occur.

In general, NO reversibly binds with the heme-containing moieties of a number of enzymes, including cytochrome P450 enzymes, thus tonically inhibiting their products. For example, NO apparently inhibits the lipoxygenase pathway in some tissues, and there is recent evidence that NO tonically inhibits production of 20-HETE by the P4504A enzyme. Furthermore, 20-HETE plays a significant role in the vasoconstrictor response to acute NOS inhibition in the kidney and systemic vasculature, although the importance of this system in responses to chronic NOS inhibition has not been investigated. However, it is likely that some of the constrictor responses seen with chronic NOS inhibition may result from enhancement of the actions of various vasoconstrictor arachidonic acid products.
Role of Other Factors

Because of the ubiquitous nature of NO, many cellular processes are likely to be distorted as a result of chronic inhibition of NO. NO plays an important role in apoptosis in some circumstances and exerts mainly antiproliferative actions in the vasculature; thus chronic removal of NO will lead directly to increased tissue mass. In addition to inhibition of all NOS isoforms, chronic L-NAME treatment may have other unrelated effects that can affect hypertension and/or kidney dysfunction. For example, the cardiac hypertrophy seen with L-NAME–induced hypertension is much less than that with equivalent degrees of hypertension produced by other maneuvers, suggesting that NOS inhibition (or at least L-NAME) may exert some direct antiproliferative actions. Because NO is itself mainly antiproliferative, this implies a nonselective action of L-NAME, possibly via its known antimuscarinic effects and perhaps by inhibition of ornithine decarboxylase or some other nonspecific inhibitory action on cardiovascular growth(s). It is certainly true that the features of high-dose chronic L-NAME–induced hypertension and kidney damage differ from chronic L-NNA in some respects, which emphasizes the probability that unrelated side effects of these l-arginine analogues probably contribute to the pathology in this model.

Chronic NOS Inhibition as a Model of Organ Damage

In addition to its pronounced effect on circulatory function, chronic NOS inhibition can deeply affect the structure of the vasculature, including the renal architecture and myocardial and nervous tissue. A variety of parenchymal lesions has been found, especially in the kidney, which so far has been the best-studied target organ in this model.

Five modalities of renal injury have been described in conjunction with chronic NOS inhibition: (1) Classic glomerulosclerosis consists of glomerular accumulation of hyaline material with collapse of capillary loops and adhesion to the parietal layer of Bowman’s capsule. (2) Glomerular ischemia consists of uniform collapse of the glomerular tuft and the capillary loops with pronounced thickening and even duplication of the basement membrane. This abnormality has been shown previously in association with human essential hypertension. It has also been described in the neighborhood of the scarred areas in the renal ablation model. These glomeruli are likely responsible for the enhanced renin secretion observed in the late phases of the chronic NOS inhibition model, although direct evidence favoring this hypothesis is lacking. (3) Glomerular segmental necrosis appears as sharply delimited areas where lysis of necrotic material may result in the formation of microaneurysms. (4) Interstitial expansion shows infiltration by fibroblasts and deposition of collagen-like material along with tubular atrophy and vacuolization. (5) Microvascular lesions range from arteriolar wall thickening to “onion skin” proliferation with complete luminal occlusion, fibrinoid necrosis of the vascular wall, and periarteriolar fibrosis. All these types of renal injury are associated with progressive albuminuria, which can be amplified nearly to the nephrotic range by concomitant salt overload, indicating that functional impairment of the glomerular wall barrier also occurs in this model. The functional and structural grounds for this latter abnormality are unknown. However, preliminary evidence has been reported that progressive depletion of negative charge in the glomerular basement membrane occurs in rats receiving L-NAME for 1 month. Concomitant salt overload aggravates this abnormality and promotes the appearance of a size defect, which may explain the massive albuminuria observed in this setting.

Tissue injury associated with chronic NOS inhibition is not confined to the kidney. Rats receiving chronic L-NAME treatment exhibit focal areas of myocardial necrosis along with focal areas of fibrosis that may reflect organization of necrotic tissue. The development of these lesions could not be ascribed to either systemic hypertension or activation of the RAS, suggesting that NO inhibition may exert a specific deleterious effect on the myocardium. Chronic NOS inhibition may also severely damage the CNS. For example, a 100% incidence of stroke was described in rats receiving an NO inhibitor for up to 6 months, and a 79% incidence of motor dysfunction was described in rats treated with L-NAME for 11 weeks. At autopsy, spinal cord infarcts were encountered in 90% of these animals; 30% exhibited brain lesions as well. These observations may help to explain the high mortality observed in the chronic NOS inhibition model.

Summary and Perspectives

Since the advent of the chronic NOS inhibition model, it has become clear that NO is an indispensable and irreplaceable element in the maintenance of circulatory integrity, regulating such diverse functions as vascular tone, renal salt excretion, and renin secretion. Further investigation is needed to establish the relative importance of NO derived from the various NOS isoforms in controlling renal and systemic hemodynamics in health or disease.

References


Chronic Nitric Oxide Inhibition


Key Words: models cardiovascular diseases nitric oxide synthase nitric oxide blood pressure renin-angiotensin system vasodilation
Chronic Nitric Oxide Inhibition Model Six Years On
Roberto Zatz and Christine Baylis

Hypertension. 1998;32:958-964
doi: 10.1161/01.HYP.32.6.958

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/32/6/958

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/