

Interaction of Endothelial Nitric Oxide and Angiotensin in the Circulation

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Abstract—Discovery of the unexpected intercellular messenger and transmitter nitric oxide (NO) was the highlight of highly competitive investigations to identify the nature of endothelium-derived relaxing factor. This labile, gaseous molecule plays obligatory roles as one of the most promising physiological regulators in cardiovascular function. Its biological effects include vasodilatation, increased regional blood perfusion, lowering of systemic blood pressure, and antithrombosis and anti-atherosclerosis effects, which counteract the vascular actions of endogenous angiotensin (ANG) II. Interactions of these vasodilator and vasoconstrictor substances in the circulation have been a topic that has drawn the special interest of both cardiovascular researchers and clinicians. Therapeutic agents that inhibit the synthesis and action of ANG II are widely accepted to be essential in treating circulatory and metabolic dysfunctions, including hypertension and diabetes mellitus, and increased availability of NO is one

of the most important pharmacological mechanisms underlying their beneficial actions. ANG II provokes vascular actions through various receptor subtypes (AT₁, AT₂, and AT₄), which are differently involved in NO synthesis and actions. ANG II and its derivatives, ANG III, ANG IV, and ANG-(1-7), alter vascular contractility with different mechanisms of action in relation to NO. This review article summarizes information concerning advances in research on interactions between NO and ANG in reference to ANG receptor subtypes, radical oxygen species, particularly superoxide anions, ANG-converting enzyme inhibitors, and ANG receptor blockers in patients with cardiovascular disease, healthy individuals, and experimental animals. Interactions of ANG and endothelium-derived relaxing factor other than NO, such as prostaglandin I₂ and endothelium-derived hyperpolarizing factor, are also described.

I. Introduction

Endothelium-derived relaxing factor (EDRF¹), first discovered by Furchgott and Zawadzki (1980), was identified to be nitric oxide (NO) by three different groups,

¹ Abbreviations: EDRF, endothelium-derived relaxing factor; ANG, angiotensin; NO, nitric oxide; AT, angiotensin receptor subtype; ACE, angiotensin-converting enzyme; ROS, reactive oxygen species; PG, prostaglandin; EDHF, endothelium-derived hyperpolarizing factor; NOS, nitric-oxide synthase; nNOS, neuronal nitric-oxide synthase; eNOS, endothelial nitric-oxide synthase; iNOS inducible nitric-oxide synthase; L-NMMA, N^G-monomethyl-L-arginine; L-NA, N^G-nitro-L-arginine; L-NAME, N^G-nitro-L-arginine methyl ester; ADMA, asymmetric dimethylarginine; PG, prostaglandin; ACh, acetylcholine; SHR, spontaneously hypertensive rat(s); PD123319, S-(+)-1-[(4-(dimethylamino)-3-methylphenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid; CGP 42112A, N- α -nicotinoyl-Tyr-(N- α -CBZ-Arg)-Lys-His-Pro-Ile-OH; Hoe-140, D-arginyl-L-arginyl-L-prolyl-*trans*-4-hydroxy-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-D-1,2,2,4-tetrahydro-3-isoquinolinecarbonyl-L-(2*a*,3*b*,7*ab*)-octahydro-1H-indole-2-carbonyl-L-arginine (icatibant); PD13177, 1-(4-amino-3-methylphenyl)-methyl-5-diphenyl-acetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid; AVE 0991, 5-formyl-4-methoxy-2-phenyl-1-[[4-[2-(ethylaminocarbonylsulfonamido)-5-isobutyl-3-thienyl]-phenyl]-methyl]-imidazole; A-779, (D-Ala⁷)-angiotensin I/II-(1-7); CGS 24592, (S)-N-[2-(phosphonomethylamino-3-(4-biphenyl)-propionyl]-3-aminopropionic acid; PD123177, 1-(4-amino-3-methylphenyl)-methyl-5-diphenyl-acetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid; SOD, superoxide dismutase; GFR,

Furchgott (1988), Ignarro et al. (1987), and Palmer et al., (1987). Introduction of NO synthesis inhibitors (Palmer et al., 1988) greatly contributed to clarifying the physiological roles of NO not only in the vasculature but also in the central and peripheral nervous systems, immune system, and other miscellaneous biological reactions. NO is now regarded as an intercellular messenger or transmitter that plays a pivotal role in circulatory regulations, including vasodilatation, increased blood flow, lowered systemic blood pressure, and inhibitions of platelet aggregation and adhesion, leukocyte adhesion and transmigration, smooth muscle proliferation, and low-density lipoprotein oxidation.

glomerular filtration rate; ARB, angiotensin receptor blocker; SHRSP, stroke-prone spontaneously hypertensive rat(s); Dup 753, losartan; CV11974, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid; NO_x, nitrate/nitrite; DOCA, deoxycorticosterone acetate; ET, endothelin; VEGF, vascular endothelial growth factor; TCV-116, (\pm)-1-(cyclohexyloxy-carbonyloxy)-ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate; VIVALDI, investigate the efficacy of telmisartan versus valsartan in hypertensive type 2 diabetic patients; Cx, connexin; PD98059, 2'-amino-3'-methoxyflavone; TGF, tubuloglomerular feedback; PRA, plasma renin activity; EXP3174, 2-butyl-4-chloro-1-((2'-(1H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)-1H-imidazole-5-carboxylic acid; E4177, 3-[(2'-carboxybiphenyl-4-yl)methyl]-2-cyclopropyl-7-methyl-3 H-imidazo[4,5-b]pyridine.

Angiotensin (ANG) II has long been known to be an intense vasoconstrictor peptide that is responsible for hypertension, decreased regional blood flow, impaired renal function, atherosclerosis, and cardiac hypertrophy. Therefore, suppression of the renin-ANG system is quite an important strategy for preventing and treating cardiovascular dysfunction, particularly essential hypertension. From the early period of NO discovery, counteracting the effects of endogenous NO on ANG II has been a major concern of cardiovascular researchers and clinicians. Recent studies have revealed that members of the ANG family have different hemodynamic actions and that the various ANG II receptor subtypes contribute to heterogeneous actions on blood vessels. ANG II acts directly on its type 1 (AT_1) receptors to cause vascular smooth muscle contraction and also elicits vasoconstriction indirectly by forming reactive oxygen species (ROS) that scavenge NO. Imbalanced functioning of NO and ANG II in vasculatures is considered to be one of the important pathogenic factors in cardiovascular disease. Therefore, in addition to simply reducing the synthesis of ANG II by ANG I-converting enzyme (ACE) inhibition or inhibiting the action of ANG II on AT_1 receptors responsible for vasoconstriction, important pharmacological strategies for treatment of essential hypertension include increased availability of counteracting vasodilators. Besides NO, prostaglandin (PG) I_2 formed in endothelial cells (Weksler et al., 1977) and endothelium-derived hyperpolarizing factors (EDHF) (Chen et al., 1988) also play roles in cardiovascular physiology and pathophysiology.

This review article covers areas of research about the interactions between EDRF, mainly endothelial NO,

and ANG in the circulation in reference to the mechanisms underlying actions of the ANG family on EDRF release and superoxide generation and those of ACE inhibitors and ANG receptor blockers in various vascular beds of humans in health and disease as well as in those of experimental animals.

II. Endothelium-Derived Relaxing Factor and Angiotensin: Synthesis and Mechanisms of Action on Blood Vessels

A. Nitric Oxide

NO is produced when L-arginine is transformed to L-citrulline by catalysis of nitric-oxide synthase (NOS) in the presence of O_2 and the cofactors NADPH, tetrahydrobiopterin, calmodulin, heme, FAD, and FMN. Ca^{2+} is required for the activation of neuronal NOS (nNOS, NOS I) and endothelial NOS (eNOS, NOS III) but not inducible or immunological NOS (iNOS, NOS II). nNOS, mostly a soluble enzyme, is constitutively expressed in the brain, peripheral nerves, including parasympathetic postganglionic nerves innervating blood vessels (nitrergic nerve), and kidneys (Bredt et al., 1990). eNOS is also constitutively expressed mostly in particulate fractions of the endothelial cell (Förstermann et al., 1991). iNOS is not constitutively expressed but is induced mainly in macrophages with bacterial lipopolysaccharide and cytokines.

eNOS binds to caveolin-1 in the caveolae, microdomains of the plasma membrane. Caveolin-1 inhibits eNOS activity, and this interaction is regulated by Ca^{2+} /calmodulin (Michel et al., 1997). eNOS intracellularly migrates in response to increased cytosolic Ca^{2+} in the

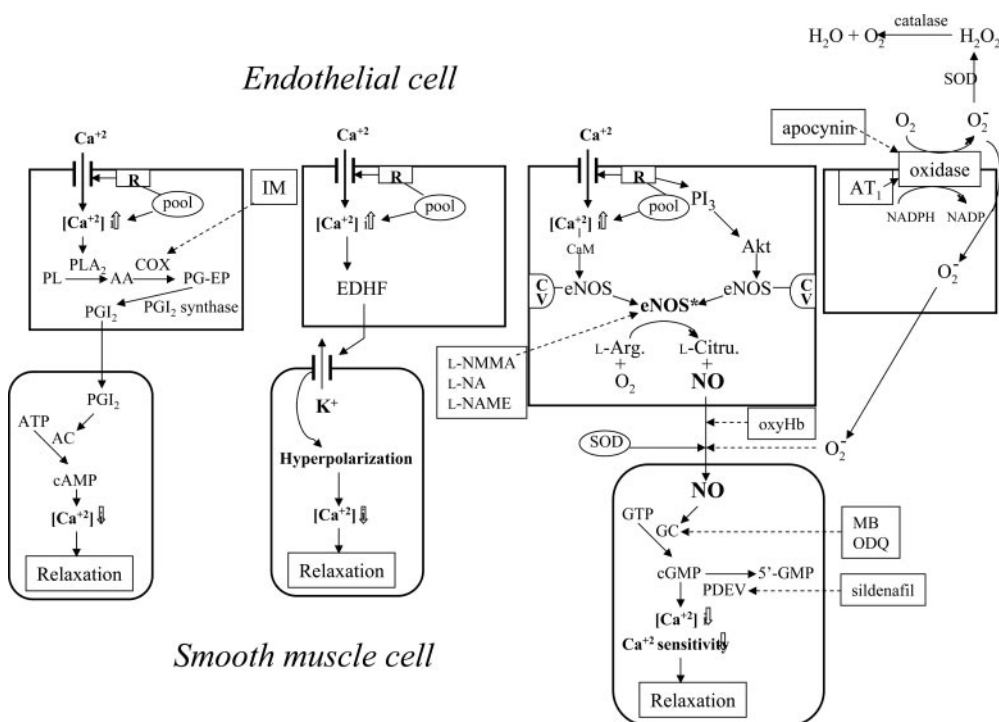


FIG. 1. Possible mechanisms of action of angiotensins on vascular endothelial and smooth muscle cells. R in endothelial cell membranes denotes receptors responding to angiotensins, bradykinin, and mechanical stress. AT_1 in the top right endothelial cell denotes AT_1 receptor subtype. Pool, intracellular Ca^{2+} storage site; PL, phospholipid; PLA₂, phospholipase A₂; AA, arachidonic acid; COX, cyclooxygenase; PG-EP, prostaglandin endoperoxide; IM, indomethacin; PI₃, phosphatidylinositol 3-kinase; CaM, calmodulin; eNOS*, activated eNOS; CV, caveolin-1; L-Arg., L-arginine; L-Citru., L-citrulline; oxidase, O_2^- superoxide anion; AC, adenylyl cyclase; GC, soluble guanylyl cyclase; PDE5, phosphodiesterase type 5; MB, methylene blue.

presence of calmodulin (Fig. 1) and becomes activated for NO synthesis. The transmembrane influx of Ca^{2+} and its mobilization from intracellular storage sites are caused by stimulation of drug receptors, such as muscarinic, bradykinin, and ANG receptors, located on the endothelial cell membrane or by mechanical stimuli, such as shear stress and vascular smooth muscle stretch. Recent studies have provided a novel hypothesis that shear stress, bradykinin, or insulin induce the phosphorylation of Ser^{1177/1179} of eNOS through phosphatidylinositol-3 kinase and the downstream serine/threonine protein kinase Akt (protein kinase B), resulting in enhanced NO formation (Dimmeler et al., 1999; Fulton et al., 1999). This mechanism does not require the increase in intracellular Ca^{2+} for NO production (Fig. 1).

The synthesis of NO by NOS isoforms is inhibited by L-arginine analogs, including *N*^G-monomethyl-L-arginine (L-NMMA), *N*^G-nitro-L-arginine (L-NA), *N*^G-nitro-L-arginine methyl ester (L-NAME), and asymmetric dimethylarginine (ADMA) (Vallance et al., 1992). 7-Nitroindazol is one of the most promising nNOS inhibitors so far introduced (Moore et al., 1993).

NO or nitrovasodilators activate soluble guanylyl cyclase and produce cyclic GMP from GTP in smooth muscle cells. Methylene blue, hemoglobin, and 1*H*[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one (Garthwaite et al., 1995) inhibit the guanylyl cyclase activity. Accumulation of cyclic GMP causes activation of cyclic GMP-dependent protein kinase that is involved in the reduction of intracellular Ca^{2+} and a decrease in the sensitivity of contractile elements to Ca^{2+} . Cyclic GMP is degraded by phosphodiesterase type-5 to 5'-GMP.

B. Prostaglandin I_2 (Prostacyclin)

The PG family, including PGI_2 , is synthesized from arachidonic acid formed from phospholipids through phospholipase A_2 . Cyclooxygenase synthesizes PG endoperoxides from arachidonic acid, and its activity is inhibited by aspirin, indomethacin, ibuprofen, and other nonsteroidal anti-inflammatory drugs. An enzyme that transforms PG endoperoxides to PGI_2 was found in microsomes prepared from the aorta (Moncada et al., 1976) and in cultured endothelial cells (Weksler et al., 1977). Activation of receptors by agonists or mechanical stress applied to the endothelial cell membrane leads to transmembrane Ca^{2+} influx; the cations activate phospholipase A_2 to form arachidonic acid, thus increasing the PGI_2 synthesis (Fig. 1). PGI_2 liberated from endothelial cells binds to prostacyclin receptors located in muscle cell membranes, activates adenylyl cyclase, and stimulates cyclic AMP production, resulting in vascular smooth muscle relaxation.

C. Endothelium-Derived Hyperpolarizing Factor

Endothelium-dependent vasodilatation is not always blocked by inhibitors of NOS and cyclooxygenase. Chen

et al. (1998) found that acetylcholine (ACh) elicited relaxation and hyperpolarization of muscle cell membranes in the rat aorta and pulmonary artery with intact endothelium. The mechanical response was abolished by hemoglobin and methylene blue without any effect on hyperpolarization, suggesting that ACh releases two different substances, NO and EDHF, from endothelial cells. The electrical and mechanical responses mediated by EDHF are blocked by treatment with K^+ channel inhibitors or exposure to high K^+ media. Ca^{2+} -activated K^+ channels seem to play a major role in hyperpolarization that is responsible for muscle relaxation (Fig. 1). Although different mechanisms of action of EDHF are reported in a variety of blood vessels, there is still considerable debate regarding the nature of EDHF (Busse et al., 2002; Triggle et al., 2002).

D. Angiotensin

ANG II, the most active ANG peptide, is derived from angiotensinogen in two enzymatic steps. First, renin cleaves the decapeptide ANG I from the amino terminus of angiotensinogen (renin substrate). Then ACE removes the carboxy-terminal dipeptide of ANG I to produce the octapeptide ANG II. ANG II is degraded subsequently by peptidases to yield ANG III, ANG IV, and ANG-(1-7) (Haulica et al., 2005). These enzymatic steps are summarized in Fig. 2. ANG II binds to G protein-coupled receptors in cell membranes, resulting in biological actions.

III. Angiotensin-Induced, Endothelium-Derived Relaxing Factor-Mediated Vasodilatation

A. Angiotensin II-Induced Vasodilatation

1. *In Vitro Studies.* It was demonstrated that ANG II elicited an intracellular cyclic GMP production possibly mediated by NO in murine neuroblastoma NIE-115 cells (Zarahn et al., 1992) and neuroblastoma neuro-2A cells (Chaki and Inagami, 1993). The former authors suggested that AT_1 receptor-mediated mobilization of intracellular Ca^{2+} is involved in this response, whereas the latter authors concluded that the newly found ANG II receptor may be responsible for activation of guanylyl cyclase that is mediated by NO formed through Ca^{2+} influx. Porsti et al. (1993) noted ANG II-induced biphasic changes of coronary perfusion pressure in isolated perfused rabbit hearts: an initial increase was followed by a decrease, an effect that was independent of NO and PGI_2 . Their conclusion was that the ANG II-induced vasodilatation may reflect rapid desensitization of the arterial muscle to the vasoconstrictor effect.

Hannan et al. (2003) provided evidence that AT_2 receptor-mediated inhibition of ANG II-induced contraction of rat uterine artery segments may involve NO production. Batenburg et al. (2004) concluded that AT_2 receptor-mediated vasodilatation in human coronary microarteries seems to be mediated by bradykinin B_2

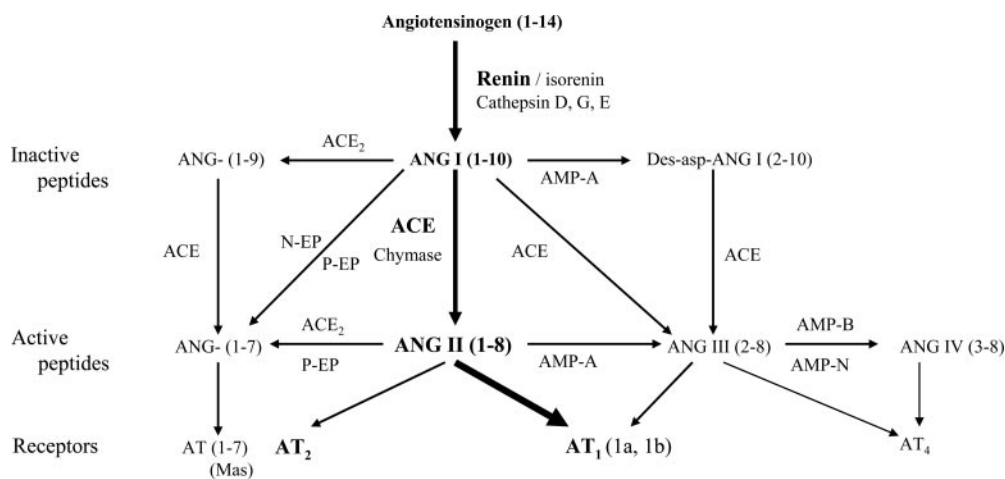


FIG. 2. Cascade of bioactive angiotensins. ACE₂, ACE-related carboxypeptidase; AMP-A, aminopeptidase A; AMP-B, aminopeptidase B; AMP-N, aminopeptidase N; N-EP, neutral endopeptidase; P-EP, prolylendopeptidase.

receptors and NO. ANG II stimulates dilatation of bovine adrenal cortical arteries, possibly through endothelial cell AT₂ receptor activation and NO release (Gauthier et al., 2005). Cosentino et al. (2005) suggested that the losartan-unmasked AT₂ receptor-mediated vasodilatation seen in the aorta isolated from SHR may contribute to the beneficial hemodynamic effects of AT₁ receptor blockade. Arun et al. (2004) noted that ANG II-induced relaxation, evident only in the presence of the AT₁ blocker, was enhanced in aortic rings isolated from diabetic rats but not control rats, the response being attenuated by L-NAME or ATP-sensitive K⁺ channel blockers and abolished by treatment with both inhibitors. [³H]ANG II saturation binding at the AT₂ receptor was enhanced in aortic membranes from diabetic rats compared with control rats. They concluded that AT₂ receptor density and AT₂-induced relaxations mediated by NO and ATP-sensitive K⁺ channels are enhanced in the diabetic rat aorta. There was evidence that ANG II evoked AT₁ receptor-mediated vasoconstriction and AT₂ receptor-mediated vasodilatation in isolated porcine coronary arterioles and that ANG II at a subvasomotor level impaired endothelium-dependent NO-mediated dilatation attributable to elevated superoxide production via AT₁ receptor activation of NADPH oxidase (Zhang et al., 2003). In aortic rings from mice subjected to abdominal aortic banding that increased blood pressure, plasma renin levels, and AT₂ receptor mRNA, the contractile response to ANG II was depressed and was restored by the AT₂ receptor antagonist PD123319 or the bradykinin B₂ receptor antagonist; the cyclic GMP content in aortas of banding mice was greater than that of sham-operated mice, and ANG II increased the nucleotide content only in the aorta of banding mice (Hiyoshi et al., 2004). Aortic banding seems to induce up-regulation of the AT₂ receptor through increased circulating ANG II via the AT₁ receptor, thereby activating a vasodilatory pathway in vessels through the AT₂ receptor via the kinin/NO/cyclic GMP system. Olson et al. (2004) found that ANG II stimulated an increase in NOS

mRNA, protein expression, and NO production via AT₂ receptors, whereas signaling via the AT₁ receptor negatively regulated NO production in pulmonary endothelial cells. According to Zhao et al. (2005), ANG II stimulates an increase in NOS mRNA levels, eNOS protein expression, and NO production via the AT₂ receptor, whereas ANG II seems to down-regulate eNOS protein expression via an AT₁ receptor-linked pathway involving the G_{αq} protein/phosphatidylinositol phospholipase C/Ca²⁺/protein kinase C-α signaling pathway in bovine pulmonary artery endothelial cells. Andresen et al. (2005) provided evidence supporting the hypothesis that AT₂ receptors in rat preglomerular smooth muscle cells inhibit AT₁-mediated phospholipase D activation through a NO/cyclic GMP-dependent mechanism most likely mediated by phosphorylation of RhoA at Ser¹⁸⁸. Hiyoshi et al. (2005) noted that the mRNA levels of AT₂ receptor, but not those of AT₁ and bradykinin B₂ receptors, and cyclic GMP levels increased in aortas from mice with two-kidney, one-clip hypertension; the aortic levels of eNOS, phosphorylated eNOS at Ser¹¹⁷⁷, total Akt, and phosphorylated Akt at Ser⁴⁷³ (Fig. 1) also increased. The administration of PD123319 to the hypertensive mice decreased phosphorylated eNOS and cyclic GMP to sham levels without affecting blood pressure and the levels of eNOS, Akt, and phosphorylated Akt. Therefore, it was suggested that NO production is enhanced by increased eNOS phosphorylation via the activation of AT₂ receptors in the course of two-kidney, one-clip hypertension. Hill-Kapturczak et al. (1999) provided evidence that ANG II-stimulated NO release from porcine pulmonary endothelial cells is mediated, at least in part, through ANG IV and AT₄ receptors.

In isolated microperfused rabbit afferent arterioles, activation of the AT₂ receptor seemed to cause endothelium-dependent vasodilatation via a cytochrome P-450 pathway, possibly by epoxyeicosatrienoic acids, rather than the NO pathway (Arima et al., 1997; Kohagura et al., 2000). According to de Godoy et al. (2004), the ANG II-induced relaxation of rat anococcygeus smooth muscle

seems to be mediated by stimulation of AT_2 receptors and activation of the nNOS/soluble guanylyl cyclase pathway. Fukuda et al. (2005) suggested that AT_2 receptors located in smooth muscle of rat aortic rings may mediate vasorelaxation via stimulation of the NO-cyclic GMP pathway, vasodilator cyclooxygenase products, and voltage-dependent and Ca^{2+} -activated large-conductance K^+ channels.

In isolated canine coronary and mesenteric arteries and monkey mesenteric arteries, ANG II-induced contractions, susceptible to the nonselective ANG II receptor antagonist saralasin, were potentiated by treatment with aspirin and indomethacin, whereas monkey and canine cerebral arterial contractions evoked by the peptide were suppressed by the cyclooxygenase inhibitors, suggesting that ANG II releases vasodilator PGs, possibly PGI_2 , in the peripheral arteries and vasoconstrictor PGs in cerebral arteries (Minami and Toda, 1988; Toda et al., 1990). It was not determined whether NO was also released by ANG II from these isolated arteries. Evidence for interactions between PGI_2 and NO has been reported in endothelial cells. According to Hardy et al. (1998), NO-induced vasorelaxation of piglet retinal and choroidal arteries seems to be mediated by stimulating PGI_2 formation of endothelial origin via a mechanism independent of guanylyl cyclase, which involves the opening of Ca^{2+} -activated K^+ channels. Niwano et al. (2003) suggested that the stable analog of PGI_2 beraprost increases eNOS expression through a cyclic AMP-responsive element in human and bovine aortic endothelial cells.

2. Studies on Gene-Targeted Mice. Siragy et al. (1999) noted that mice lacking the AT_2 receptor had low basal levels of renal interstitial fluid bradykinin and cyclic GMP, an index of NO production, compared with wild type mice; in wild type, but not AT_2 -null mice, dietary sodium restriction or ANG II infusion increased renal interstitial fluid bradykinin and cyclic GMP. Therefore, the authors suggested that the AT_2 receptor plays a counterregulatory protective role mediated by bradykinin and NO against the antinatriuretic and pressor actions of ANG II. According to Brede et al. (2003), experimental myocardial cryoinjury led to an increased heart weight/body weight ratio in AT_2 -deficient mice compared with control mice; expression of eNOS was lower in hearts from AT_2 -deficient mice, with eNOS down-regulation being accompanied by a decrease in cardiac cyclic GMP. The authors concluded that AT_2 receptors seem to exert an antihypertrophic effect in cardiac remodeling after myocardial cryoinjury and link the expression of cardiac eNOS to AT_2 receptor activation. In perfused carotid arteries from wild-type mice, inhibition of AT_2 receptors reduced NO-mediated, flow-induced dilatation but had no effect in tissue kallikrein-deficient mice; the B_2 receptor antagonist reduced the response to flow in the wild-type mice, but not in

AT_2 -deficient mice, suggesting that the presence of functional AT_2 receptors is necessary to observe the contribution of the vascular kinin-kallikrein system to flow-dependent dilatation (Bergaya et al., 2004).

Chronic infusion of ANG II into AT_2 -overexpression mice abolished the AT_1 -mediated pressor effect, which was blocked by icatibant, a B_2 receptor antagonist, and L-NAME. Aortic explants from transgenic mice showed increased cyclic GMP production and diminished ANG II-induced vascular constriction, these AT_2 -mediated effects being abolished by removal of the endothelium or treatment with icatibant and L-NAME, suggesting that AT_2 receptors in aortic smooth muscle cells stimulate the production of bradykinin, which stimulates the NO/cyclic GMP system in a paracrine manner to promote vasodilatation (Tsutsumi et al., 1999). Kurisu et al. (2003) obtained evidence from studies on AT_2 receptor transgenic and wild-type mice that stimulation of AT_2 receptors present in cardiomyocytes may attenuate perivascular fibrosis by a kinin/NO-dependent mechanism.

3. In Vivo Studies. In anesthetized rats, intravenous infusion of subpressor doses of ANG II increased tissue NO concentrations in the renal medulla to a greater extent than in the renal cortex, and renal medullary interstitial infusion of L-NAME blocked ANG II-induced NO increases in the renal medulla but not in the renal cortex (Zou et al., 1998). They concluded that small elevations of circulating ANG II levels increase medullary NO production and concentration, which seem to play an important role in buffering against the vasoconstrictor effects of this peptide and in maintaining a constancy of medullary blood flow. Hennington et al. (1998) noted that in rats treated with captopril, acute suprarenal infusion of ANG II increased renal eNOS mRNA but had no effect on renal eNOS protein concentration; in contrast, chronic infusion of ANG II for 10 days had no effect on renal eNOS mRNA levels but increased eNOS protein, suggesting that ANG II can stimulate eNOS synthesis and thus may enhance NO production. Losartan prevented increased vasopressor response to ANG II in hypertensive rats, and this effect was associated with restoration of NOS mRNA expression and NOS activity; in addition, ANG II-dependent NO release in hypertensive rats was potentiated by treatment with losartan (Martinez et al., 2002).

In rat choroidal plexus, phentolamine attenuated the blood flow-lowering effect of a moderate ANG II dose and unmasked the vasodilator actions of the peptide at high concentrations; in L-NAME-treated rats, high ANG II lowered blood flow and increased vascular resistance, indicating that choroidal vasodilator actions of ANG II may be mediated by NO derived from the endothelium and nitrenergic nerves (Chodobski et al., 1999). In newborn pigs equipped with a closed cranial window, the AT_2 receptor agonist CGP 42112A induced vasodilatation associated with elevated cyclic GMP in artificial cerebrospinal fluids, both of which were blocked by

L-NA, indicating that stimulated NO release may contribute to AT₂-induced vasodilatation (Baramov and Armstead, 2005). Lambers et al. (2000) found that in nonpregnant sheep treated with an AT₁ receptor antagonist, vasodilatation was induced by intra-arterial infusion of ANG II in the uterine artery, which was reversed by administration of the AT₂ receptor antagonist or by L-NAME, suggesting that the AT₂ receptor subtype may modulate uterine vascular responses to ANG II potentially by release of NO. In anesthetized pigs, the baseline output of jejunal luminal NO correlated to baseline mucosal iNOS protein content, and treatment with the AT₂ agonist CGP 42112A increased luminal NO output, with the agonistic action being reversed by the AT₂ receptor antagonist, suggesting an involvement of AT₂ receptors in increasing the luminal NO output (Ewert et al., 2003).

4. Involvement of Angiotensin II Receptors Other Than Angiotensin Receptor Type 2. A number of reports in the literature so far have suggested the involvement of AT₂ receptors in the ANG II-induced release of NO from the endothelium. However, evidence against this hypothesis has also been reported. McLay et al. (1995) indicated that the ANG II-induced increase in NO production in primary cultures of human proximal tubular cells may not be mediated by AT₁ and AT₂ receptors but are instead mediated by a novel, as yet unidentified, ANG receptor. Saito et al. (1996) provided evidence that ANG II stimulates NO release by activation of Ca²⁺/calmodulin-dependent constitutive NOS via AT₁ receptors in cultured bovine endothelial cells. Patzak et al. (2004) also suggested an ANG II-induced NO release in afferent arterioles isolated from mice, which is mediated by AT₁ receptor subtypes. Sarkis et al. (2003) demonstrated that in anesthetized Lyon rats, after i.v. ANG II, the initial renal medullary vasoconstriction was followed by a long-lasting vasodilatation and that blockade of AT₁ receptors abolished all the effects of ANG II, whereas AT₂ receptor blockade did not change these effects. Furthermore, indomethacin decreased the medullary vasodilatation induced by low doses of ANG II, and, in contrast, L-NAME and the bradykinin B₂ receptor antagonist lowered the medullary vasodilatation at the high doses of ANG II. It seems that AT₁ receptor-mediated medullary vasodilator response to low doses of ANG II is mainly due to the release of PGs, whereas the dilator response to high doses has additional NO- and kinin-dependent components. Losartan had no effect on basal ovarian blood flow in rats but blocked the ANG II-induced flow reduction, and, in contrast, the AT₂ receptor antagonist PD123319 increased ovarian basal blood flow and failed to reverse the effect of exogenous ANG II, indicating that under physiological conditions, ovarian blood flow of the rat is negatively regulated by ANG II through AT₂ receptors (Mitsube et al., 2003). Bayraktutan and Ulker (2003) suggested that ANG II

stimulates NO production in rat coronary microvascular endothelial cells in both an AT₁- and AT₂-receptor-regulated manner.

Heinemann et al. (1997) noted that intravenous injections of ANG II increased blood pressure, which was accompanied by a decrease in blood flow through the superior mesenteric artery and an increase in femoral blood flow, possibly due to vasodilatation; telmisartan prevented all of the hemodynamic responses, and the ANG II-evoked femoral vasodilatation was suppressed by L-NAME. The femoral vasodilator response to ANG II depended on the increase in vascular perfusion pressure, because vasodilatation was reversed to vasoconstriction when blood pressure remained constant. These results demonstrate that the effects of ANG II to increase systemic blood pressure and the resulting rise of perfusion pressure in the femoral artery stimulate the formation of NO and thereby dilate the femoral arterial beds.

B. Angiotensin III [Angiotensin-(2-8)]-Induced Vasodilatation

ANG III as well as ANG I, II, IV, and ANG-(1-7) increased nitrite release from microvessels or large coronary arteries isolated from the canine heart, the effect being blocked by L-NAME, HOE-140, and protease inhibitors, suggesting that formation of NO from coronary arteries and microvessels in response to ANG peptides is due to the activation of local kinin production in the coronary vascular wall (Seyedi et al., 1995). These results indicated the involvement of AT₁ and AT₂ receptors in the ANG III-induced NO release. Li et al. (1995) found that in rat aortic rings, concentration-contractile response curves of ANG II, III, and IV were shifted to the right by losartan; however, PD123177 shifted leftward only the curve of ANG III and destruction of the endothelium or incubation with L-NMMA enhanced the contractile response to all three peptides. ANG III seems to release NO from the aortic endothelium through activation of AT₂ receptor subtypes.

In the conscious rabbit, intravenous boluses of ANG III produced a pressor followed by a depressor response; losartan blocked both responses, whereas PD123319 had no effect on either element of the response, leading to a conclusion that the depressor effect is mediated by AT₁ receptors and there is no indication that AT₂ receptors could be involved (Rowe and Dixon, 2000).

C. Angiotensin-(1-7)-Induced Vasodilatation

This peptide is a bioactive component of the renin-angiotensin system that is endogenously formed by several endopeptidases and carboxypeptidases from either ANG I or ANG II (Benter et al., 1993; Erdos et al., 2002; Ferrario and Chappell, 2004). Ferrario et al. (2005) found a role for ACE₂ in ANG-(1-7) formation from ANG II in the kidney of normotensive rats and found that renal cortex ACE₂ activity was augmented in rats med-

icated with lisinopril or losartan. Because plasma levels of ANG-(1-7) are elevated during ACE inhibition or AT₁ blockade (Fig. 2), part of the effects of therapeutics that inhibit ACE activity and block AT₁ receptors may be mediated through ANG-(1-7) (Iyer et al., 2000; Ferrario and Chappell, 2004; Igase et al., 2005). ANG-(1-7) is expected to act as a counteracting factor for the vasoconstrictor effects of ANG II (Haulica et al., 2005).

ANG-(1-7) may oppose the actions of ANG II directly or as a result of increasing NO or PGs (Chappell et al., 1998). In feline hindquarters and mesenteric vascular beds, injections of ANG-(1-7) caused vasodilatation or modest vasoconstriction, depending on the dose; the vasoconstriction was blocked by an AT₁ receptor antagonist but not by a cyclooxygenase inhibitor, and the vasodilatation was partially attenuated by L-NAME (Osei et al., 1993). ANG-(1-7)-induced relaxation of porcine coronary artery rings was endothelium-dependent and suppressed by L-NA but was not affected by AT₁ or AT₂ receptor blockade or cyclooxygenase inhibition, suggesting that the relaxation to this peptide is mediated by the release of NO from the endothelium through activation of an, as yet unidentified, ANG receptor (Porsti et al., 1996). Similar results were also obtained in canine coronary arteries (Brosnihan et al., 1996). There was evidence supporting the hypothesis that ANG-(1-7) acts as a local synergistic modulator of kinin-induced vasodilatation by inhibiting ACE and releasing NO (Li et al., 1997). There was evidence suggesting that the AT₂ receptor mediates ANG-(1-7)-induced relaxation of porcine coronary arteries associated with NO and kinins (Gorelik et al., 1998). It was suggested that the antiangiogenic effect of ANG-(1-7) in the mouse sponge model of angiogenesis is associated with NO release by activation of an ANG receptor distinct from AT₁ and AT₂ (Machado et al., 2001). In preexisting (skin) and newly formed vasculature (14-day-old polyurethane sponge implants) in mice, ANG-(1-7)-induced vasodilator effects was prevented by the specific receptor antagonist (D-Ala⁷)-ANG-(1-7) and abolished by NOS inhibitors, suggesting that this peptide contributes to the vasodilatation via NO also in newly formed vascular beds (Machado et al., 2002). ANG-(1-7) and AVE 0991 released NO and superoxide anions from bovine aortic endothelial cells, the effect being inhibited by a selective ANG-(1-7) antagonist, and an AT₂ antagonist inhibited AVE 0991-stimulated NO production but had no inhibitory effect on superoxide production (Wiemer et al., 2002).

Santos et al. (2003) demonstrated that genetic deletion of the G-protein-coupled receptor encoded by the Mas protooncogene abolished the binding of ANG-(1-7) to mouse kidneys and that Mas-deficient aortas lost the ANG-(1-7)-induced relaxant response, thus identifying Mas as a functional receptor for ANG-(1-7). Lemos et al. (2005) obtained results showing that ANG-(1-7) and AVE 0991, a nonpeptide mimetic of the effects of ANG-

(1-7), produced an NO-dependent vasodilator effect in the mouse aorta that is mediated by the G protein-coupled receptor Mas. In the presence of losartan, ANG-(1-7) induced a decrease in perfusion pressure of isolated, perfused mouse hearts, which was blocked by the Mas antagonist A-779, indomethacin, and L-NAME; in contrast, in the presence of PD123319, ANG-(1-7) increased the perfusion pressure, suggesting that ANG-(1-7) produces complex vascular effects in isolated mouse hearts involving interaction of its receptor with AT₁- and AT₂-related mechanisms, leading to the release of NO and PGs (Castro et al., 2005). From studies on ANG-(1-7) receptor Mas-knockout mice and on Mas-transfected mice, Pinheiro et al. (2004) provided evidence that AVE 0991 is a Mas receptor agonist and that the antidiuretic effect of AVE 0991 is mediated by AT₂ and AT₁ receptors, and NO release from Mas-transfected Chinese hamster ovary cells is mediated by ANG-(1-7) receptors.

On the other hand, Sasaki et al. (2001) provided evidence that ANG-(1-7)-evoked vasodilatation was independent of NO synthesis in forearm circulation of normotensive subjects and patients with essential hypertension. It was suggested that in rat aortic rings, ANG-(1-7) elicits an endothelium-dependent antagonism of ANG II, which involves AT₂ and ANG-(1-7) receptors but is independent of NO production (Roks et al., 2004). There is evidence for the involvement of PGs in the vascular actions of ANG-(1-7). In SHR treated with either lisinopril or losartan or a combination of both drugs, neutralization of circulating ANG-(1-7) by monoclonal antibody and CGS 24592, a blocker of ANG-(1-7) formation, resulted in an increase in blood pressure, and indomethacin increased blood pressure to an extent similar to that of CGS 24592, suggesting that vasodilatory PGs mediate the antihypertensive effects of endogenous ANG-(1-7) in lisinopril/losartan therapy (Iyer et al., 2000). Tallant and Clark (2003) also suggested that ANG-(1-7) inhibits vascular growth through the release of PGI₂, through the PGI₂-mediated production of cyclic AMP, and activation of cyclic AMP-dependent protein kinase. In SHR treated with L-NAME, ANG-(1-7) attenuated development of severe hypertension and end-organ damage; PGs seemed to participate in the hypotensive and cardioprotective effects of this peptide (Benter et al., 2006).

Gironacci et al. (2004a,b) noted that in hypothalami isolated from aortic coarcted hypertensive rats or SHR, ANG-(1-7) diminished the K⁺-evoked norepinephrine release and blocked the ANG II-enhanced amine release induced by K⁺, the responses being prevented by an ANG-(1-7) specific antagonist, AT₂ receptor antagonist, B₂ receptor antagonist, L-NAME, and soluble guanylyl cyclase inhibitor as well as by a cyclic GMP-dependent protein kinase inhibitor. They concluded that ANG-(1-7) decreases norepinephrine release from the hypothalamus via the ANG-(1-7) or AT₂ receptors, acting through

a bradykinin/NO-mediated mechanism that stimulates cyclic GMP/protein kinase signaling; thus, this peptide may decrease sympathetic nervous system activity and exert an antihypertensive effect.

D. Angiotensin IV [Angiotensin-(3-8)]-Induced Vasodilatation

The hexapeptide ANG IV is an active metabolite of ANG II. In the rat subjected to experimental subarachnoid hemorrhage, ANG IV increased cerebral blood flow, and this effect was not influenced by pretreatment with saralasin or an NOS inhibitor (Naveri et al., 1994). Naveri (1995) suggested that ANG IV increased cerebral blood flow after subarachnoid hemorrhage, possibly by dilating cerebral vessels through stimulation of the AT₄ receptor but not the release of NO. In contrast, Kramar et al. (1998) noted that in anesthetized rats, the ANG IV-induced increase in cerebral blood flow was blocked by pretreatment with L-NAME and thus suggested that cerebral vasodilatation is dependent upon the synthesis and release of NO from the endothelium. There are many reports in the literature supporting the involvement of NO in ANG IV-induced vasodilatation. From incubated canine large coronary arteries and coronary microvessels, ANG I, II, III, IV, and ANG-(1-7) increased the release of nitrite, and this effect was blocked by L-NAME and HOE-140; only AT₂ receptors mediated nitrite release after ANG IV, whereas AT₁ and AT₂ receptors were involved in the release of nitrite in response to other ANGs (Seyeki et al., 1995). In the isolated perfused rat lung, ANG IV showed vasoconstrictor activity that was decreased by an AT₁ receptor antagonist and enhanced by L-NAME and meclofenamate, suggesting that responses to ANG IV are modulated by the release of NO and vasodilator PGs (Nossaman et al., 1995). A similar conclusion was also obtained in the renal vascular response, since in anesthetized SHR and normotensive rats, intrarenal infusion of ANG IV produced biphasic vasoconstrictor responses: a rapid, transient response followed by a sustained lesser level of vasoconstriction; the initial response was enhanced by L-NAME but not affected by indomethacin, and the simultaneous administration of these inhibitors resulted in a greater sustained level of vasoconstriction, which was inhibited by losartan (Yoshida et al., 1996). Coleman et al. (1998) noted that intrarenal infusions of ANG IV produced an increase in renal cortical blood flow without altering systemic blood pressure, and divalinal ANG IV, an AT₄ receptor antagonist, or L-NMMA completely blocked the effect of ANG IV, suggesting that ANG IV exerts a unique influence upon renal hemodynamics via the AT₄ receptor subtype that is responsible for the release of NO. In porcine pulmonary arterial endothelial cells, ANG IV increased eNOS activity as well as cellular cyclic GMP content, and divalinal ANG IV, but not saralasin, losartan, or PD12377, inhibited

the effects of ANG IV (Patel et al., 1998). L-NAME or methylene blue but not indomethacin diminished ANG IV-stimulated levels of cyclic GMP. Collectively, ANG IV seems to bind to AT₄ receptors, activates eNOS, stimulates cyclic GMP accumulation in endothelial cells, and causes pulmonary arterial vasodilatation. It is likely that ANG IV-mediated activation of eNOS is regulated by intracellular Ca²⁺ mobilization and by increased expression of the Ca²⁺ binding protein calreticulin (Patel et al., 1999) and that intracellular Ca²⁺ is mobilized through receptor-coupled G-protein/phospholipase C/PI₃/kinase signaling mechanisms (Chen et al., 2000).

IV. Radical Oxygen Species Production Stimulated by Angiotensin II

Wilson (1990) noted that the free radical scavengers superoxide dismutase (SOD), catalase, SOD-catalase, and dimethyl sulfoxide inhibited vascular hyperpermeability and endothelial and smooth muscle cellular damage in intestinal small arteries from rats made acutely hypertensive with ANG II infusions and suggested that free radicals play a role in the pathogenesis of hypertensive vascular disease. NADPH oxidase was found to be a major source of superoxide anions detected by lucigenin-elicited chemiluminescence in bovine coronary artery endothelium (Mohazzab et al., 1994). Infusion of ANG II increased systemic blood pressure and doubled vascular superoxide anion production predominantly from the vascular media in rats; the predominant source of superoxide was thus suggested to be an NADH/NADPH-dependent, membrane-bound oxidase (Rajagopalan et al., 1996). ANG- but not norepinephrine-induced hypertension was associated with impaired relaxations to ACh and nitroglycerin; these relaxations were corrected by SOD, and losartan normalized the superoxide production and the relaxations, suggesting that AT₁ receptor stimulation increases superoxide production via NADH/NADPH oxidase activation (Fig. 1). The acute superoxide-producing effect is likely to be specific to ANG II in the rat mesenteric microcirculation (Kawazoe et al., 1999). Infusion of ANG II into rats for 7 days increased ROS in tubular cells of the kidney and stimulated protein expression of p27 (Kip1), an inhibitor of cyclin-dependent kinases, and the radical scavenger dimethylthiourea abolished this protein expression, indicating that ANG II seems to induce p27 expression *in vivo* that is mediated by ROS (Wolf et al., 2001). Superoxide anions depressed the modulatory influence of endogenous NO on ANG II-induced afferent arteriolar constriction in rats with insulin-dependent diabetes mellitus (Schoonmaker et al., 2000).

In early renovascular hypertension in pigs, increases in plasma renin activity and arterial pressure were associated with increased systemic oxidative stress (Lerman et al., 2001). There was evidence that ANG II at a subpressor level impaired endothelium-dependent NO-

mediated dilatation in isolated porcine coronary arterioles, and this action was attributable to elevated superoxide production via AT_1 receptor activation by NADPH oxidase (Zhang et al., 2003). In the anesthetized SHR, tempol, a membrane-permeable mimetic of SOD, given in the drinking water decreased arterial pressure and increased renal medullary blood flow without altering total renal blood flow and attenuated the ANG II-induced decrease in medullary blood flow but not that in renal blood flow, suggesting that tempol enhances vasodilator mechanisms of the medullary circulation, possibly by interacting with the NO system (Feng et al., 2001). Shinozaki et al. (2004a,b) noted that losartan normalized blood pressure, NADPH oxidase activity, endothelial function, and ANG II-induced vasoconstriction in fructose-fed mice that were made insulin resistant. In addition, expression of AT_1 receptor mRNA was enhanced in fructose-fed mice and NADPH oxidase protein expression was increased in these animals, whereas the expression was decreased in fructose-fed, AT_1 knockout mice.

In anesthetized rabbits, topical application of ANG II inhibited vasodilatation of cerebral arterioles to the endothelium-dependent agonist bradykinin, and a superoxide scavenger and an inhibitor of NADPH oxidase (diphenylene iodonium) prevented the inhibitory effect, implicating the superoxide-mediated vascular dysfunction by ANG II (Didion and Faraci, 2003). Rugale et al. (2005) found that enalapril and the NADPH oxidase inhibitor apocynin reduced the overproduction of superoxide anions by rat left ventricle and reduced the rise in advanced oxidation protein products induced by ANG II and thereby suggested that the antioxidant effect of enalapril may participate in the preventive and therapeutic effects on the ANG II-induced cardiovascular and renal alterations. In anesthetized mice, intravenous ANG II attenuated the cerebral blood flow increase produced by mechanical stimulation of the vibrissae; the effect was blocked by losartan and SOD and was not observed in mice lacking the gp91 phox subunit of NADPH oxidase (Kazama et al., 2004). ANG II increased ROS production in cerebral microvessels, an effect blocked by the ROS scavenger and by apocynin. Therefore, these authors suggest that ANG II impairs functional hyperemia by activating AT_1 receptors and inducing ROS production via a gp91 phox containing NADPH oxidase. Kinugawa et al. (2003) provided evidence that endothelial stunning is caused by oxidant processes inhibited by ascorbate in conscious dogs, and the activation of NADPH oxidase by increased ANG II plays an important role in this process. There were higher baseline renal blood flow and lower renal vascular resistance in gp91 (an NADPH oxidase subunit) gene knockout mice compared with wild-type mice without a difference in arterial pressure; intravenous infusion of ANG II caused a lesser degree of renal blood flow decrease and urinary excretion of nitrate/nitrite was higher in the

knockout mice, indicating an increase in NO bioavailability that could be the cause of high renal blood flow in gp91 gene knockout mice (Haque and Majid, 2004). The mechanism of ANG II-mediated renal vascular action seems to involve concomitant generation of superoxide anions. In SHR, urinary isoprostane excretion, as a measure of ROS activity, and nNOS immunoreactivity of juxtaglomerular apparatus were higher than those in Wistar-Kyoto rats; apocynin, a specific NADPH oxidase inhibitor, reduced isoprostane excretion, whereas renin mRNA, plasma renin activity, glomerular filtration rate (GFR), and systolic blood pressure remained unchanged, suggesting that NADPH oxidase is an important contributor to elevated levels of ROS in hypertension (Paliege et al., 2006).

Mori et al. (2006) concluded in their review article that ANG II-induced oxidative stress within the renal medulla can induce hypertension and can also make the kidney functionally more vulnerable to the effects of ANG II. Sulfhydryl-containing ACE inhibitors (captopril, enalapril, zofenopril, and feniapril) were shown to be effective scavengers of nonsuperoxide free radicals; captopril also scavenged the other toxic ROS hydrogen peroxide and singlet oxygen and inhibited microsomal lipid peroxidation (Chopra et al., 1992). Takai et al. (2005) showed that a lipophilic ARB, telmisartan, which was superior to losartan, prevented NADPH oxidase activity in the aorta from stroke-prone SHR (SHRSP) and thereby conferred vascular protection from remodeling.

Both superoxide anion and hydrogen peroxide production by leukocytes and the plasma levels of lipid peroxides were higher and plasma nitrite levels were lower in patients with uncontrolled essential hypertension compared with normal control subjects; ANG II stimulated free radical generation in normal leukocytes, suggesting that an increase in free radical generation and a simultaneous decrease in the production of NO and antioxidants occurs in essential hypertension (Kumar and Das, 1993). In healthy humans, the *in vivo* forearm vasoconstrictor actions of ANG II were enhanced during clamping of NO concentrations by using the combination of L-NMMA and sodium nitroprusside and attenuated during administration of vitamin C, suggesting direct ANG II-associated stimulation of endothelial NO and of oxygen radicals, respectively (Dijkhorst-Oei et al., 1999). In internal mammalian artery rings sampled during bypass surgery from patients with stable coronary artery disease, physical exercise training before the surgery resulted in improved ACh-mediated vasodilatation and reduced vascular expression of NADPH oxidase and AT_1 receptor subtypes, resulting in decreased local ROS generation (Adams et al., 2005). Wolf (2000) suggested that drugs interfering with ANG II effects may serve as antioxidants, preventing vascular and renal changes, but the clinical studies are not so straightforward.

V. Vasodilatation Induced by Angiotensin I-Converting Enzyme (Kininase II) Inhibitors Associated with Endothelial Nitric Oxide via Bradykinin

The vasodilator effect of bradykinin on coronary flow in the isolated perfused rat heart was potentiated when cysteine or the sulfhydryl-containing ACE inhibitors captopril and zofenoprilate were administered simultaneously (van Gilst et al., 1991). L-Arginine increased the effect of captopril, whereas the NOS inhibitor L-NMMA antagonized the effect of captopril. These authors also revealed that in patients with stable, exercise-induced angina pectoris, captopril given 1 h before exercise improved the ST-segment depression, maximal workload, and time to angina compared with placebo, suggesting that the sulfhydryl group of certain ACE inhibitors can potentiate their effect on the endogenous nitrovasodilator EDRF and that this may lead to improved performance in patients with angina. De Graeff and van Gilst (1992) hypothesized that ACE inhibitors may cause coronary vasodilatation by a bradykinin-mediated release of EDRF. Similar results suggesting the involvement of reduced bradykinin degradation and increased endothelium-derived NO formation in the vasodilator effect of ACE inhibitors were also obtained in renal blood flow of conscious rabbits (Evans et al., 1994), coronary blood flow of chronically instrumented, conscious dogs (Zaninger et al., 1994), and isolated, perfused porcine ciliary vasculature (Meyer et al., 1995). Hajj-ali and Zimmerman (1992) noted that L-NA reversed partially the increase in renal blood flow of anesthetized rabbits caused by Dup 753, an AII receptor blocker, and almost completely reversed the effect of lisinopril, an ACE inhibitor, suggesting that NO plays an important role in the renal hemodynamic effect of the ACE inhibitor, more so than its contribution to the effect of the ARB. The different efficacy of these inhibitors may be explained by the hypothesis that ACE inhibitors induce the vasodilator effect in association with NO released via inhibition of bradykinin degradation and with other mechanisms derived from decreased AII actions. Kitakaze et al. (1995) demonstrated that in open-chest dogs, in which the left anterior descending coronary artery was perfused through a bypass tube from the carotid artery, the increased coronary blood flow by cilazaprilat was attenuated by HOE-140, an inhibitor of B₂ bradykinin receptors, and by L-NAME, and intracoronary administration of bradykinin mimicked the effects of the ACE inhibitor; CV11974, an ARB, increased coronary blood flow to a lesser extent than cilazaprilat. Therefore, the authors concluded that the ACE inhibition can increase coronary blood flow primarily due to accumulation of bradykinin and production of NO by the myocardium. Kitakaze et al. (1998) also reported that ACE inhibitors increased cardiac NO levels via the accumulation of bradykinin in the ischemic myocardium. E4177, an ARB, dilated affer-

ent and efferent arterioles in superficial nephrons of the canine kidney, and cilazaprilat caused further arteriolar dilatation and a further increase in sodium excretion; effects of this ACE inhibitor were abolished by a bradykinin antagonist, suggesting an extra action of ACE inhibition in addition to ANG II receptor blockade (Matsuda et al., 1999). There is evidence supporting the idea that ACE inhibition increases the coronary blood flow by a bradykinin-mediated, NO-dependent mechanism in dogs with myocardial ischemia (Kitakaze et al., 2002) and those with pacing-induced dilated cardiomyopathy (Nikolaidis et al., 2002).

In contrast, Sudhir et al. (1993) provided evidence suggesting that inhibition of AT₁ receptors in the dog coronary circulation in vivo results in vasodilator responses greater in magnitude than those with ACE inhibition. The reason for the opposite results from those by others was not determined.

In bradykinin B₂ receptor knockout mice with ANG II infusion (Ang II/B₂R^{-/-} mice), mean arterial pressure was higher than in ANG II-infused wild-type (Ang II/B₂R^{+/+}) mice under anesthesia; short-term NOS inhibition by L-NAME caused a greater increase in arterial pressure in Ang II/B₂R^{+/+} mice than in Ang II/B₂R^{-/-} mice, so that the mean arterial pressure after NOS inhibition in Ang II/B₂R^{+/+} approached that of Ang II/B₂R^{-/-} mice (Cervenka et al., 2001). Therefore, they postulated that the kallikrein-kinin system selectively buffers the vasoconstrictor activity of ANG II via the release of NO. From studies with conductance and resistance coronary vessels in conscious dogs, Su et al. (2000) drew a conclusion that stimulation of B₁ receptors produces vasodilatation, which is mediated by NO but not modulated by ACE, whereas the vasodilator response to B₁ receptor stimulation is not as great as that produced by B₂ receptor stimulation. In contrast to the literature so far reported for involvement of NO in ACE inhibitor-induced vasodilatation, Ehring et al. (1994) obtained evidence that the attenuation of myocardial stunning by ramiprilat in anesthetized open-chest dogs involved a signal cascade of bradykinin and PGs but not NO. In chronically instrumented dogs, S-nitrosocaptopril, a hybrid compound of NO and captopril, and nitroglycerin increased epicardial coronary diameter and coronary blood flow, whereas captopril had no effect on coronary diameter and blood flow, suggesting that S-nitrosocaptopril may dilate coronary arteries by virtue of its NO moiety rather than by its ACE inhibitory properties (Nakae et al., 1995).

In isolated canine coronary microvessels with intact endothelium, ramiprilat, bradykinin, kallikrein, and kininogen increased nitrite production, and the stimulating effect was blocked by L-NA, HOE-140, or the kinin antibody, suggesting that either increasing kininogen to promote endogenous kinin formation or inhibiting ACE to decrease kinin breakdown increases NO production (Zhang et al., 1997a). According to Wiemer et al. (1994),

cultured porcine brain capillary endothelial cells are capable of producing and releasing kinins in amounts that lead via stimulation of B₂-kinin receptors to an enhanced intracellular Ca²⁺ concentration as well as NO and PGI₂ synthesis and release, provided that degradation of kinins is prevented by inhibition of endothelial ACE.

Rosenkranz et al. (2002) noted that in isolated rat hearts, the acute antihypertrophic action of bradykinin was accompanied by increased left ventricular cyclic GMP, and the inhibitory effect of ramiprilat on ANG II-induced increase in phenylalanine incorporation was attenuated by HOE-140 or 1H[1,2,4]oxadiazolo[4,3- α]quinoxalin-1-one, a selective guanylyl cyclase inhibitor (Garthwaite et al., 1995), suggesting that elevation of cardiomyocyte cyclic GMP, possibly via endothelial NO (Yayama et al., 1998), may be an important antihypertrophic mechanism used by bradykinin and remipril in the heart. Gryglewski et al. (2003) provided evidence supporting the idea that in anesthetized rats ACE inhibitors induce thrombolysis via accumulation of endogenous kinins in the endothelium and subsequent activation of B₂ receptors followed by the release of NO and PGI₂.

Brosnihan et al. (1998) summarized mechanisms of ANG-(1-7) underlying the coronary vasodilatation in their review. The ANG-(1-7)-induced vasodilatation mediated by endothelium-dependent release of NO is attenuated by the B₂ receptor antagonist HOE-140 (icatibant); AT₁ and AT₂ receptors are not involved in the effect of ANG-(1-7). This peptide potentiates bradykinin-induced vasodilatation but not the response to ACh or sodium nitroprusside and retards the degradation of bradykinin, like ACE inhibitors. Thus, they postulated novel actions of ANG-(1-7) as a vasodilator and a local synergistic modulator of kinin-induced vasodilation in coronary arteries.

A. Human Studies

In the skin of human volunteers and rabbits, captopril injected intradermally increased skin blood flow, and this response was abolished by coinjecting either an NOS inhibitor or a cyclooxygenase inhibitor. Intradermal bradykinin increased rabbit skin blood flow; the responses to bradykinin and captopril were abolished by coinjecting a B₂ receptor antagonist or inhibitors of NOS or cyclooxygenase (Warren and Loi, 1995). Captopril seems to increase skin microvascular blood flow in humans and rabbits secondary to an increase in endogenous bradykinin; this stimulates B₂ receptors with subsequent release of NO or PGs. In coronary microvessels from the heart obtained from patients with end-stage heart failure, bradykinin, kininogen, and ACE inhibitors (ramiprilat, enalaprilat, and captopril) increased nitrite in the incubation media; nitrite production in response to ACE inhibition was blocked by L-NAME and icatibant, indicating that ACE/kininase II inhibitors may increase NO production by the coronary microvasculature in the failing human heart through an increase in available kinins (Kichuk et al., 1997).

VI. Mechanisms Underlying Vasodilatation Induced by Angiotensin Receptor Type 1 Blockade

In anesthetized dogs, losartan, a selective AT₁-receptor antagonist, increased circumflex coronary artery cross-sectional area and coronary blood flow to a greater extent than the ACE inhibitor enalaprilat, and losartan-induced coronary vasodilatation was inhibited by L-NAME but not by indomethacin and propranolol, suggesting that the induced response associated with inhibition of AT₁-receptors is at least partly mediated by endothelial NO (Sudhir et al., 1993). The greater effectiveness of the AT₁ antagonist may be explained by blockade of actions of ANG II that is formed not only through ACE but also alternative pathways such as that with chymase (Fig. 2). A coronary blood flow increase by the AT₁-receptor antagonist was also observed in open-chest dogs with ischemic myocardium (Kitakaze et al., 1995). In hearts isolated from SHR, minimum coronary vascular resistance was greater than in those from the Wistar-Kyoto rat, and treatment for 2 weeks with the AT₁-antagonist reduced the vascular resistance in SHR; although L-NAME failed to increase the coronary vascular resistance in SHR, treatment with ARB restored the response to L-NAME (Takeda et al., 1994). ARB seems to improve the NO availability in SHR coronary blood vessels. Involvement of NO in the vasodilatation induced by losartan was found in anesthetized and conscious rats (Sigmon and Beierwaltes, 1993a; Sigmon et al., 1994).

ACh relaxed the isolated aorta from renal hypertensive rats less than that from normotensive rats, and losartan enhanced the ACh-induced, NO-mediated relaxation (Lee and Shin, 1997). Moreover, ACh lowered the mean arterial pressure less effectively in hypertensive rats than in normotensive ones, the depressor response being potentiated by losartan. The authors suggested that NO may interact with the renin-ANG system in controlling the vascular tension and systemic arterial circulation in renal hypertensive rats. In anesthetized rats, candesartan reduced arterial pressure and renal vascular resistance; pretreatment with L-NAME did not affect the depressor effect but blunted the renal response to the ARB, suggesting that AT₁-receptor blockade is associated with an increase in NO-dependent renal vasodilatation (Demeilliers et al., 1999). Bennai et al. (1999) noted that in the SHRSP, cerebral intraparenchymal vessels showed lesions of the vascular wall and its periphery, and renal lesions were more pronounced. Beneficial effects of candesartan were more evident in the brain than in the kidney. In untreated SHRSP, eNOS immunoreactivity was decreased, but iNOS increased, and these changes were prevented in the ARB-treated group. A "role switch" of vascular eNOS in hypertension from physiological eNOS toward deleterious iNOS is suggested, and its

prevention by the ARB points to an ANG-dependent, NO-mediated pathway that may impair endothelial function and aggravate defects of the blood-brain barrier and kidney structures. Yamakawa et al. (2003) also observed that decreased eNOS and increased iNOS protein and mRNA in the common carotid artery, circle of Willis, and brain microvessel of SHR, compared with normotensive rats, were reversed by long-term AT₁ receptor blockade.

The highly lipophilic ARB telmisartan (Wienen et al., 2000) has a peroxisome proliferator-activated receptor- γ agonistic action (Benson et al., 2004; Schupp et al., 2004) that is responsible for increasing the release of NO from human umbilical vein endothelial cells (Polikandriotis et al., 2005) and ameliorating endothelial dysfunction in conduit arteries of patients with type 2 diabetes (Martens et al., 2005). This action as a peroxisome proliferator-activated receptor- γ ligand might be beyond the actions on the renin-ANG system.

In patients with essential hypertension, the decrease of forearm blood flow in response to L-NMMA was augmented after treatment for 6 weeks with valsartan; however, no improvement was found after placebo and treatment with hydrochlorothiazide (Klingbeil et al., 2003). The authors concluded that AT₁-receptor blockade improved basal NO production and release and that the effect seems to be blood pressure-independent, as the blood pressure fall with the diuretic failed to increase NO availability. Van der Linde et al. (2003) reported that in hypertensive patients with a hydrochlorothiazide-activated renin-ANG system, unopposed activity of ANG II was not involved in the L-NAME-induced pressor response and renal vasoconstrictor response, whereas the L-NAME-induced decrease in glomerular filtration rate was enhanced, suggesting greater dependence of GFR on NO-mediated vasodilator tone during sodium depletion.

Concerning the findings obtained from experimental animals and patients, ARB seems to have beneficial actions on cardiovascular hemodynamics via endogenous NO that is independent of kininase II inhibition and bradykinin accumulation. Possible mechanisms of ARB actions in vivo include the following: 1) ARB blockade of the binding of ANG II with AT₁-receptors facilitates actions of the peptide on other ANG receptors, such as AT₂ and AT₄, that contribute to the release of endothelial NO; 2) increased blood flow by inhibition of vasoconstrictor response to endogenous ANG II facilitates the flow-dependent NO synthesis and release from the endothelium; 3) increased generation of ROS formed by stimulation of AT₁-receptors is attenuated; 4) reduced eNOS and increased iNOS protein and mRNA expression seen in hypertension is normalized by AT₁ inhibition; and 5) ANG-(1-7) or ANG IV formed from ANG II during AT₁ blockade elicits NO-mediated vasodilatation. Other mechanisms may also be involved in the ARB actions as its beneficial effects have been reported in *in vitro* studies performed with arti-

ficial bathing media. Some of the proposed mechanisms (numbers 2 and 3) also are involved in NO-mediated actions of ACE inhibitors by reducing the synthesis of ANG II.

VII. Interaction between Endothelial Nitric Oxide and Angiotensin II in Patients and Healthy Subjects

A. Coronary Blood Flow Response

In patients with idiopathic dilated cardiomyopathy, pacing tachycardia increased coronary blood flow and coronary artery diameter, the effect being enhanced after administration of enalaprilat; the effect of this ACE inhibitor was abolished by intracoronary administration of L-NMMA, suggesting that NO seems to play an important role in mediating the vasodilator effects of enalaprilat in these patients (Mohri et al., 2000). These favorable effects of enalaprilat on the coronary circulation may be of clinical significance in patients with heart failure due to nonischemic idiopathic dilated cardiomyopathy. Nickenig et al. (2000) found that quinapril acutely improved endothelial dysfunction on the macrovascular as well as the microvascular level, whereas losartan did not alter macrovascular function but facilitated microvascular endothelial function in patients with nonlimiting coronary artery disease. Treatment with losartan blunted the vascular effect of quinapril, suggesting that the combined therapy may not exert a synergistic beneficial impact on the coronary vasculature. Compared with control subjects, patients with syndrome X had reduced coronary flow reserve, reduced plasma levels of NO_x (NO₂ + NO₃), increased plasma levels of ADMA, and reduced endothelial function; after 8 weeks of treatment with enalapril, exercise duration and coronary flow reserve improved, plasma NO_x levels increased, and plasma ADMA decreased (Chen et al., 2002). Long-term ACE inhibitor treatment with enalapril improved coronary microvascular function as well as myocardial ischemia in patients with syndrome X, possibly associated with the improvement of endothelial NO bioavailability with the reduction of plasma ADMA levels. According to Hornig et al. (2001), 4 weeks of therapy with ramipril or losartan improved endothelial function to a similar extent in patients with coronary artery disease by increasing the bioavailability of NO that may be related to reduction of oxidative stress within the arterial wall, mediated in part by increased extracellular SOD. There was evidence supporting the concept that oxidative stress may contribute not only to endothelial dysfunction but also to coronary artery disease activity in patients with documented coronary artery disease (Heizer et al., 2001). The ANG II-induced contraction of human coronary microarteries was attenuated by irbesartan and potentiated by PD123319; the potentiation was larger in older donors and was not observed in the presence of L-NAME or HOE-140 and

after removal of the endothelium, suggesting that AT_2 receptor-mediated human coronary arteriolar dilatation is mediated by B_2 receptors and NO, and the contribution increases with age (Batenburg et al., 2004). However, the unexpected data about the involvement of B_2 receptors in this mechanism have not actually been verified.

The heart in patients with unstable angina undergoing coronary bypass surgery produced ANG II in a greater amount than in patients with stable angina undergoing the surgery. Ventricular biopsy samples from the unstable angina patients showed numerous lymphocytes, macrophages, and endothelial cells, and they had overexpression of angiotensinogen, ACE, and AT_1 receptor genes as well as up-regulation of tumor necrosis factor- α , interferon- γ , and iNOS, indicating that locally generated ANG II seems to amplify the immuno-mediated inflammatory process of coronary microvessels occurring in unstable angina (Neri Serneri et al., 2004).

B. Renovascular Response

The renal vasodilator response to L-arginine, a substrate of NO synthesis, observed in normotensive subjects was abolished in patients with untreated hypertension and restored only in the group treated with an ACE inhibitor, suggesting that abnormal renal resistance may underlie essential hypertension (Mimran et al., 1995). Treatment of patients with essential hypertension for 12 weeks with imidapril increased L-arginine-induced renovascular relaxation and urinary excretion of NO_x , whereas amlodipine had no effect, indicating that ACE inhibition improves impaired endothelium-dependent renovascular relaxation in hypertensive patients due to the increase in NO production and that the reduction in blood pressure with a Ca^{2+} antagonist does not play a role in the potentiation of the L-arginine/NO-mediated effects (Higashi et al., 1998). Delles et al. (2002) provided evidence that, in contrast to the effects of either substance alone, a combination of a half dose of eprosartan with a half dose of enalapril had a prominent effect on renal perfusion in patients with mild hypertension, suggesting that the effects of eprosartan on renal plasma flow are mediated, at least in part, by an increased bioavailability of NO in the renal vasculature. In patients with IgA nephropathy, treatment with enalapril and losartan did not affect GFR but increased effective renal plasma flow and blood NO levels; in healthy control subjects, neither drug was able to increase blood NO levels (Roccatello et al., 2000). This NO increase could contribute to changes of effective renal plasma flow in renal disease states. However, in patients with essential hypertension, endogenous NO may contribute to the regulation of GFR, since amlodipine, a relatively afferent arteriolar dilator, attenuated the L-NMMA-induced reduction of renal blood flow and increased GFR, whereas valsartan, a relatively efferent arteriolar dilator, did not affect the L-NMMA-induced action

and GFR (Delles et al., 2004). In hypertensive patients with an activated renin-ANG system, unopposed activity of ANG II was not involved in the L-NAME-induced pressor response and renal vasoconstrictor response, whereas the L-NAME-induced decrease in GFR was enhanced, indicating a greater dependence of GFR on NO-mediated vasodilator tone during sodium depletion (Van der Linde et al., 2003). In patients with hepatic cirrhosis and portal hypertension, GFR and effective renal plasma flow were lower than in the control subjects, and, under basal conditions, cyclic GMP and NO levels in plasma and urine were higher; the renal plasma flow change was more marked in the patient group and the GFR values were similar in both groups (Rodriguez et al., 1999). It was concluded that the increased cyclic GMP and NO levels in plasma and urine imply a maintained vasodilatory action that may at least partly compensate for the vasoconstrictor effect of ANG II in patients with hepatic cirrhosis and portal hypertension. Wierema et al. (2001) found that in patients with unilateral renal artery stenosis, L-NMMA did not affect mean renal blood flow in the stenotic kidney but reduced it in the nonstenotic kidney; in patients with bilateral renal artery stenosis, L-NMMA reduced the renal blood flow. In the nonstenotic kidney in unilateral renal artery stenosis, NO bioavailability increased. Therefore, it was suggested that a compensatory mechanism, regulated by NO and possibly ANG II, may preserve renal function.

According to Lansang and Hollenberg (2002), in three groups of subjects, those with type 2 diabetes and nephropathy, those with type 1 diabetes without nephropathy, and healthy volunteers subjected to short-term hyperglycemia, baseline renal plasma flow was positively correlated with the renal plasma flow response to blocking the renin-ANG system. It was suggested that there was a link between the renal vasodilator response, mediated by NO, and the activation of the intrarenal renin-ANG system. In the VIVALDI trial, the ability of telmisartan and valsartan to reduce the progression of diabetic nephropathy (associated with proteinuria) in a large cohort of patients with type 2 diabetes mellitus during 1 year of treatment was studied (Boger et al., 2005). The effects of telmisartan on plasma levels of ADMA and urinary excretion rates of 8-iso-PGF $_{2\alpha}$, a novel marker of oxidative stress, will enhance our understanding of the roles of dysfunctional NO metabolism in the pathogenesis of end-organ damage and its prevention by pharmacotherapy with ARB.

C. Forearm and Other Regional Blood Flow Responses

In healthy subjects, baseline forearm blood flow remained unchanged with indomethacin and losartan, but was decreased by L-NMMA; ANG II-induced vasoconstriction was unaffected by indomethacin and L-NMME but was inhibited by losartan, suggesting that neither endogenous ANG II nor cyclooxygenase products play a role in the control of forearm vascular tone in healthy

subjects, whereas endogenous NO production does (Baan et al., 1997). During a "free" NO system, forearm blood flow decreased upon ANG II infusion in healthy subjects, whereas during an "NO clamp," a balanced coinfusion of L-NMMA and sodium nitroprusside, the vasoconstriction was enhanced; ANG II-induced vasoconstriction was attenuated by vitamin C, suggesting a direct ANG II-associated stimulation of endothelial NO and oxygen radicals in humans (Dijkhorst-Oei et al., 1999). Before applying the NO clamp, ANG II caused reductions of forearm blood flow in healthy subjects to a greater extent than in patients with preascitic cirrhosis, whereas during the NO clamp, ANG II-induced vasoconstriction was enhanced in cirrhotic patients but unchanged in control subjects (Helmy et al., 2003). The reduced vasoconstriction to ANG II in cirrhotic patients may be due to enhanced NO generation mediated by ANG II. The vasoconstrictor response of the forearm vasculature to ANG II was greater in obese men with a positive family history of hypertension than in nonobese men, whereas the endothelium-dependent forearm blood flow increase in response to ACh was similar (Nielsen et al., 2004).

ACE inhibitors improved flow-dependent vasodilatation in skeletal muscle that was impaired in patients with chronic heart failure, possibly by increasing endothelial synthesis of NO and/or PGs (Drexler et al., 1995). ACE inhibition also increased leg blood flow in patients with diabetes and hypertension (Giugliano et al., 1998), femoral blood flow in patients with coronary artery disease (Prasad et al., 1999), and forearm blood flow in healthy volunteers (Haefeli et al., 1997), patients with essential hypertension (Higashi et al., 2001, 2002; On et al., 2002), and chronic cigarette smokers (Butler et al., 2001), possibly by increased NO production and release from the endothelium. In contrast, Creager and Roddy (1994) reported that antihypertensive therapy for up to 7 to 8 weeks with captopril and enalapril does not improve endothelium-dependent vasodilatation in hypertensive patients. There was evidence suggesting that the genotypes associated with an increased risk for esophageal varices is linked to higher plasma levels of NO and reduced levels of ACE, and these genotypes could have a vasodilatory effect in the systemic and splanchnic circulation, thus favoring the development of portocollaterals (Coto et al., 2001).

In patients with essential hypertension, after treatment with valsartan, the decrease in forearm blood flow in response to L-NMMA was augmented, suggesting that the AT₁ receptor blockade improves basal NO production and release (Klingbeil et al., 2003). Sim et al. (2004) drew a similar conclusion that losartan increased the vasoconstriction in response to L-NMMA and tended to improve the vasodilator response to ACh, from findings obtained in normal, salt-replete men. In normotensive subjects, L-NMMA infusion decreased retinal capillary flow and flickering light that stimulates NO release

increased mean blood flow velocity in the central retinal artery; in contrast, no change to these provocative tests was seen in hypertensive patients, in whom treatment with candesartan restored a normal pattern of reactivity (Delles et al., 2004).

D. Blood Pressure Response

In patients with essential hypertension, intravenously infused L-NMMA increased mean arterial pressure and systemic vascular resistance, whereas cardiac output was decreased; enalapril decreased blood pressure, whereas the L-NMMA-induced increase in systemic vascular resistance was potentiated by ACE inhibition, indicating that antihypertensive therapy with enalapril increases NO dependence of systemic vascular tone (Dijkhorst-Oei et al., 1998). Antihypertensive therapy with enalapril seems to increase the NO dependence of systemic vascular tone; however, this phenomenon cannot be observed in the renal circulation. Imidapril augmented the forearm blood flow response to reactive hyperemia after 28 weeks of treatment in the mild and moderate hypertensive groups but not in the severe hypertensive group; infusion of L-NMMA abolished the enhancement of reactive hyperemia in the mild and moderate hypertensive groups treated with imidapril, implying that the effect of imidapril on endothelial function is affected by the severity of hypertension and that ACE inhibitor-induced augmentation of reactive hyperemia may be due to increased NO production (Higashi et al., (2002).

On the basis of studies with isolated internal thoracic artery rings from hypertensive and normotensive patients, Deja et al. (2005) provided evidence that therapy with ACE inhibitors seems to improve endothelial function of hypertensive patients mainly by enhancing the vasodilator responses mediated by EDHF but not by NO or PGI₂.

E. Other Responses

Brown et al. (2006) provided evidence from studies on normotensive salt-replete subjects treated for 4 weeks with L-arginine, ramipril, or L-arginine plus ramipril that during ACE inhibition, endogenous NO decreases plasminogen activator inhibitor-1 antigen and improves fibrinolytic balance.

VIII. Interaction between Endothelial Nitric Oxide and Angiotensin II in Experimental Animals

A. Systemic Blood Pressure

Ribeiro et al. (1992) obtained data suggesting that chronic NO blockade may constitute a new model of severe arterial hypertension in rats and that activation of the renin-ANG system may account, at least in part, for the vasoconstrictor activity after NO synthesis inhibition. In conscious rats, chronic administration of L-

NAME produced sustained hypertension and increased renal vascular resistance; acute blockade of AT₁ receptors with losartan had little effect, acute blockade of the α_1 -adrenoceptor produced moderate falls in blood pressure, and the combination of AT₁ and α_1 -receptor blockade profoundly lowered blood pressure, suggesting that in the sustained phase of chronic NO blockade, the hypertension is largely due to the combined activities of AT₁ and α_1 -adrenoceptor stimulation (Qiu et al., 1994). Sigmon and Beierwaltes (1998) found that losartan did not attenuate the systemic and renal vasoconstriction in response to L-NAME in two-kidney-one-clip hypertensive rats and suggested that NO contributes dilator tone to buffer the hypertension and maintains perfusion in kidneys by counterbalancing ANG-independent vasoconstriction. On the other hand, in normal rats made hypertensive by chronic inhibition of NO, renal blood flow and papillary blood flow were lower than in the control subjects, and acute and chronic administration of losartan decreased mean arterial pressure and increased renal blood flow, indicating that the arterial hypertension, renal vasoconstriction, and reduced renal blood flow present in chronic NO-deficient hypertensive rats may be due to the effects of ANG II, via stimulation of AT₁ receptors (Ortiz et al., 1998). There was evidence that NO counteracts the vasoconstrictor effect of ANG II in normotensive rats, whereas this protective mechanism is impaired in renovascular hypertensive rats (Sanchez-Mendoza et al., 1998). In rats with renovascular hypertension, treatment with losartan prevented increased vascular responses to ANG II, and this effect was associated with restoration of NOS mRNA expression and NOS activity; furthermore, ANG-dependent NO release was potentiated by losartan treatment (Martinez et al., 2002). The data suggest that during development of hypertension, ANG II down-regulates NOS mRNA expression, blunting NO vasodilator tone and increasing vascular sensitivity to vasoconstrictor agents. In uninephrectomized rats made hypertensive by administration of L-NAME, DOCA-salt, or L-NAME plus DOCA-salt, blood pressure was normalized by losartan independently of its effects on endothelial functions, and in DOCA-salt-hypertensive rats, losartan normalized the phenylephrine hyperreactivity through an endothelium-dependent mechanism (K-Laflamme et al., 1998). Both NO and ANG II seem to play a role in the early development of hypertension and organ hypertrophy in DOCA hypertension. It was suggested that an impaired NO counterregulatory system in the outer medulla of Dahl salt-sensitive rats makes them more susceptible to the hypertensive actions of small elevations in ANG II (Szentivanyi et al., 2002).

Symons et al. (1999b) provided evidence that NO opposed ANG II-induced increases in arterial pressure and in renal and skeletal muscle resistance during treadmill running in normal rats and rats with heart failure. In ANG II-infused hypertensive rats, decreases in renal

blood flow and GFR were greater and Ca²⁺-dependent NOS activity was greater in the cortex, but not the medulla, compared with control rats, the effect being associated with marked activation of eNOS protein levels and smaller increases in nNOS protein levels, supporting the hypothesis that cortical Ca²⁺-dependent NOS, primarily eNOS, is stimulated during the early phase of ANG-induced hypertension (Navar et al., 2000). Systemic or intracerebroventricular administration of losartan not only inhibited the pressor response to footshocks applied to rats but resulted in vasodepression; PD123319 did not alter the response to footshocks, but simultaneous blockade of AT₁ and AT₂ receptors eliminated the vasodepressor response unmasked in losartan-pretreated rats (Sosa-Canache et al., 2000). The depressor response to footshocks in losartan-treated rats was blunted by L-NAME or icatibant, suggesting a role for AT₂ receptor in the regulation of arterial blood pressure, possibly through the release of peripheral or brain NO and kinins. Abdominal aortic banding in mice elevated blood pressure and plasma renin concentration, together with up-regulation of the AT₂ receptor in the aorta; this effect of banding was abolished by losartan administration (Hiyoshi et al., 2004). In normal dogs, intrarenal ANG II infusion decreased renal plasma flow and GFR and increased mean arterial pressure, whereas in dogs with chronic intrarenal NOS blockade by L-NAME, decreases in renal plasma flow and GFR and an increase in arterial pressure associated with ANG II were blunted, indicating that chronic inhibition of NO synthesis within the kidney seems to attenuate the long-term renal and arterial pressure responses by ANG II (Schnackenberg et al., 1997).

In bile duct-ligated cirrhotic rats with portal hypertension, treatment for 1 week with losartan decreased portal pressure and ameliorated hyperdynamic circulation associated with a blunted vascular response to L-NAME infusion, and aortic eNOS protein expression was reduced (Yang et al., 2002). In addition to the suppression of the renin-ANG axis, the reduced eNOS protein expression may play a partial role in the mechanism of action of losartan in cirrhotic rats. In anesthetized rats, after hemorrhage, mean arterial pressure fell and was accompanied by a reduction of mesenteric blood flow; systemic pressor and mesenteric vasoconstrictor responses to ANG II and the hypotensive effect of telmisartan became blunted after hemorrhage, and L-NAME restored the systemic pressor response to ANG II (Pieber et al., 1999). The impaired vascular responses to ANG II at an early stage of hemorrhagic hypotension may involve NO.

B. Regional Blood Flow

In conscious rats, acute ANG II infusion reduced stomach and hind limb vascular conductance only after L-NAME, indicating that NO opposes ANG II-induced vasoconstriction in these circulations. In contrast, ANG

II decreased vascular conductance in the kidneys and small and large intestine regardless of whether NOS inhibition was present; therefore, the constrictor effects of L-NAME and ANG II are additive in these vascular beds (Symons et al., 1999a). The ability of NO to oppose ANG II-induced vasoconstriction is not homogeneous among various regional circulations. Nishiyama et al. (2001) noted, using radioactive microspheres, that conscious rats receiving s.c. infusions of ANG II showed higher mean arterial pressure and total peripheral resistance and lower blood flow rates in the brain, spleen, large intestine, and skin, without any change in the lung, heart, liver, kidney, adrenal gland, small intestine, and skeletal muscle, compared with vehicle-infused rats. Treating ANG II-infused rats with L-NAME caused widespread increases in regional vascular resistance and reduced blood flow rates only in the kidney and skeletal muscle; an NO donor partially reversed blood flow rates in both organs, suggesting that NO counteracts, at least in part, the vasoconstrictor effects of elevated ANG II levels in renal and skeletal muscle vascular beds, and thus NO is an important modulator in the regulation of blood flow to these organs during the development of ANG II-induced hypertension.

In anesthetized dogs, blocking ANG II and endothelin (ET) caused a synergistic fall in mean arterial pressure. Pulmonary vascular resistance was not altered by blocking ANG II, ET, or both but increased during NO and PG blockade, when ET receptors had not been blocked. In the kidney, blocking ANG II increased regional blood flow and GFR, whereas blocking ET did not alter regional blood flow but decreased GFR, and inhibiting NO and PG decreased regional blood flow when ANG II or ET was blocked. ANG II or ET blockade did not alter iliac blood flow, and inhibiting NO and PG decreased iliac blood flow when ANG II or ET was blocked (Gomez-Alamillo et al., 2003). These results suggest that regional differences in the interactions between endogenous ANG II, ET, NO, and PG are important determinants in systemic, pulmonary, and regional hemodynamics.

C. Renal Vasculature

1. In Vivo Study in Rats. In anesthetized rats, L-NAME increased blood pressure and decreased renal blood flow; in rats pretreated with Dup 753 or enalaprilat, L-NAME increased blood pressure to an extent similar to that in untreated rats, but renal blood flow was unchanged. In addition, in enalaprilat-treated rats, L-NAME caused a transient increase in renal blood flow (Sigmon et al., 1992). These findings suggest that renal EDRF, possibly NO, buffers the vasoconstrictor influence of endogenous ANG, particularly in the kidney. In two-kidney, one clip hypertensive rats, L-NAME decreased renal blood flow in the nonclipped kidney and did not change the flow in clipped kidney; treatment of the hypertensive rats with losartan did not change blood

flow in the nonclipped kidney, but normalized it in the clipped one. With losartan, L-NAME decreased renal blood flow in the nonclipped kidney but did not influence it in the clipped kidney (Sigmon and Beierwaltes, 1993b). Therefore, NO-induced vasodilatation seems to be a regulatory response to maintain contralateral renal perfusion despite elevated ANG after renal artery stenosis in two-kidney, one clip hypertension. Sigmon et al. (1993) suggested that EDRF is a more important regulator of renal blood flow than of femoral blood flow in rats. From studies on rats receiving short-term (30–90 min i.v.) or prolonged (5–6 days s.c.) ANG II infusions that caused equivalent changes in blood pressure and renal blood flow, Deng et al. (1996) noted that short-term ANG II infusions increased NO generation and the dependence of the renal circulation on NO, whereas ACh-induced NO release was enhanced selectively during long-term ANG II infusions. Thus, they suggested that during long-term ANG II, renal NO release may become uncoupled from shear stress yet remains highly responsive to receptor-mediated stimulation. However, the data obtained by Parekh et al. (1996) indicated that the antagonism by NO against vasoconstriction in the rat kidney in response to acute ANG II infusions does not seem to be due to a constrictor-induced production of NO. Madrid et al. (1997b) provided evidence supporting the view that renal cortical and medullary vasoconstriction induced by a low dose of L-NAME is caused by potentiation of the vasoconstrictor influence of ANG II and renal sympathetic nerves, whereas a higher dose of L-NAME induces a renal cortical vasoconstriction through potentiation of the renin-ANG system, and the fall of papillary blood flow seems to be caused by NO suppression. It was reported that short-term NOS blockade caused a pressor and renal vasoconstrictor response, without affecting renal autoregulation, and losartan restored the effects of mild NOS inhibition but failed to exert vasorelaxation during strong NOS blockade in rats (Turkstra et al., 1998a). L-NA-induced reductions in renal blood flow were greater in ANG II-infused hypertensive rats than in controls, despite the fact that basal renal blood flow was similar in hypertensive and control rats, suggesting that a compensatory increase in NO activity partially counteracts the vasoconstrictor influence of elevated ANG II levels to regulate renal hemodynamics (Chin et al., 1998). In uninephrectomized rats exposed to infusions of ANG II for 5 days, intravenous ANG II did not change cortical or medullary blood flow or mean arterial pressure, whereas rats with blunted medullary NOS activity by medullary interstitial L-NAME infusion responded to intravenous ANG II with a reduction in medullary blood flow and an increase in arterial pressure, suggesting that the relative insensitivity of rats to long-term elevations of circulating ANG II is due to the potent counterregulatory actions of the NO system, especially within the renal medulla (Szentivanyi et al., 1999). Intravenous infusions of subpressor

dose of ANG II did not alter renal cortical and medullary blood flow or medullary partial O₂ pressure; under treatment with L-NAME in renal medullary interstitial space, ANG II decreased medullary blood flow and O₂ pressure, but it had no effect on cortical blood flow (Zou et al., 1998). ANG II infusion increased tissue NO concentration in the renal cortex and medulla. The authors concluded that a small elevation of circulating ANG II levels increases medullary NO production, which seems to play an important role in buffering against the vasoconstrictor effects of this peptide. Badzyska et al. (2004) found that ANG II infusion decreased the tissue NO signal in the renal cortex and medulla in rats, and tempol prevented the effect on medullary, but not cortical, NO. Tissue superoxide generation stimulated by the peptide may reduce local bioavailability of NO.

Clayton et al. (1998) suggested that the renal hemodynamic effects of ANG II in the rat kidney are modulated by NO and PGs. Intravenous administration of ANG II did not affect inner medullary blood flow in control rats and those pretreated with L-NAME but decreased it in indomethacin-pretreated rats, indicating that within the inner medulla, PGs, but not NO, seem to counteract the vasopressor effect of circulating ANG II (Badzyska et al., 2003).

Rudenstam et al. (2000) provided evidence suggesting that the increase in papillary blood flow in rats to ANG II seen after enalapril treatment is mediated possibly via effects of the ACE inhibitor on kinin breakdown and NO formation. In SHR, low-dose ANG II reduced renal medullary blood flow, and this effect was abolished by L-arginine given into the renal medulla; in SHR treated with enalapril for 10 weeks, ANG II did not alter the blood flow, but sensitivity to ANG II was unmasked after L-NAME was infused into the renal medulla (Dukacz et al., 2001). In addition, endothelium-dependent vasodilatation of aortic rings was greater in enalapril-treated SHR compared with control SHR. These results indicate that sensitivity to ANG II in SHR may be due to an impaired counterregulatory effect of NO and that long-term treatment with the ACE inhibitor improves endothelial function and decreases the sensitivity of medullary blood flow to ANG II. Treatment of renovascular hypertensive rats with losartan prevented the increased vascular response to ANG II, and this effect was associated with restoration of NOS mRNA expression and NOS activity; furthermore, ANG II-dependent NO release in hypertensive rats was potentiated by losartan (Martinez et al., 2002). During development of hypertension, ANG II seems to down-regulate NOS mRNA expression, blunting NO vasodilatory tone and increasing vascular sensitivity to vasoconstrictor agents in the renal circulation. Kidneys of L-NAME-treated rats (for 19 days) had fewer normal glomeruli and vasculatures in the cortex and medulla than those of control rats; losartan normalized the values to control levels, suggesting that chronic NOS inhibition produces a generalized rar-

efaction of renal capillaries and that the reduction in vasculature is mediated by ANG II through AT₁ receptors (Fortepiani et al., 2003).

Acute intrarenal administration of the nNOS-specific inhibitor *S*-methyl-L-thiocitrulline resulted in a decrease in renal plasma flow, GFR, and sodium excretion in control rats, the effects being prevented by candesartan, whereas in ANG II-infused hypertensive rats, the nNOS inhibitor did not decrease renal plasma flow, GFR, and sodium excretion (Cervenka et al., 2001). These authors suggested that in normotensive rats, nNOS-derived NO counteracts ANG II-mediated vasoconstriction in the pre- and postglomerular microcirculation, and hypertensive rats exhibit an impaired ability to release NO by nNOS. However, authors from the same group (Vaneckova et al., 2002) concluded that in rats consuming a low-salt diet, NO derived by nNOS does not seem to participate in counteracting the vasoconstrictor influences of elevated circulating and/or intrarenal ANG II levels. Intrarenal injections of ANG II decreased renal blood flow in rats treated for 1 week with the nNOS inhibitor 7-NI to a lesser extent than in control rats, suggesting that the diminished blood flow response to ANG II after nNOS blockade may be due to down-regulation of ANG II receptors (Ollerstam et al., 2002).

Renal artery infusions of ANG IV produced an increase in renal cortical blood flow without altering systemic blood pressure, and pretreatment with divalinal ANG II or L-NMMA blocked the effect of ANG IV; the infusion of ANG II decreased cortical blood flow, accompanied by an elevation in systemic blood pressure, and divalinal ANG II failed to influence the effects of ANG II, indicating that ANG IV exerts renal vasodilatation by acting on AT₄ receptor subtypes and releasing NO (Coleman et al., 1998). On the other hand, Duke et al. (2005) obtained results suggesting that AT₁ receptors mediate renal medullary vasodilatation, possibly associated with the release of NO and PGs, which is opposed by AT₂ receptor activation, and in rats with two-kidney, one-clip hypertension, AT₂-receptor activation tonically constricts the medullary circulation.

In pregnant rats, the renal circulation had a reduced sensitivity to ANG II compared with that in nonpregnant rats, and the renal response to ANG II in the L-NAME-treated pregnant rats was similar to that in control pregnant rats (Novak et al., 1997). In rats with experimental high-output congestive heart failure, endothelium-dependent (by ACh) and -independent increases in renal blood flow (by the NO donor *S*-nitroso-*N*-acetylpenicillamine) were attenuated; likewise, the effects of ACh on urinary sodium and cyclic GMP excretion were also diminished in rats with heart failure. Administration of ARB restored the renal vasodilator responses to ACh in heart failure rats (Abassi et al., 1997). This impairment in NO-mediated renal vasodilatation in experimental congestive heart failure seems to

be related to increased activity of the renin-ANG system. According to Komers et al. (2000), compared with normal rats, diabetic rats demonstrated enhanced renal hemodynamic responses to nNOS inhibition by 7-NI and *S*-methyl-L-thiocitrulline, suggesting increased basal activity of nNOS in the diabetic kidney; furthermore, the renal responses in diabetic, but not normal, rats were attenuated by losartan, implicating ANG II as an important modulator of the NO pathway in diabetes. Ajayi et al. (2001) noted that endogenous NO homeostatically opposed ANG II/phenylephrine-mediated renal vasoconstriction and that ACh caused a profound paradoxical fall in renal cortical perfusion in rats with acute renal failure, but not in healthy rats. Their evidence led them to speculate that the paradoxical fall in renal cortical perfusion induced by ACh in rats with renal failure results from the formation of peroxynitrite, which acts as a renal vasoconstrictor, after the combination of ischemia-generated superoxide anions with endothelial NO released by ACh.

2. *In Vivo Study in Mice.* AT₂ receptor-deficient mice showed up-regulation of nNOS and iNOS but not eNOS, and DOCA-salt increased iNOS expression and mean arterial pressure more in knockout mice than in wild-type mice; iNOS blockade did not lower blood pressure (Obst et al., 2004). DOCA-salt decreased renal blood flow and the glomerular filtration rate in both groups. The authors concluded that AT₂ receptor deletion and concomitant up-regulation of the AT₁ receptor seem to be associated with up-regulation of nNOS and iNOS but that iNOS may not be involved in the hemodynamics, although it may contribute to organ damage. Kihara et al. (2006) noted that expression and activity of eNOS were lower in the renal vessels of angiotensinogen-gene knockout mice (showing sodium/water depletion and severe hypotension) compared with wild-type mice; dietary salt loading enhanced renal eNOS levels and increased blood pressure in knockout mice, whereas, in contrast, in wild-type mice, altered salt intake or hydralazine had no effect on renal eNOS levels. It was suggested that perfusion pressure plays an essential role in maintaining renal vascular eNOS activity, whereas ANG II plays a supportive role, especially when renal circulation is impaired. During the infusion of L-NAME in anesthetized wild-type and nNOS null mutant mice, both types of mice showed increased arterial blood pressure and decreased blood flow in the renal cortex and medulla; in contrast, blood pressure and renal blood flow were unaffected after L-NAME administration to eNOS-null mutant mice, indicating that NO derived from eNOS regulates baseline vascular resistance in mice (Mattson and Meister, 2005). Furthermore, intravenous ANG II led to a decrease in renal cortical blood flow in wild-type and eNOS or nNOS knockout mice; however, ANG II increased medullary blood flow in wild-type and eNOS knockout mice but did not elicit such an effect in nNOS knockout mice and in

wild-type and eNOS knockout mice treated with L-NAME, suggesting that NO produced by nNOS mediates an increase in medullary blood flow in response to ANG II.

3. *In Vivo Study in Dogs, Sheep, Pigs, and Rabbits.*

Schnackenberg et al. (1995) found that intrarenal infusion of ANG II in anesthetized dogs had a predominant effect on postglomerular resistance, whereas in dogs treated with L-NAME, ANG II had a profound effect on preglomerular resistance, suggesting that NO may play an important role in protecting mainly preglomerular vessels and to a lesser extent postglomerular vessels from ANG II-induced renal vasoconstriction. The renal blood flow response to intrarenal injection of ANG II in anesthetized dogs was augmented by L-NA, and simultaneous infusion of L-arginine prevented the potentiating effect of L-NA; during infusion of sodium nitroprusside, an NO donor, the L-NA-induced potentiation of ANG II actions disappeared, suggesting that basally released NO plays an important role in the regulation of renal hemodynamics by modulating the renal vasoconstrictor actions of ANG II (Aki et al., 1997). A similar conclusion was also obtained by Berthold et al. (1999) from studies on conscious dogs, who showed thattrandolaprilat caused an increase in renal blood flow that was suppressed by treatment with L-NAME; however, when renal vascular NO concentrations were clamped at control levels during NOS inhibition by infusing the NO donor, the vasodilator response to the ACE inhibitor was restored. Kramer et al. (2004) noted that an intrarenal arterial injection of L-NAME led to a decrease in total renal blood flow and single nephron glomerular blood flow, measured by micropuncture, and the increase in arteriolar resistance was more pronounced at the efferent arterioles than at the afferent ones; indomethacin had no effect on glomerular hemodynamics and the effects of L-NAME were unaltered by pretreatment with indomethacin and the ARB. Therefore, the authors concluded that the tonic activity of intrarenal NOS seems to play an important role in maintaining glomerular hemodynamics in the canine kidney. According to Llinas et al. (1997), renal vasoconstriction and increased proximal sodium reabsorption during the reduction of NO and PG synthesis were induced by increasing endogenous ANG II levels in dogs. It was suggested that endogenous intrarenal NO and PGs may serve as homeostatic mediators of ANG II effects when the intrarenal levels are elevated, as occurs in salt-sensitive hypertension. Matsuda et al. (1999) provided evidence that zonal heterogeneity in renal bradykinin/NO levels and segmental differences in reactivity to bradykinin contribute to the diverse responsiveness of canine renal afferent and efferent arterioles to cilazaprilat. Matsuda et al. (2004) also suggested that cilazaprilat exerts multiple vasodilator mechanisms; blockade of ANG II activity seems to be a dominant mechanism in superficial afferent arterioles, whereas the bradykinin-

induced NO acts on superficial efferent arterioles and juxtamedullary afferent and efferent arterioles. A putative EDHF may be an additional mechanism for the ACE inhibitor-induced vasodilatation of juxtamedullary afferent arterioles in dogs in vivo.

In conscious sheep, intravenous or intrarenal infusions of cortisol elicited an increase in renal blood flow that was not prevented by renal vasoconstriction with intrarenal ANG II but was attenuated by L-NA (De Matteo and May, 1997). In fetal sheep (aged 116–118 days), injection of L-NA caused a rise in mean blood pressure and a decrease in renal blood flow velocity and tended to reduce the vascular response to ACh; chronic treatment with L-NA enhanced the pressor response to ANG II, suggesting that endothelial production of NO maintains normal fetal blood pressure and renal vascular resistance (Yu et al., 2002). Intrarenal infusion of L-NAME led to a greater decrease in renal blood flow in fetal piglets (aged 3 weeks) than in adult pigs; ARB increased renal blood flow in the piglet but did not alter it in the adult (Solhaug et al., 1996b). The authors concluded that ANG II may be a more important vasoconstrictor in the developing kidney and that NO is a more important regulator of renal function in the developing kidney through modulation of the renin-ANG system.

In anesthetized rabbits, ANG II increased medullary perfusion in the face of reduced cortical perfusion; administration of indomethacin caused reductions in total renal blood flow, cortical perfusion, and medullary perfusion, and abolished the increase in medullary perfusion induced by ANG II, suggesting that vasodilator cyclooxygenase products contribute to the maintenance of resting renal vascular tone and also mediate the ANG II-induced increase in medullary perfusion (Oliver et al., 2002). Candesartan blunted electrical renal nerve stimulation-induced reductions in renal blood flow, cortical perfusion, and medullary perfusion, and L-NA enhanced the inhibitory responses to nerve stimulation of renal blood flow, cortical perfusion, and medullary perfusion; renal arterial infusion of ANG II enhanced responses of medullary perfusion to nerve stimulation in L-NA treated but not in vehicle-treated rabbits (Rajapakse et al., 2005). It seems that endogenous ANG II enhances, whereas NO blunts, neurally mediated vasoconstriction in the renal cortical and medullary circulations.

4. In Vitro Study. In the in vitro blood-perfused juxtamedullary nephron from rats, L-NA elicited afferent and efferent arteriolar constriction and blocked the vasodilator response to ACh; the vasoconstrictor effect of L-NA was attenuated in kidneys from rats pretreated with enalaprilat or losartan, suggesting that EDRF is continuously released in a quantity sufficient to affect both afferent and efferent arterioles in vitro and that EDRF seems to interact with the renin-ANG system to control the arteriolar resistance (Ohishi et al., 1992). The ANG II-induced reduction of afferent and efferent arteriolar diameters was enhanced during L-NA treat-

ment in the in vitro blood-perfused juxtamedullary nephron; however, this enhancement was not observed when tissue NO activity was fixed at basal levels by exposure to sodium nitroprusside, indicating that endogenous NO modulates the vasoconstrictor effect of ANG II in both afferent and efferent arterioles and that this process does not seem to require stimulation of NO synthesis (Ikenaga et al., 1996). In isolated microperfused rabbit afferent arterioles, ANG II-induced vasoconstriction was weaker in the presence than in the absence of luminal flow; disrupting the endothelium augmented the action of ANG II in free-flow but not nonflow arterioles, and treatment with L-NAME or indomethacin augmented the ANG II action more in free-flow than in nonflow arterioles, thus abolishing the differences between them (Juncos et al., 1996). Therefore, it was suggested that intraluminal flow modulates the vasoconstrictor action of ANG II in afferent arterioles via endothelium-derived NO and PGs. On the other hand, NOS inhibitors had no effect on efferent arteriolar constriction induced by ANG II (Ito et al., 1997). In preparations in which afferent arterioles and the macula densa were microperfused, inhibition of macula densa NOS augmented the arteriolar constriction when the NaCl concentration at the macula densa was high, suggesting that the macula densa produces NO.

Ichihara et al. (1998) obtained evidence indicating that nNOS exerts a differential modulatory action on the rat juxtamedullary microvasculature by enhancing efferent, but not afferent, arteriolar responsiveness to ANG II. Renal arterial injection of ANG II decreased renal blood flow to a great extent in control rats than in rats treated for 1 week with the nNOS inhibitor 7-NI, and it increased cytosolic Ca^{2+} concentrations in smooth muscle cells from afferent arterioles of control rats but not those of nNOS inhibitor-treated rats (Ollerstam et al., 2002). Their explanation was that ANG II receptors may be down-regulated by chronic nNOS inhibition.

In rat microvessels of the isolated perfused hydronephrotic kidney, insulin had no effect on basal vascular diameter but reversed the ANG II/norepinephrine-induced tone of afferent and efferent arterioles, with the vasodilator response being blocked by L-NA, indicating that the action of insulin to dilate the renal microvasculature, only seen during ANG/norepinephrine-induced vasoconstriction but not under basal conditions, may be mediated by NO (Hayashi et al., 1997). Authors from the same group (Ozawa et al., 2004) obtained data indicating that free radicals contribute to ANG II-induced constriction to a greater magnitude than contractions in response to norepinephrine and KCl in afferent arterioles of isolated perfused rat hydronephrotic kidneys, and they suggested that the heterogeneity of the responsiveness to tempol is attributed to both the level of free radicals produced and sensitivity of the underlying vasoconstrictions to NO. Acute constriction of the descending vasa recta was diminished, and the NO generation

rate was increased by chronic ANG II infusion for 11 to 13 days in rats; superoxide levels in vasa recta from ANG II-perfused rats were similar to those in controls, and tempol increased NO generation more in ANG II-perfused rats. Furthermore, the cytosolic Ca^{2+} response to ACh in the vasa recta endothelium was diminished by chronic ANG II treatment, but the capacity of ACh to increase NO generation was unaltered (Zhang et al., 2005). It was suggested that generation of superoxide from the descending vasa recta is not affected by chronic ANG exposure, but basal NO synthesis is increased.

D. Coronary Vasculature and the Heart

1. Coronary Vasculature. In isolated perfused rabbit hearts, ANG II infusion induced an initial increase followed by a decrease in coronary perfusion pressure until a plateau was reached, and the peptide also augmented PGI_2 release from the coronary vascular bed; these effects of ANG II were inhibited by an AT_1 receptor antagonist but not by an AT_2 receptor antagonist (Porsti et al., 1993). A cyclooxygenase inhibitor had no effect on the ANG II-induced changes in perfusion pressure, and L-NA potentiated the vasoconstriction induced by ANG II. The effects of ANG II in the rabbit heart seem to be mediated via the AT_1 receptor subtype localized in coronary endothelial and smooth muscle cells. In rings of canine isolated coronary arteries with intact endothelium, bradykinin evoked relaxations that were enhanced by perindoprilat and inhibited by L-NA; rings treated with L-NA showed hyperpolarization in smooth muscle cell membranes in response to bradykinin (Mombouli et al., 1996). The responses to endothelium-derived NO and hyperpolarizing factor were more evident in coronary arteries from exercise-trained dogs than in those from sedentary dogs, suggesting that exercise-training augments the sensitivity of the canine coronary artery to bradykinin that is responsible for endothelium-dependent dilatation. Kininogen and three ACE inhibitors increased nitrite production in coronary microvessels and reduced cardiac O_2 consumption in myocardium, with both of the effects being blocked by L-NAME, L-NA, HOE-140, or serine protease, indicating that stimulation of kinin production increases NO formation and is important in the control of cardiac O_2 consumption (Zhang et al., 1997b). The synergistic effect on NO formation was observed in canine coronary microvessels when amlodipine was combined with ACE inhibitors (Zhang et al., 2000). Zhang et al. (2003) provided evidence for the notion that ANG II at a subvasomotor level impairs endothelium-dependent, NO-mediated dilatation of porcine coronary arterioles attributable to elevated superoxide production via AT_1 receptor activation of NADPH oxidase.

In anesthetized dogs, coronary vasodilatation in response to AT_1 receptor antagonists was blunted by pretreatment with glybenclamide, a specific inhibitor of ATP-activated K^+ channels, and partly suppressed by

PD123319, but not affected by either an adenosine receptor antagonist or an NOS inhibitor, suggesting that endogenous ANG II contributes to the maintenance of basal coronary vascular tone by acting at ATP-activated K^+ channels through AT_2 receptors (Tada et al., 1997). There were findings supporting the idea that despite maintenance of a high blood pressure in SHR chronically receiving L-NAME, a low-dose of the valsartan-enalapril combination improved endothelial function and histopathology of the heart and increased coronary reserve (de Gasparo et al., 2002). Kitakaze et al. (2002) also provided evidence that the combination of an ACE inhibitor and ARB mediates greater increases in coronary blood flow and more cardioprotective effects through bradykinin-dependent mechanisms than either drug alone in dogs with myocardial ischemia. Reduced aortic and coronary flow indices in the working heart of SHR with failing hearts were improved by ramipril, furosemide, and ramipril plus furosemide, three treatment regimens enhancing the reduced Ca^{2+} ionophore-induced NO release from aortic endothelial cells. Concomitantly, ramipril and ramipril plus furosemide reduced the increased Ca^{2+} ionophore-stimulated superoxide production in the aortic endothelium and attenuated the increase in endothelial peroxynitrite concentration, which was observed in the placebo-treated SHR, suggesting that the ACE inhibitor and the loop diuretic act synergistically to enhance bioavailability of endothelium-derived NO (Linz et al., 2003). On the basis of findings obtained from eNOS-knockout and wild-type mice with chronic infusion of ADMA, Suda et al. (2004) concluded that long-term vascular effects of ADMA are not solely mediated by inhibition of endothelial NO synthesis but are also mediated by direct up-regulation of ACE and increased oxidative stress through AT_1 receptors. Talukder et al. (2004) noted that acute and chronic treatment with temocapril augmented the coronary blood flow response to bradykinin in aged control and eNOS-knockout mice, and the antihypertensive effect of ACE inhibition was greater in aged eNOS knockout mice than young eNOS knockout mice or young and aged control mice, indicating that the coronary flow response to bradykinin is preserved in aged mice even in the absence of eNOS and that an ACE inhibitor augments this response by both eNOS-dependent and -independent mechanisms.

2. Myocardium. In the heart of open-chest dogs, in which the coronary artery was perfused through an extracorporeal bypass tube, imidaprilat or cilazaprilat infused into the bypass tube increased coronary blood flow that had been reduced by partial occlusion of the tube, and each drug also raised bradykinin and NO concentrations of coronary venous blood, the effects being attenuated by HOE-140 or L-NAME; increases in cardiac bradykinin and NO levels were observed in response to imidaprilat or cilazaprilat (Kitakaze et al., 1998). ACE inhibitors seem to increase cardiac NO levels via the

accumulation of bradykinin in the ischemic myocardium. Quinaprilat reduced the infarct size of the heart in rabbits that underwent 30 min of ischemia and 48 h of reperfusion, and this effect was blocked by L-NAME; the ACE inhibitor did not affect the myocardial interstitial hydroxy radicals, as measured by 2,5-dihydroxybenzoic acid, but increased the NO_x level during ischemia and reperfusion, suggesting that quinaprilat reduces myocardial infarct size through a mechanism involving NO production (Chen et al., 2003). In a rat coronary stenosis model, myocardial perfusion, coronary endothelial NO function, and myocardial contractility were impaired, and myocardial mitochondrial respiration was exhausted; treatment with quinapril or candesartan ameliorated these parameters without modifying the epicardial coronary stenosis severity (Sato et al., 2003). Long-term treatment with quinapril resulted in improved endothelium-dependent, ACh-induced aortic relaxation in rats subjected to coronary ligation to induce myocardial infarction, which could be attributed to improvement of EDHF- but not NO/PG-mediated relaxation (Westendorp et al., 2005). Withdrawal of the therapy impaired the EDHF-mediated relaxation, suggesting that withdrawal of chronic ACE inhibition after myocardial infarction should be considered carefully, as profound endothelial dysfunction may develop rapidly. Thai et al. (2003) suggested that AT₁ receptor blockade by candesartan enhanced vasorelaxation in heart failure of infarcted rats by increasing NO bioavailability, in part via an AT₂ receptor-mediated up-regulation of eNOS protein. In isolated working rat hearts subjected to ischemia and reperfusion, losartan reduced postischemic contractile dysfunction, creatine kinase release, myocardial ultrastructural damage, and albumin extravasation and increased eNOS mRNA levels, indicating that the cardioprotective effects of AT₁ receptor blockade are likely to be associated with inducing eNOS overexpression and reducing the postischemic hyperpermeability of the coronary microcirculation (Barsotti et al., 2001). AT₂ receptor activation and signaling via bradykinin, protein kinase C, and cyclic GMP were suggested to contribute to cardioprotection associated with AT₁ receptor blockade during ischemia-reperfusion injury in dogs (Jugdutt and Balghith, 2001). On the other hand, there was evidence indicating that increased expression of eNOS in the mouse myocardium by ANG II stimulation is mediated by the calcineurin pathway and is induced by the AT₂ receptor (Ritter et al., 2003).

In obese Zucker rats treated with perindopril, there was a correlation between both the amount of vascular endothelial growth factor (VEGF) in myocardium and the number of capillaries and VEGF and eNOS expression in myocardial capillaries, suggesting that ACE inhibition improves myocardial angiogenesis in this animal model and that this effect is associated with the bradykinin/eNOS/VEGF pathway (Toblli et al., 2004). In the heart excised, stored for 24 h, and then perfused

with blood from a support rabbit that was treated with telmisartan, plasma ANG II levels and coronary blood flow were higher, cardiac output was better, serum NO levels in the coronary effluent were higher, and the coronary blood flow response to ACh was more evident, compared with the heart perfused with blood from non-treated rabbits (Kajihara et al., 2005). Therefore, it was concluded that AT₁ receptor blockade improves ventricular and endothelial function after 24-h heart preservation and that AT₁ activation seems to play a critical role in reperfusion injury.

E. Cerebral Vasculature

Trauernicht et al. (2003) noted that ACh- and ADP-induced dilatation of pial arterioles was impaired in diabetic compared with nondiabetic rats, and enalapril prevented diabetes-induced impairment of NOS-dependent vasodilatation. eNOS protein was higher in diabetic than in nondiabetic rats, and enalapril did not produce a further increase in eNOS protein. They speculated that the protective role of enalapril may be independent of an alteration in eNOS protein in cerebral microvessels. Imidaprilat decreased blood pressure, increased plasma levels of NO₂/NO₃, enlarged arteriolar diameters, and caused an increase in red cell velocity and mean blood flow in pial arterioles of stroke-prone SHR (Sasaki et al., 2000). In newborn pigs equipped with a closed cranial window, ANG II and an AT₁ receptor agonist elicited pial artery dilatation that was unchanged by L-NA, whereas vasodilatation induced by an AT₂ receptor agonist was blocked by an NOS inhibitor, indicating that stimulated NO release contributes to AT₂ but not AT₁ receptor-mediated vasodilatation (Baranov and Armstead, 2005). In pigs, ANG II seems to elicit dilatation via AT₁ receptor activation, in which NO is not involved. In the rat middle cerebral artery, ANG II-induced dilatation was partially antagonized by inhibitors of NOS and cyclooxygenase and the remaining dilatation was inhibited by K⁺ channel blockers; the peptide-induced vasodilatation was blocked by candesartan and PD123319, suggesting that the cerebral arterial dilatation in response to ANG II is mediated by NO, PGI₂, and EDHF through activation of AT₁ and AT₂ receptors (Wackenfors et al., 2006). In anesthetized rabbits, topical application of ANG II had no effect on the basal diameter of cerebral arterioles but produced an inhibition of vasodilatation to bradykinin that was prevented by a superoxide scavenger or an NAD(P)H oxidase inhibitor, suggesting that local ANG II produces superoxide-mediated vascular dysfunction in cerebral microvessels and that the source of superoxide may be an NAD(P)H oxidase (Didion and Faraci, 2003). Kazama et al. (2004) also demonstrated that ANG II impaired functional hyperemia by activating AT₁ receptors and inducing production of ROS via a gp91 phox containing NADPH oxidase in mice.

The middle cerebral and common carotid arteries of SHR exhibited inward eutrophic remodeling, with a decreased lumen diameter and increased media thickness and decreased eNOS and increased iNOS protein and mRNA compared with Wistar-Kyoto rats; both remodeling and alterations in eNOS and iNOS expression in SHR were reversed by long-term AT₁ receptor inhibition by candesartan, indicating that AT₁ receptor activation is crucial for the maintenance of the pathological alterations in cerebrovascular circulation during hypertension (Yamakawa et al., 2003). In SHR, AT₁ receptor inhibition reversed the pathological vascular hypertrophy, increased and normalized eNOS expression, and decreased intracellular adhesion molecule-1 expression and the number of adherent and infiltrating macrophages in brain microvessel and middle cerebral artery (Ando et al., 2004). In SHRSP, imidapril delayed He-Ne laser-induced cerebral thrombosis and increased the plasma concentration of NO metabolites, and the concurrent administration of L-NAME with imidapril reversed the effects of ACE inhibition, implying that imidapril protects cerebral vessels in stroke-prone SHR by elevating the release of NO, thereby improving the cerebral circulation and reducing the tendency toward thrombosis and stroke (Sasaki et al., 2000).

F. Pulmonary Vasculature

In isolated rat lungs, vasoconstriction in response to ANG II and acute hypoxia was increased by chronic treatment with L-NAME, and EDRF or NO proved to be less important for basal tone regulation in the pulmonary than in the systemic circulation (Hampl et al., 1993). The pressor responses to ANG II and hypoxia of lungs isolated from rats exposed to NO gas were potentiated and their depressor response to bradykinin was impaired; the expression of eNOS mRNA was not affected by exposure to NO gas (Oka et al., 1996). The authors suggested that pulmonary endogenous NO production is reversibly reduced after short-term NO inhalation, which probably inhibits eNOS activity. In the isolated blood-perfused rat lung, L-NAME increased pulmonary arterial pressure and also enhanced the pressor response to ANG II or hypoxia, and the AT₁ receptor blockade did not alter the pressor response to hypoxia, whereas responses to ANG II were reduced, suggesting that the tonic release of NO modulates the baseline tone of pulmonary vasculatures and that the response to hypoxia is modulated by NO production but not by changes in ANG II levels in the isolated rat lung (Feng et al., 1994). Transfer of the eNOS gene to the lung of the mouse *in vivo* reduced pulmonary vascular resistance and pulmonary pressor responses to ANG II and hypoxia and enhanced pulmonary vasodepressor responses to bradykinin and zaprinast, a cyclic GMP phosphodiesterase type-5 inhibitor, suggesting that *in vivo* gene transfer may be a useful therapeutic intervention for the

treatment of pulmonary hypertensive disorders (Champion et al., 1999).

Patel et al. (1998) demonstrated that ANG IV-specific (AT₄) receptors were present in porcine pulmonary arterial endothelial cells and that ANG IV increased the constitutive eNOS activity as well as the cellular cyclic GMP content without changes in eNOS protein; divalinal ANG IV, but not inhibitors of AT₁ and AT₂ receptors, inhibited the ANG II- and ANG IV-stimulated increases in eNOS activity and cyclic GMP content, as did L-NAME or methylene blue. In addition, studies with precontracted porcine pulmonary arterial rings showed that ANG IV caused an endothelium-dependent relaxation that was blocked by L-NAME or methylene blue. Therefore, ANG IV seems to bind to AT₄ receptors, activate eNOS by post-transcriptional modulation, and stimulate cyclic GMP accumulation in porcine pulmonary arterial endothelial cells. ANG IV is expected to play a role in the regulation of blood flow in the pulmonary circulation.

G. Mesenteric Vasculature

There was evidence indicating that a sustained reduction of blood flow in the swine newborn intestine decreased constitutive NO production, which in turn caused a generalized enhancement of the contractile efficacy of ANG II, norepinephrine, and ET-1 (Nowicki, 1999). Chu and Beilin (1993) obtained results suggesting that diminished reactivity to ANG II in *in situ* blood-perfused mesenteric resistance vessels of the pregnant SHR was only partially dependent on NO. In cirrhotic rats produced by bile duct ligation, losartan treatment decreased portal pressure and ameliorated hyperdynamic circulation associated with a blunted vascular response to L-NAME infusion and also reduced eNOS protein expression, implying that in addition to suppression of the renin-ANG axis, the reduced aortic eNOS protein expression may play a partial role in the mechanism of action of losartan in cirrhotic rats (Yang et al., 2002).

Kawazoe et al. (1999) noted that suppression of rat mesenteric microcirculation in response to superfused ANG II was enhanced in the presence of NOS inhibition and was attenuated by treatment with SOD; superoxide production was increased by ANG II, suggesting that acute superoxide generation contributes to ANG II-induced vasoconstriction possibly via scavenging NO. ANG II infusion increased systolic blood pressure in mice, NADPH activity in mesenteric resistance vessels, and expression of p22phox mRNA; ANG II infusion enhanced the contractile response to ANG II, which was normalized by tempol and ebselen, a peroxynitrite scavenger (Wang et al., 2006). In addition, the endothelium-dependent ACh-induced relaxation was impaired in ANG-infused mice and was partially inhibited by L-NA in vessels from control mice but not those from ANG-infused mice; residual EDHF-like relaxation was not different between these groups. The slow pressor re-

response to ANG II infusion in mouse mesenteric resistance vessels seems to impair the NO-mediated component of endothelium-dependent relaxation, which is mediated by superoxide and peroxynitrite in vascular smooth muscle cells.

Several reports in the literature have concentrated on the contribution of EDHF to modulations of the renin-ANG system. Endothelium-dependent, NO-mediated relaxations of mesenteric artery rings to ACh and ADP were similar in Wistar-Kyoto rats and quinapril-treated SHR and more pronounced than in untreated SHR, whereas in artery rings exposed to high K^+ solutions to block the EDHF-induced relaxation, no differences were found in relaxations to ACh and ADP between the study groups (Kahonen et al., 1995). These authors concluded that enhanced endothelium-dependent relaxation after long-term ACE inhibition might be attributed to increased endothelium-dependent hyperpolarization. The ACh-induced hyperpolarization in the mesenteric arteries of SHR treated with enalapril or a combination of hydralazine and hydrochlorothiazide improved to a level comparable to that in Wistar-Kyoto rats; EDHF-mediated relaxation, as assessed by L-NA-resistant relaxations to ACh, was improved in treated SHR, whereas in the arteries, in which responses to EDHF were blocked by exposure to high K^+ media, no difference was found in relaxations to ACh among treated and untreated SHR and Wistar-Kyoto rats (Onaka et al., 1998). It was concluded that antihypertensive treatment improved EDHF-mediated hyperpolarization and relaxation in SHR mesenteric arteries, whereas NO-mediated relaxation did not seem to be modulated by drug therapy. Maeso et al. (1998) provided evidence that diminished EDHF is likely to account for the reduced relaxation to ACh associated with aging in mesenteric vasculatures from SHR and that the enhancement of ACh-induced relaxations by losartan seems to be dependent of increased NO availability. In the isolated mesenteric arterial bed from pregnant SHR, vasodilator responses to bradykinin were less than those from nonpregnant SHR, and captopril potentiated the bradykinin action and abolished the differences between pregnant and nonpregnant SHR; bradykinin-induced vasodilatation was reduced by L-NAME and was abolished in the presence of L-NAME plus high K^+ solution (Resende et al., 2004). It was concluded that increased ACE activity may be involved in the pregnancy-associated reduction in vascular responses to bradykinin in the mesenteric arteries of hypertensive rats and that the vasodilatation seems to be mediated by NO and EDHF.

Goto et al. (2000a,b, 2004) reported that EDHF-mediated relaxation in mesenteric arteries was improved in SHR treated with TCV-116, an AT_1 receptor antagonist, and enalapril and also in aged SHR treated with enalapril, but not with hydralazine. There is evidence for the involvement of gap junctions, consisting of connexins (Cxs), in EDHF-mediated responses (Chaytor et al.,

1998). The decreased expressions of Cx37 and Cx40 in endothelial cells of the SHR mesenteric artery were increased by treatment with candesartan but not by the combination of hydralazine and hydrochlorothiazide, suggesting that AT_1 blockade corrects the decreased expressions of Cx37 and Cx40 in hypertensive rats independently of blood pressure. It remains to be clarified whether these changes in Cxs are related to endothelial function, particularly that attributable to EDHF (Kansui et al., 2004). Fujiki et al. (2005) found that temocapril enhanced EDHF-mediated relaxation and hyperpolarization of mouse mesenteric arteries to ACh, and catalase, a specific scavenger of hydrogen peroxide, abolished the effects of ACE inhibition without any change in responses to sodium nitroprusside or a direct Ca^{2+} -activated K^+ channel opener; temocapril treatment up-regulated the expression of eNOS, this effect being absent in eNOS-knockout mice. It seems that endothelium-derived hydrogen peroxide accounts for the enhancing effect of temocapril on EDHF-mediated responses caused in part by eNOS up-regulation.

H. Placental and Uterine Vasculatures

In anesthetized rats, suffusion of ACh over the uterus dilated circumferential arterioles, the effect being inhibited by L-NA or ibuprofen alone and abolished by L-NA with ibuprofen; ANG II-induced vasoconstriction was enhanced by ibuprofen or L-NA and further enhanced by their combination, suggesting that ACh can release either NO or cyclooxygenase products to cause uterine arteriolar dilatation and that constrictor responses evoked by ANG II are attenuated by both NO and vasodilator PG release (Saha et al., 1998). Lambers et al. (2000) found that in nonpregnant, estrogenized ewes, ANG II injected into the uterine artery produced decreases in uterine blood flow, which were potentiated by PD123319; uterine vasodilatation noted under treatment with the AT_1 antagonist L-158809 was reversed by the AT_2 antagonist or by L-NAME. Therefore, they concluded that the AT_2 receptor subtype may modulate uterine vascular responses to ANG II potentially by release of NO. Zheng et al. (2005b) noted that ANG II elevated eNOS protein, increased NO_x production, and increased phosphorylated extracellular signal-regulated kinase 1/2 protein levels in ovine fetoplacental artery endothelial cells; PD98059, a selective mitogen-activated protein kinase kinase 1/2 inhibitor, inhibited these responses to ANG II. Increased NO_x production by ANG II seems to be associated with elevated eNOS protein expression, which is mediated at least in part via activation of the mitogen-activated protein kinase kinase 1 and 2/extracellular signal-regulated kinase 1/2 cascade. Zheng et al. (2005a) reviewed the findings, suggesting that elevations of ANG II in the fetal circulation may play a role in the marked increase in fetoplacental angiogenesis and that ANG II-elevated endothelial NO

production may partly attenuate ANG II-induced vasoconstriction in vascular smooth muscle.

In ewe fetuses subjected to bypass through central cannulation and perfusion with a pulsatile blood pump, levels of plasma and urinary NO metabolites and plasma and urine cyclic GMP were higher than in those with steady blood flow, and plasma renin concentration increased and lactate concentration elevated during bypass only in the steady-flow group (Vedrinne et al., 2000). Improved placental and peripheral perfusion during fetal pulsatile-flow bypass may be mediated by preservation of fetal/maternal endothelial NO biosynthetic mechanisms and/or decreased activation of the fetal renin-ANG pathway.

I. Other Vasculatures

In the perfused porcine retinal central artery, topical ANG II caused small vasoconstrictions, which were enhanced after inhibition of PG synthesis and further enhanced by L-NA, suggesting that porcine retinal arterioles have the ability to regulate vasoconstriction in response to ANG II by synthesis and release of endogenous NO and vasodilating PGs (Kulkarni et al., 2002). In isolated perfused porcine ciliary arteries and isolated ciliary arterial preparations, enalaprilat or benazepril augmented vasodilation to bradykinin, and the bradykinin antagonist HOE-140 reduced the vasodilator response to bradykinin, suggesting that ACE inhibitors prevent the effects of ANG I and augment endothelium-dependent dilatation of ophthalmic microvasculature to bradykinin, which releases NO through B₂ receptors (Meyer et al., 1995).

Compared with control rats, in diabetic rats that showed a reduction in sciatic nerve blood flow, nerve conduction velocity, and compound muscle action potential amplitudes, ANG II was more potent in producing vasoconstriction; cilazapril supplementation reversed the impaired functions, and topical application of L-NA to the sciatic nerve reduced the inhibition of nerve blood flow seen in experimental diabetic nephropathy (Kihara et al., 1999). Diabetic nephropathy may have an increasing vasopressor action with ANG II, possibly due to NOS inhibition, and ACE inhibitors are likely to have potential in the treatment of diabetic nephropathy.

Intravenous administration of candesartan reduced the vascular resistance in the rat submandibular gland; by contrast, L-NAME increased the resistance both in candesartan-treated and nontreated rats, with the increase in resistance being greater after blockade of AT₁ receptors, suggesting that NO-dependent tone of glandular vessels may be enhanced under AT₁ receptor blockade (Vag et al., 2002).

Heinemann et al. (1997) found that an intravenous bolus injection of ANG II increased blood pressure, which was accompanied by a decrease in blood flow through the mesenteric artery and an increase in femoral blood flow; telmisartan prevented all hemodynamic

responses to ANG II. The femoral vasodilator response to ANG II was reversed to vasoconstriction when blood pressure was maintained at a constant level, and it was also suppressed by L-NAME and reversed to vasoconstriction by combined treatment with L-NAME and indomethacin. The authors concluded that the effect of ANG II to increase systemic blood pressure and the resulting rise of perfusion pressure in the femoral artery seem to stimulate the formation of NO and PGs and thereby dilate the femoral arterial bed. Rabbit knee joint vascular resistance was increased by locally administered ANG II; losartan did not change the basal vascular resistance but abolished the effect of ANG II, whereas L-NAME increased joint vascular resistance but did not affect the response to ANG II, suggesting that the basal release of NO plays a role in the regulation of resting knee joint blood flow, but NO does not affect the AT₁ receptor-mediated vasoconstriction of joint blood vessels (Najafipour and Ketabchi, 2003).

J. Kidney

1. Renal Function

a. Studies in rats. L-NA-treated rats presented renal vasoconstriction and hypoperfusion, as well as a fall in GFR and an increase in filtration fraction, and treatment with losartan normalized GFR but not filtration fraction or renal vascular resistance (Ribeiro et al., 1992). NOS inhibition decreased urine flow and sodium excretion in rats; however, during blockade of AT₁ receptors by losartan, L-NA infusion failed to decrease urine flow and sodium excretion, even when renal arterial pressure was controlled, indicating that AT₁ receptor activation by endogenous ANG II probably contributes to the reductions in renal blood flow, GFR, and sodium excretion observed during NOS inhibition (Takenaka et al., 1993). According to Turkstra et al. (1998b), NO may well be released upon tubuloglomerular feedback (TGF) activation, and, by contrast, ANG II is not dynamically involved in TGF activation but may modulate the TGF response; thus, dynamic release of NO during TGF activation mitigates the TGF response, so that it will offset the action of a primary vasoconstrictor mediator. Cyclosporine A nephrotoxicity in rats was associated with baseline decrements in single-nephron GFR, single-nephron plasma flow, and kidney tissue ANG II levels and with a blunted hemodynamic response to glycine. L-Arginine feeding decreased baseline preglomerular resistance and restored the glomerular hemodynamic response to glycine under nephrotoxicity, suggesting that the induced nephrotoxicity may diminish NO activity within the kidney, and this activity may be partially restored by arginine feeding (De Nicola et al., 1993). Fujihara et al. (1995) reported that NOS inhibition aggravated parenchymal injury and functional impairment in the rat remnant kidney (four-fifths nephrectomy) that may involve glomerular hypertension and renin-ANG activation. In SHR, treatment with L-

NAME increased renal cortical tissue levels of ANG II that were related to glomerular cell deletion and apoptosis together with the pathophysiological changes of severe nephrosclerosis and impaired renal dynamics (Ono et al., 2001). Kidneys of L-NAME-treated rats had fewer normal glomeruli and fewer vasculatures in the cortex, outer medulla, and inner medulla; losartan normalized the values to control levels, suggesting that a generalized rarefaction of renal capillaries by chronic NOS inhibition is mediated by ANG II through AT₁ receptors (Fortepiani et al., 2003). L-NMMA and the nNOS inhibitor S-methyl-L-thiocitrulline decreased rat renal blood flow, but L-NA plus losartan did not; L-NMMA increased metabolic efficiency in the kidneys of control and losartan-treated rats, and the nNOS inhibitor also increased metabolic efficiency and mitochondrial oxygen consumption in proximal tubules (Deng et al., 2005). It seems that nonselective NOS inhibition increases the oxygen costs of kidney function independently of ANG II and that kidney nNOS is responsible for these in vivo and in vitro effects. Solhaug et al. (1996a) suggested that NO is vital in the developing kidney to maintain normal physiological function and to protect the immature kidney during pathophysiological stress.

Springate et al. (1997) noted that mouse renin gene-transgenic rats had a blunted pressure-diuresis-natriuresis response that was corrected by inhibition of the renin-ANG system and suggested that their production of NO was normal. It was suggested that the infusion of L-arginine caused diuresis and natriuresis, possibly via the formation of NO in the rat kidney and that endogenous ANG II was not involved in the L-arginine-induced renal actions (Urabe et al., 1996). The administration of the PD123319 to L-NAME-pretreated rats shifted the slope of the pressure-diuresis-natriuresis responses toward control values, indicating that the impairment produced by NOS blockade on pressure-diuresis is dependent on the activation of AT₂ receptors (Madrid et al., 1997a). There was evidence that activation of the renin-ANG system during sodium depletion increased renal NO production directly through stimulation of AT₂ receptors by ANG II (Siragy and Carey, 1997) and also indirectly from AT₂ receptor stimulation of bradykinin via the B₂ receptor (Abadir et al., 2003). AT₂ receptor-deficient mice, in which AT₁ receptors were up-regulated, showed nNOS and iNOS up-regulation; under DOCA-salt, renal iNOS expression was further increased, but iNOS inhibition did not change blood pressure (Obst et al., 2004). It seems that iNOS is not involved in the hemodynamics but contributes to organ damage. Valles and Manucha (2000) found that in the inner medullary collecting duct segments dissected from the obstructed side in rat unilaterally obstructed kidneys, the bafilomycin-sensitive H⁺-ATPase activity was intensively decreased compared with that from the non-obstructive side, and incubation of the obstructed collecting duct in L-NAME and aminoguanidine, an iNOS

inhibitor, increased the H⁺-ATPase activity; a greater increase in iNOS than in calcium/calmodulin-dependent NOS was observed. The inhibitory effect of obstruction was abolished by losartan. It was suggested that endogenous NO increased by iNOS is involved in the inhibition of H⁺-ATPase activity in the obstructed medullary collecting duct and that the recovery of H⁺-ATPase activity induced by ANG receptor blockade may be related to a decrease in iNOS activity. In the proximal tubule isolated from rats, the AT₂ receptor agonist CGP42112A caused an inhibition of Na⁺,K⁺-ATPase activity and a stimulation of NO production and cyclic GMP accumulation, these effects being abolished by PD123319, L-NAME, and 1*H*[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one, a guanylyl cyclase inhibitor (Hakam and Hussain, 2006). The authors suggested that the activation of AT₂ receptors via stimulation of the NO/cyclic GMP pathway causes inhibition of Na⁺,K⁺-ATPase activity in the proximal tubule, providing a plausible mechanism responsible for the AT₂ receptor-mediated diuresis/natriuresis in rodents. Baiardi et al. (2005) obtained evidence supporting an important role for AT₂ receptors in the regulation of renal function and in the protective effects of estrogen in the rat kidney.

Wickman et al. (2001) noted that two-kidney, one-clip renal hypertension was associated with reduced levels of eNOS protein in the renal medulla of clipped and contralateral kidneys, and eNOS expression in both kidneys was not changed despite expected large changes in hemodynamics of the two kidneys. The reduced level of eNOS may be associated with a reduction in medullary blood flow. In rats with two-kidney, one figure-eight wrap (Grollman) hypertension, renal interstitial fluid bradykinin, NO_x, and cyclic GMP were higher in the contralateral kidney than in the wrapped kidney; losartan normalized systolic blood pressure and increased renal function, interstitial fluid bradykinin, NO_x, and cyclic GMP only in the contralateral kidneys, whereas PD123319 increased blood pressure and decreased these interstitial fluid substances in both kidneys, suggesting that ANG II mediates renal production of bradykinin, which in turn, releases NO and cyclic GMP via stimulation of AT₂ receptors (Siragy and Carey, 1999). Li et al. (2004) found that rats with diabetes mellitus exhibited glomerular hemodynamic alteration and renal hypertrophy, and treatment with either insulin or candesartan ameliorated these changes, possibly by a suppression of enhanced renal expression of eNOS in diabetic rats.

b. Studies in dogs and rabbits. In anesthetized dogs, Llinas et al. (1995) obtained evidence suggesting that the increase in proximal sodium reabsorption induced by NO synthesis inhibition is mediated by endogenous ANG II levels and that endogenous NO modulates the vasoconstrictor and antinatriuretic effects of ANG II during an extracellular volume expansion. Intrarenal arterial infusion of L-NA decreased renal blood flow and urine flow and increased filtration fraction, but did not

alter GFR, and L-NA, together with losartan, reduced renal blood flow, urine flow, and GFR; L-NA enhanced the renal nerve stimulation-induced decreases in renal blood flow, GFR, urine flow, and urinary excretion of sodium, with these L-NA-induced enhancements being unaffected by losartan (Egi et al., 1995). It is likely that endogenous NO acts as an inhibitory mediator of renal noradrenergic neurotransmission, and enhancement of this neurotransmission induced by NO blockade is independent of the action of endogenous ANG II on the AT₁ receptors.

Intrarenal arterial infusion of ANG II reduced GFR and urinary sodium excretion in denervated kidneys of anesthetized rabbits treated with L-NAME; intrarenal administration of an NO donor attenuated the reduction in urinary sodium excretion induced by the agonist without affecting the ANG II-induced reduction in GFR, suggesting that the NO donor can suppress the ANG II-evoked tubular reabsorption and thereby attenuates the agonist-induced antinatriuresis in the denervated and endogenous NO-depleted rabbit kidney (Ono et al., 1998).

2. Renin. Plasma renin activity (PRA) was elevated after chronic treatment of awake rats with L-NA, which caused marked renal vasoconstriction and hypoperfusion; as expected, inhibition of ANG II was associated with a much greater increase in PRA in rats treated with L-NAME and losartan (Ribeiro et al., 1992). Sigmon et al. (1992) noted that bolus injections of L-NAME decreased PRA and increased mean blood pressure in anesthetized rats, whereas in the rats instrumented with an intra-aortic balloon catheter to control renal perfusion pressure and pretreated with propranolol, L-NAME increased PRA, suggesting that when renal perfusion pressure and β -adrenergic activity are controlled, NOS inhibition results in an increase in PRA.

On the other hand, in the isolated perfused rat kidney, L-NAME caused an increase in perfusion pressure, a decrease in renal perfusate flow, and an inhibition of renin release that was independent of a rise in perfusion pressure, confirming the intervention of the L-arginine/NO pathway in the vasodilatation of this kidney model and demonstrating the inhibitory effect of NOS inhibition on renin release (Gardes et al., 1992). Scholz and Kurtz (1993) also obtained evidence that NO and related activators of soluble guanylyl cyclase stimulate renin secretion from the isolated perfused rat kidney. Researchers from the same group (Schricker and Kurtz, 1993) suggested that liberators of NO have two effects on renin secretion from isolated renal juxtaglomerular cells: an inhibitory effect mediated by stimulation of soluble guanylyl cyclase activity and a stimulatory effect mediated by an as yet unknown pathway that requires extracellular Ca²⁺. PRA was suppressed in L-NAME-treated rats, in which the renal perfusion pressure was increased, compared with control rats; such an inhibition was seen when the perfusion pressure was con-

trolled, unchanged, or reduced, suggesting that the intrarenal pressure-sensing mechanism for renin release does not require NO synthesis (Johnson and Freeman, 1994). In addition, in bilaterally renal-denervated rats, L-NAME again suppressed PRA, and infusions of sodium nitroprusside completely inhibited the effect of L-NAME. NO may function as a paracrine stimulatory mechanism for the local regulation of renin release. In conscious rats without renal clips, L-NAME led to a decrease in PRA and renal renin mRNA levels; unilateral renal clipping increased PRA and renin mRNA levels to a greater extent in vehicle-treated than in L-NAME-treated rats, whereas in the contralateral as opposed to clipped kidneys, renin mRNA was decreased less in vehicle-treated than in L-NAME-treated rats, suggesting that endothelial NO is involved in the control of the renin gene by renal perfusion pressure (Schricker et al., 1994). These authors (Schricker et al., 1995) also obtained findings suggesting that renin mRNA levels are tonically increased by NO and that the action of NO is counteracted by ANG II. Based on the findings obtained from the phenotype of two common mouse models, C-57L/6J (C-57) that carries only the *Ren-1c* gene and 129/SvJ (Sv-129) with both *Ren-1d* and *Ren-2*, Lum et al. (2004) concluded that Sv-129 mice with two renin genes have higher blood pressure but lower plasma and renal renin than C-57 mice with one renin gene and that in Sv-129 mice, the influence of NO on renal but not systemic resistance may be exaggerated. Beierwaltes (2006) suggested that endogenous renal cyclic GMP inhibits, thereby diminishing renal metabolism of cyclic AMP, and the resulting increase in cyclic AMP serves as an endogenous stimulus for renin secretion and that NO can indirectly stimulate renin secretion through its second messenger cyclic GMP.

In afferent arterioles isolated from the rat kidney, the adenylyl cyclase activator forskolin elicited an increase in renin release that was blocked when rats were chronically treated with L-NAME; similar results were obtained in cortical slices from the rat kidney, suggesting that this phenomenon is independent of the presence of macula densa cells (Chatziantoniou et al., 1996). In addition, the lack of regulation of renin release after L-NAME treatment was reversed by the NO donor SIN-1 in the arterioles and cortical slices. These data indicate that the adenylyl cyclase-mediated mechanism regulating renin release is impaired when NO synthesis is inhibited. Tharaux et al. (1997) reported that in afferent arterioles isolated from rats treated with ramipril, renin mRNA levels, total renin content, and renin secretion were increased compared with untreated controls, with the effect of ACE inhibition being abolished by L-NAME; similar data were found in the arterioles from furosemide-treated rats, suggesting that NO acts on renin activation by a mechanism independent of ANG II. The inhibitory effect of L-NAME on the activation of renin secretion was abolished when afferent arterioles were

treated with nifedipine, an L-type Ca^{2+} channel blocker. Therefore, the authors suggested that the physiological mechanism regulating activation of renin synthesis and secretion are impaired during NO synthesis inhibition, probably because of increased Ca^{2+} influx.

In anesthetized dogs, L-NA infused into the renal artery reduced basal renal blood flow, urine flow, and sodium and potassium excretion without any change in systemic blood pressure, GFR, and basal renin release; however, renin release stimulated by a fall of renal perfusion pressure was reduced by L-NA, indicating that renal NO modulates both renal blood flow and renin release in vivo (Naess et al., 1993). In conscious dogs, L-NAME given as a bolus increased renal artery pressure, decreased renal blood flow, and decreased renin release, whereas GFR did not change; the inhibition of renin release by NOS inhibition was pressure-dependent in the low pressure range (Persson et al., 1993).

In summary, most, but not all, of the literature introduced in this review provided evidence to hypothesize that renin secretion is stimulated by NO irrespective of renal perfusion pressure, which may be associated with increased renin gene expression.

K. Other Organs and Tissues

In the rat mesenteric microcirculation in vivo, iloprost, a PGI_2 analog, inhibited the ANG II-induced increase in leukocyte rolling flux, adhesion, and emigration and returned leukocyte rolling velocity to basal levels, and similar findings were obtained with cyclic AMP-elevating agents such as the β_2 -adrenoceptor agonist salbutamol, forskolin, and theophylline; NO donors or 8-bromo-cyclic GMP also reduced the leukocyte-endothelial cell interactions elicited by ANG II (Alvarez et al., 2001). Salbutamol preadministration did not modify these interactions elicited by L-NAME or L-NAME plus ANG II, suggesting that the inhibitory leukocyte effects caused by cyclic AMP-dependent mechanisms are mediated through NO release. Cyclic AMP elevating agents and NO donors might constitute a powerful therapeutic tool that can control the leukocyte recruitment characteristic of the vascular lesions, in which ANG II plays a critical role. Alvarez et al. (2002) also obtained evidence suggesting that the antiatherogenic effects of estrogens may be mediated by inhibition of ANG II-induced leukocyte recruitment through endothelial NO and PGI_2 release. Nabah et al. (2005) noted that L-NAME caused an increase in arteriolar leukocyte adhesion and leukocyte-endothelial cell interactions in rat mesenteric post-capillary venules, with losartan inhibiting the L-NAME effects; L-NAME provoked increased expression of P-selectin, E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in the arterial endothelium, which was attenuated by losartan. It was concluded that NOS inhibition results in the attachment of leukocytes to the arterial endothelium, a critical event in disease states such as hypertension and atherosclerosis,

which could be prevented by the administration of AT_1 receptor antagonists. Losartan, EXP3174, or valsartan caused NO release from platelets and human umbilical vein endothelial cells, which was attenuated by L-NAME, with their NO-releasing effects being greater in platelets than in endothelial cells; the inhibiting effects of AT_1 receptor antagonists on collagen-stimulated adhesion and thromboxane A_2 analog-stimulated aggregation of platelets were reduced by L-NAME (Kalinowski et al., 2002). The data obtained indicate a crucial role for NO in the arterial antithrombotic effects of AT_1 receptor antagonists. Bradykinin B_2 receptor knockout mice had elevated plasma ANG II, elevated plasma 6-keto- $\text{PGF}_{1\alpha}$ (a stable metabolite of PGI_2), elevated serum nitrate, and increased AT_2 receptor mRNA and protein expression; L-NAME shortened the thrombosis time, and treatment with PD123319 normalized the thrombosis time, nitrate, and 6-keto $\text{PGF}_{1\alpha}$ (Shariat-Madar, 2006). In mice lacking B_2 receptors, ANG II binding to overexpressed AT_2 receptors probably promotes thromboprotection by elevating NO and PGI_2 .

In the adrenal gland, AT_2 receptor expression was down-regulated in rats with experimental sepsis, whereas tissue cytokine concentrations were elevated and iNOS expression was induced; incubation of PC12 cells with proinflammatory cytokines resulted in a diminished expression of AT_2 receptors, which was prevented by coincubation of the cells with L-NAME, indicating that the expression of AT_2 receptors in the adrenal gland in the model of sepsis is down-regulated in an NO-dependent manner (Bucher et al., 2001). The authors speculated that because AT_2 receptors are thought to be involved in the stimulated secretion of adrenal catecholamines, the diminished expression of AT_2 receptors could play an important role in the pathogenesis of septic shock via impaired ANG II-induced adrenal catecholamine release.

The clitoris is an important erectile organ for sexual arousal and decreased clitoral blood flow is associated with arousal disorder in women (Goldstein and Berman, 1998). Contractions in response to ANG II of the rabbit clitoral cavernosum were inhibited by AT_1 receptor blockade by Dup 753, unaffected by PD123319, and enhanced by L-NAME (Park et al., 2000). The rank order of potency of contraction was ANG II > ANG I > ANG III > ANG IV. Contractions induced by ANG III and ANG IV were accentuated by L-NAME and amastatin, an aminopeptidase inhibitor, suggesting that peptides of the ANG family cross-talk with the NO system and aminopeptidase is involved in the modulation of the tone of clitoral cavernosum smooth muscle by ANG III and ANG IV (Park et al., 2002).

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