Review Article

CMJ

www.cmj.ac.kr

Altered Nitric Oxide System in Cardiovascular and Renal Diseases

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Nitric oxide (NO) is synthesized by a family of NO synthases (NOS), including neuronal, inducible, and endothelial NOS (n/i/eNOS). NO-mediated effects can be beneficial or harmful depending on the specific risk factors affecting the disease. In hypertension, the vascular relaxation response to acetylcholine is blunted, and that to direct NO donors is maintained. A reduction in the activity of eNOS is mainly responsible for the elevation of blood pressure, and an abnormal expression of iNOS is likely to be related to the progression of vascular dysfunction. While eNOS/nNOS-derived NO is protective against the development of atherosclerosis, iNOS-derived NO may be proatherogenic. eNOS-derived NO may prevent the progression of myocardial infarction. Myocardial ischemia/reperfusion injury is significantly enhanced in eNOS-deficient animals. An important component of heart failure is the loss of coronary vascular eNOS activity. A pressure-overload may cause severer left ventricular hypertrophy and dysfunction in eNOS null mice than in wild-type mice. iNOS-derived NO has detrimental effects on the myocardium. NO plays an important role in regulating the angiogenesis and slowing the interstitial fibrosis of the obstructed kidney. In unilateral ureteral obstruction, the expression of eNOS was decreased in the affected kidney. In triply n/i/eNOS null mice, nephrogenic diabetes insipidus developed along with reduced aquaporin-2 abundance. In chronic kidney disease model of subtotal-nephrectomized rats, treatment with NOS inhibitors decreased systemic NO production and induced left ventricular systolic dysfunction (renocardiac syndrome).

Key Words: *Nitric oxide; Hypertension; Atherosclerosis; Ischemia / reperfusion injury; Heart failure; Nephrogenic diabetes insipidus; Ureteral obstruction; Cardio-renal syndrome*

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Article History:
Received February 12, 2016
Revised March 14, 2016
Accepted March 22, 2016

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INTRODUCTION

Although being initially identified as a vasodilator, nitric oxide (NO) has emerged as an important mediator in a quite diverse range of biological functions. The components of NO system are expressed virtually in all tissues and organs under physiological and pathological conditions. In the cardiovascular system, NO plays a role in the regulation of vascular tone, cardiac contractility, vascular remodeling, and baroreflex function. It also has specific functions in the kidney, regulating hemodynamics, salt and water reabsorption, renin secretion, and tubuloglomerular feedback. Abnormalities of its bioavailability are causally related to various cardiovascular and renal disorders.

1. Nitric oxide synthases

NO is synthesized from its precursor L-arginine by a family of NO synthases (NOS), including neuronal (nNOS), inducible (iNOS), and endothelial NOS (eNOS). nNOS is mainly expressed in the neural tissue, iNOS is upregulated in the activated macrophage, and eNOS is abundant in the endothelium where it regulates vascular tone.

NOS require tetrahydrobiopterin (BH4), among other co-factors. NOS enzymes are synthesized as monomers which need to form dimers to bind BH4 and L-arginine, before being able to catalyze NO production. Therefore, the coupling of NOS is more important for the production of NO than the actual presence of NOS proteins per se. The monomers, which are not coupled with their cofactors or substrates, generate only superoxide anions instead of NO

http://dx.doi.org/10.4068/cmj.2016.52.2.81
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from their oxygenase domain. This phenomenon is referred to as "NOS uncoupling".

eNOS is the major isoform regulating the vascular function. Its catalytic activity is initiated/enhanced by physical and chemical stimuli, such as shear stress and various neurohumoral factors. NO produced by nNOS is implicated in the regulation of neuronal excitability, long-term potentiation or depression of synaptic plasticity, and in memory and learning processes. nNOS is also expressed in cardiac and skeletal myocytes, medial smooth muscle and endothelial cells of the vasculature, adventitial layer of penile arteries, and macula densa cells in the kidney. Induction of iNOS occurs mainly in association with infection and inflammation as part of defense responses, while its expression is minimal under physiologic conditions. When iNOS is up-regulated in response to pro-inflammatory cytokines, it generates 100-1,000 fold more NO than does eNOS. An excessive NO production may exert detrimental effects on the cardiovascular function. The activation of iNOS within vascular smooth muscle cells is the major factor causing hypotension in septic shock.

The physiological role of NO in vivo has been investigated in pharmacological studies with non-selective NOS inhibitors, such as N^{ω}-nitro-L-arginine methyl ester (L-NAME) and N^{G}-monomethyl-L-arginine. However, these inhibitors may produce non-specific actions, such as antagonism of muscarinic cholinergic receptors and formation of superoxide anions. The role of NO is also explored in studies using the mice lacking a specific NOS isoform, in which the other isoforms that are not disrupted may exert a compensatory role. For instance, the loss of eNOS expression alone was compensated for by upregulation of nNOS expression. Mice that are all three NOS genes disrupted have been more recently developed. They may provide a strong and useful tool to investigate the authentic role of endogenous NO, although their survival and fertility rates are markedly reduced as compared with wild-type mice.

2. The bioavailability of NO/cGMP

The bioavailability of NO is determined by the balance between its production and degradation. Mechanisms underlying the altered bioavailability of NO differ depending on specific risk factors affecting the disease. De novo synthesis of L-arginine from L-citrulline may supply up to 10% of the endogenous plasma L-arginine. Therefore, a decreased availability of L-citrulline as well as that of L-arginine may contribute to the NO deficiency. NO generation may be reduced even when the L-arginine level is above Km (the concentration of substrates that allows half maximal rate of the enzyme-mediated reaction), and L-arginine administration may reverse endothelial dysfunction. The dependence of cellular NO production on exogenous L-arginine, despite the theoretical saturation of NOS by endogenous L-arginine, is referred to as "arginine paradox". It has been attributed to decreased competitive displacement by the endogenous competitive inhibitor asymmetrical dimethyl arginine, a metabolic by-product created during protein methylation in the cytoplasm.

NO undergoes spontaneous inactivation in the presence of oxygen or superoxide anions, so that the biological half-life of NO may vary as a function of the oxygen tension and the concentration of superoxides. The accelerated degradation of NO may further worsen its deficient production. The reduced NO bioavailability may also be caused by "NOS uncoupling". Superoxides generated from uncoupled eNOS may play a critical role in the process of various cardiovascular diseases.

NO acts in autocrine and paracrine fashions. The classical NO signaling pathway starts with the activation of soluble guanylyl cyclase (sGC) to generate its second messenger, cyclic guanosine 3',5'-monophosphate (cGMP). Cyclic nucleotides are then degraded by a family of phosphodiesterases (PDE), i.e., cAMP-sensitive PDE (PDE 3 and 4), cGMP-sensitive PDE (PDE 5), and non-selective PDE (PDE 1). Inhibitors of PDE can prolong or enhance the effects of physiological processes mediated by cAMP or cGMP.

PATHOPHYSIOLOGICAL IMPLICATIONS OF NITRIC OXIDE SYSTEM IN CARDIOVASCULAR AND RENAL DISEASES

1. Hypertension

Hypertension has been related to a diminished activity of NOS/NO/cGMP cascade. The vasorelaxation in response to endothelium-dependent vasodilators (e.g., acetylcholine) is blunted in patients with hypertension or prehypertension and various animal models of hypertension, whereas that in response to direct NO donors (e.g., sodium nitroprusside) is maintained.

A down-regulation of vascular eNOS has been known in various animal models of hypertension.[1-3] More recent studies have confirmed the causal role of deficient NO system in elevating the blood pressure, in which mice disrupted of the genes encoding NOS isoforms are absent of endothelium-dependent vasodilation and hypertensive.[4] The similar magnitude of hypertension between the triply n/i/eNOS null and the singly eNOS null mice suggests that a deficient eNOS activity is mainly responsible for the development of high blood pressure.[4,5] The expression of eNOS also decreased in the kidney in hypertension,[6,7] and the reversal of hypertension following unclipping the renal artery was associated with restoration of eNOS expression in two-kidney, one-clip (2K1C) hypertension.[7] Each unit of increase in eNOS expression led to a 0.88-fold decrease in the risk of hypertension in autosomal dominant polycystic kidney disease.[8]

The expression of nNOS decreased in the brainstem in spontaneously hypertensive rats (SHR) and Dahl salt-sensitive (DS) hypertensive rats, along with enhanced sympathetic tone.[9] It is likely that NO produced by nNOS prevents salt-sensitive hypertension, and its down-regulation contributes to salt-sensitivity in DS rats. Chronic interfer-

ence of nNOS-derived NO generation within the paraventricular nucleus, which integrates inputs regulating the sympathetic outflow, potentiates the early phase of 2K1C hypertension.[10] The vascular expression of nNOS was also decreased in deoxycorticosterone acetate (DOCA)-salt and 2K1C hypertension.[3] In transgenic rats with inducible angiotensin II (AII)-dependent malignant hypertension, the blood pressure was augmented following the administration of s-methyl-L-thiocitrulline (nNOS inhibitor).[11]

The expression and activity of iNOS in hypertension is controversial. It has either been undetected or apparently expressed in SHR and stroke-prone SHR.[1,2,12] The progression of vascular dysfunction was associated with an abnormal expression of iNOS in L-NAME-induced hypertension.[13] An upregulation of iNOS was also noted in essential hypertensive humans, along with the impaired NO-dependent vasodilation.[14] The attenuated expression of iNOS by antihypertensive therapy[1] may indicate that its upregulation is a consequence, rather than a causative factor, of high blood pressure.

NO may enhance the urinary excretion of sodium by inhibiting the tubular transport and increasing the glomerular filtration rate, of which blockade may then result in a positive sodium balance and development of hypertension. L-NAME-induced hypertension was indeed associated with decreased urinary excretion of sodium, accompanied by upregulation of various tubular sodium transporters in the kidney.[15]

An imbalance between NO and reactive oxygen species (ROS) is a pathognomonic in hypertension. The increase in superoxide generation accounts for the decreased availability of basal NO in genetic hypertension.[16] Superoxide generation increased in hypertension may also promote the expression of eNOS through transcriptional and post-transcriptional mechanisms.[17] Indeed, an increased expression and activity of eNOS has been noted in stroke-prone SHR.[16] The vascular expression of nNOS also increased in SHR, which was stimulated by AII.[12] In the kidney, both eNOS and nNOS were upregulated in AII-induced hypertensive rats, while iNOS remained unaltered.[18] The urinary excretion of NO, along with its tissue contents in the kidney, increased in SHR and AII-induced hypertensive rats.[18,19] The decreased or increased availability of NO derived from eNOS/nNOS may affect the degree of hypertension, either augmenting or ameliorating it. The upregulation of NOS may represent a secondary phenomenon counteracting the elevated blood pressure and protecting the vasculature from hypertension-induced damage.

Superoxides also interact with NO to yield peroxynitrites, reducing the biological half-life and bioavailability of NO. For instance, they decrease the bioavailability of nNOS-derived NO in the juxtaglomerular apparatus in SHR, thereby enhancing tubuloglomerular feedback responses.[20,21] The production of ROS also disturbs the balance between de novo synthesis and oxidation/degradation of BH4. A reduced bioavailability of BH4 causes uncoupling of eNOS and generates more superoxides instead of NO, such as found in SHR and DOCA-salt hypertensive rats.[22,23] The supplementation of BH4 alone may thus augment endothelium-dependent vasodilation in both normotensive and hypertensive individuals. Arginase competes with NOS for the available L-arginine, catalyzing the transformation of L-arginine to ornithine and urea; thus increasing the release of superoxides and reducing the production of NO. An inhibition of arginase improves the vascular function and reduces the blood pressure in SHR.[24]

Although superoxides may also trigger desensitization of vascular sGC, changes of vascular sGC activity are not consistent in different models of hypertension. It decreased or increased in various rat models of hypertension, despite the attenuated endothelium-dependent vasodilation.[18,25-29] It is likely that alterations in the sGC/cGMP pathway precede the occurrence of hypertension, returning to normal upon full manifestation of hypertension.[30]

An endothelial dysfunction is one of the earliest events in pulmonary arterial hypertension (PAH), which is characterized by high blood pressure and vascular remodeling in pulmonary arteries and right ventricular hypertrophy (RVH). A selective impairment of right coronary endothelial function precedes the development of monocrotaline (MCT)-induced PAH and RVH in rats.[31] The endothelium-dependent relaxation of pulmonary arteries is attenuated in association with overproduction of oxygen-derived free radicals, reduced activity of eNOS, and diminished formation of NO in chronic hypoxia-induced PAH.[32] Sildenafil (selective PDE5 inhibitor) augments the activity cGMP and ameliorates the hypoxia-induced PAH in humans and mice.[33] The alleviating effect of tetrandrine on MCT-induced PAH and RVH was related to the normalization of the NO/cGMP signaling pathway accompanied by down-regulation of iNOS and upregulation of superoxide scavengers.[34]

Adulthood hypertension may be programmed in response to a suboptimal environment in early life. It can be, conversely, prevented by appropriate measures during the period of early development (reprogramming); i.e., the perinatal environment can modulate the adult blood pressure despite the presence of a genetic predisposition. As a preventive strategy, most reprogramming interventions have been aimed at shifting the NO/ROS balance to increase the availability of NO in both genetic and acquired animal models of hypertension. The addition of melatonin to an embryo culture medium restores eNOS expression, and normalizes vascular NO availability and responsiveness to acetylcholine in resistance arteries; eventually preventing assisted reproductive technology-induced hypertension.[35] Perinatal L-citrulline or melatonin supplementation can be protective against both genetically and developmentally programmed hypertension.[36]

2. Atherosclerosis

NO reduces inflammation, proliferation of medial smooth

muscle cells, monocyte adhesion to endothelial cell monolayers, and collagen-induced platelet aggregation, providing protective effects against the development and progression of atherosclerosis. Dietary supplementation of L-arginine reduces atherosclerosis in hypercholesterolemic animals by increasing the endothelial NO production.[37] However, the effects of supplementary L-arginine were not sustained, questioning its long-term benefit in the prevention of atherosclerosis at least in humans. The anti-inflammatory and anti-atherogenic activities of NO may be rapidly dissipated by ROS. A reduced bioavailability of BH4 causes uncoupling of eNOS, thereby generating superoxides instead of NO and accelerating atherosclerosis.[38]

The vascular lesion formation is not solely attributable to an altered activity of eNOS. nNOS is up-regulated predominantly in the neointima and medial smooth muscle cells after the injury in carotid artery ligation and balloon injury models, serving as an anti-atherogenic factor.[39] While the effects of eNOS and nNOS are protective, the effect of iNOS may be proatherogenic: its up-regulation contributes to the development of vascular dysfunction and atherogenesis.

The great amount of iNOS-mediated NO formation has been linked to the generation of harmful oxidative products and the development of atherosclerosis.[40] A genetic deficiency of iNOS reduces diet-induced atherosclerosis in the apolipoprotein E-deficient mouse, in which the absence of iNOS-mediated LDL oxidation prevents the advanced lesion formation.[41] Inhibitory effects of pravastatin on atherosclerosis formation and related cardiovascular diseases are associated with a reduced generation of iNOS.[42]

3. Myocardial infarction

NO mediates cardiac functions under both normal and pathological conditions. The endothelial dysfunction may precipitate the occurrence of acute unpredictable cardiovascular events including myocardial infarction (MI), while endothelium-independent responses are not predictive of the outcome. Genetic disruption of n/i/eNOS isoforms caused development of spontaneous MI in mice, along with formation of various vascular lesions.[43] Postmortem examination revealed that 55% of the triply NOS null mice died of MI.[43] NO derived from eNOS may effectively prevent the progression of MI.[44] However, neither genetic disruption nor pharmacologic inhibition of eNOS activity alone induces MI.

NO formation in response to cholinomimetic stimulation increased in the arteries with MI in association with reduced generation of ROS and increased activities of eNOS/nNOS.[45] The increased nNOS expression would reinforce vagal inhibition of the heart rate in the infarcted heart.[46] iNOS is normally absent in the healthy heart, and its expression is induced by inflammation. The induction of iNOS expression is also motivated by ischemic stress, resulting in massive production of NO. The amelioration of MI by nebivolol in rats was related to the attenuation of iNOS and the restoration of eNOS both in vascular beds and myocytes during the acute period of MI, and the prevention of nNOS deterioration in myocardial cells during the sub-acute period of MI.[47]

4. Myocardial ischemia-reperfusion injury

The cardiac function is closely related to the endothelial function. Acute reperfusion of coronary arteries associated with sharp interruptions or reductions of coronary ischemia may result in ischemia/reperfusion (I/R) injuries; in which the responsiveness to endothelium-dependent vasodilators is reduced, along with a down-regulation of eNOS/NO due to oxidative stress. Genetic overexpression of eNOS ameliorates myocardial I/R injury, which is ablated by L-NAME.[48] NO-donating compounds including L-arginine are highly beneficial in the setting of myocardial I/R injuries.[49,50] Conversely, I/R injuries are significantly enhanced in eNOS-null mice compared with those in wild-type animals.[51]

NO has emerged as one of crucial modulators of myocardial preconditioning. An ischemic preconditioning may accelerate the recovery of endothelial function by preserving eNOS and stimulating basal NO production.[52] The transgenic mice that overexpress eNOS exclusively in cardiac myocytes cannot be preconditioned, however, since the myocardium may have been already maximally protected by NO.[53] NO derived from iNOS also mediates cardioprotection during the preconditioning process.[54]

Post-conditioning is also related to activation of the NO/cGMP signaling pathway, which depends on decreased superoxide production by reducing BH4 oxidation and NOS uncoupling at the onset of reperfusion.[55] The cardioprotective effects of ischemic or pharmacological post-conditioning were abolished by L-NAME or 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ, inhibitor of sGC), where NO donors restored the cardioprotection even in the presence of L-NAME or ODQ.[56]

5. Heart failure

The altered myocardial NO balance associated with coronary endothelial dysfunction decreases coronary flow, contributing to the progression of heart failure (HF). An important component of HF is the loss of peripheral and coronary vascular NO activity. The magnitude of decreased cardiac function is proportional to the reduced degree of NO-dependent coronary reserves, and the left ventricular (LV) ejection fraction is inversely correlated to the coronary blood flow reduction.[57] The coronary arteries from HF rats exhibited reduced NO bioavailability.[45] The improved myocardial response to mechanical stretching by catestatin in SHR, which mimics human chronic HF, was attributed to the activation of NO system.[58]

Patients with HF had endothelial dysfunction associated with reduced expression of eNOS and reduced NO bioavailability.[59] Enhanced NO modulation can prevent the onset of HF through increased eNOS/nNOS pathway activation and reduced ROS generation.[45] The protective ef-

fects of carbamylcholine on ventricular fibrillation partly depend on nNOS-mediated generation of NO.[60] On the contrary, the activity and the expression of iNOS increased in HF in humans.[59] Although the cardiomyocyte-specific overexpression of iNOS has little effects on basal contractility, it is sufficient to produce cardiomyopathy, arrhythmia, and sudden cardiac death upon activation. The upregulation of cardiomyocyte iNOS may promote progressive cardiac dysfunction and decrease LV contractility in hypothyroidism.[61] The dynamic changes in myocardial NO production with the progression of HF may represent a shift from a spatially and temporally regulated (by eNOS or nNOS) release to a deregulated and excessive release (mostly by iNOS).[62]

Activation of renin–angiotensin system (RAS) may disrupt NO downstream signaling, and medications inhibiting the activity of RAS may improve endothelial function. Angiotensin-converting enzyme (ACE) inhibitors normalize NO-dependent vasodilation in HF; of which mechanisms are related to the upregulation of eNOS, inhibition of endothelial apoptosis, and decrease vasoconstrictor prostanoids.[63] The expressions of bradykinin B2 receptor, eNOS, and vascular endothelial growth factors were reduced in the failing hearts of DS hypertensive rats; which were restored by the treatment with ACE inhibitors.[64]

6. Cardiac hypertrophy

Plasma levels of NO metabolites are markedly reduced in men with left ventricular hypertrophy (LVH).[65] A selective impairment of right coronary endothelial function precedes the development of MCT-induced RVH.[31] The endothelial function of small coronary arteries is improved and the cardiac hypertrophy is ameliorated by long-term L-arginine supplementation in SHR, suggesting a protective role of the NO system in the pathogenesis of cardiac hypertrophy.[66] Cardiac-specific overexpression of eNOS attenuates LVH induced by isoproterenol infusion[67] or by coronary artery occlusion.[68]

The expression and activity of eNOS are diminished in cardiomyocytes isolated from pressure-overloaded hearts.[69] The pressure-overload induced severer LV hypertrophy and dysfunction in eNOS null mice than in wild-type mice.[70] By contrast, an upregulation of its expression was also shown in 2K1C rats with LVH[71] and in MCT-induced PAH rats with RVH.[72] The expression of nNOS was also increased in cardiomyocytes isolated from the pressure-overloaded heart and in the hypertrophic heart in SHR.[62,73] The discrepancy between the studies, either down-regulation or upregulation of NOS isoforms, may be ascribed to the duration of the entity. It is hypothesized that the initial coronary endothelial dysfunction precipitates LVH or RVH, which is followed by an enhanced expression of nNOS/eNOS to counteract it.

Nevertheless, mice with myocardial iNOS overexpression tend to have cardiac fibrosis, cardiomyocyte death, cardiac hypertrophy, and cardiac dilatation.[74] Aortic constriction induced the expression of myocardial iNOS and LVH in mice, and the degree of LV hypertrophy and dysfunction is much less in iNOS-deficient mice than in wild-type mice.[75] Cardiac myocyte hypertrophy was not observed in nNOS null or iNOS null mice.[76] It is likely that an increase in the myocardial activity of iNOS initiates the cardiac remodeling that is characterized by ventricular hypertrophy, dilatation, and sudden cardiac death.

7. Unilateral ureteral obstruction

Unilateral ureteral obstruction (UUO) culminates in various kinds of kidney damage, such as glomerulosclerosis, tubular apoptosis, and interstitial fibrosis. The NO/cGMP signaling pathway plays an important role in regulating the angiogenesis and slowing the interstitial fibrosis in the obstructed kidney. Disruption of NOS genes markedly accelerates the lesion formation in UUO, demonstrating the role of the NO system protecting against pathological renal remodeling.[77] The tubulointerstitial fibrosis in UUO was decreased by sGC stimulation.[78]

The expression of eNOS and vascular endothelial growth factors, which can stimulate/up-regulate eNOS, were significantly decreased in the obstructed kidney.[79] The effect of adrenomedullin attenuating the interstitial fibroblast and collagen deposition in the obstructed kidney was related to increased eNOS and NO production.[80] The expression and the activity of iNOS in the obstructed kidney were not consistent. A protective effect of iNOS-derived NO was documented: the obstructed kidney of iNOS null mice exhibited more apoptotic renal tubules than the wild-type mice.[81] The cytoprotective effect of NO was lost or weakened, along with the decreased expression of iNOS in the affected kidney in rats with spontaneous congenital hydronephrosis.[82] However, the effect of melatonin to prevent kidney damage was related to a reduced expression of iNOS, suggesting a harmful effect of iNOS.[83] The activity and expression of iNOS increased in the medulla, and that of the nNOS and eNOS isoforms increased in the cortex of the obstructed kidney; in which a nonhypotensive dose of losartan prevented the fibrogenesis along with attenuated iNOS and nNOS expression and persistent levels of eNOS.[84]

Similarly, the activity and the mRNA expression of iNOS increased in the medulla and those of eNOS increased in the cortex of the obstructed kidney in children with congenital partial ureteropelvic junction obstructions.[85] The NO contents and iNOS expression were increased at transcriptional and post-transcriptional levels without apoptotic responses 5 days after the obstruction, and decreased at mRNA and protein levels with apoptosis induction at day 14 in neonatal rats with UUO.[86] The expression of iNOS and eNOS was observed from days 7 and 10 after the ligation, respectively, keeping elevated until day 21 in UUO rats.[87] The severity or the duration of UUO may influence the activity of the NO system on long-term renal injury.

8. Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus (NDI) results from an

inability to adequately concentrate the urine despite normal, if not elevated, plasma concentrations of vasopressin (VP). VP stimulates adenylyl cyclase via V2 receptors in collecting duct principal cells and increases the production of cAMP. The increase of intracellular cAMP triggers the translocation of aquaporin-2 (AQP2) to the apical membrane and, over a prolonged period, induces the upregulation of AQP2 mRNA and protein abundance, thereby increasing water permeability and reabsorption.

All components of the NO/cGMP pathway are expressed in renal epithelial cells, of which activity may also be affected by VP. In water-restricted rats, n/i/eNOS mRNA levels were increased in the kidney along with increased plasma VP concentrations, which may have a role in the adaptation of renal function to volume depletion.[88] Furthermore, AQP2 may be regulated by basal nNOS activity in the kidney.[89] NO promotes the membrane insertion of AQP2 from the cytoplasm to the apical membrane of principal cells in a cGMP-dependent manner.[90] Both sildenafil (selective PDE5 inhibitor) and 3-isobutyl-1-methylxanthine (non-selective PDE inhibitor) enhanced AQP2 expression in the apical membrane of principal cells.[91] These findings may, at least in part, explain the significant amount of AQP2 expression in Brattleboro rats having no circulating VP.

The involvement of defective NO/cGMP pathway in the development of NDI has been confirmed in n/i/eNOS null mice, in which poyuria, polydipsia, and dehydration are prominent along with significantly reduced AQP2 abundance.[5] The most common complication of chronic lithium (Li) therapy is the development of NDI; in which Li impairs the stimulatory effect of VP on adenylyl cyclase, thereby decreasing cAMP levels and water permeability in the principal cells by inhibiting the translocation and generation of AQP2. Li-induced NDI was ameliorated by sildenafil along with increased eNOS/cGMP levels and partially normalized expression of AQP2 in the medullary collecting duct.[92]

9. Cardiorenal syndrome (Renocardiac syndrome)

A highly complex interplay exists between the heart and the kidney, whereby HF and renal dysfunction have been conventionally recognized as comorbidities. A dysfunction in one organ, either the heart or the kidney, can accelerate pathological changes in the other. In severe chronic experimental HF, glomerular cGMP formation in response to atrial natriuretic peptides or SNP also decreases.[93] The risk factors for cardiovascular diseases also affect the initiation and/or progression of renal dysfunction. Conversely, chronic kidney disease (CKD) is associated with an increased risk of cardiovascular diseases to a similar degree as that of diabetes mellitus or pre-existing ischemic heart diseases.[94]

Such an interaction accounts for the pathophysiological basis for a clinical entity called cardiorenal (renocardiac) syndrome, underlying mechanisms of which include a reduced availability of NO as one of key components. The expression and the activity of eNOS and nNOS were significantly decreased not only in LV but also in the kidney of HF rats.[95] Conversely, the availability of NO may play a critical role in preserving the cardiac function in CKD.

In CKD model of subtotal-nephrectomized rats, treatment with NOS inhibitors decreased systemic NO production and induced LV systolic dysfunction.[96] The blockade of nNOS worsens LV diastolic dysfunction in rats with chronic renocardiac syndrome.[97] The expression of eNOS as well as that of iNOS was decreased both in the kidney and the vasculature of rats with chronic renal failure.[98] In the triply NOS null mice, cardiovascular risk factors (hypertension, hypercholesterolemia, and hyperglycemia) were noted in association with significant increases in plasma AII levels and urinary 8-isoprostane levels (a marker of oxidative stress); and subtotal nephrectomy caused sudden cardiac death due to acute MI as early as 4 months after the surgery.[99]

SUMMARY

The mechanisms underlying the reduced NO bioavailability and endothelial dysfunction differ according to specific risk factors affecting the disease. Hypertension has been associated with a diminished bioavailability of endothelium-derived NO and a subsequent increase in peripheral vascular resistance. The vascular relaxation in response to acetylcholine is blunted in patients with hypertension or prehypertension and various animal models of hypertension, while that in response to direct NO donors is maintained. A deficiency in eNOS activity is mainly responsible for the elevation of blood pressure, whereas an abnormal expression of iNOS is likely to be related to the progression of vascular dysfunction in hypertension. Endothelial dysfunction is one of the earliest events also in PAH. The differential regulation of the components of the NO system in different settings of hypertension may be related to specific causative factors that increase the blood pressure, the duration of hypertension, and differences in the species of affected tissues or organs, etc.

NO has protective effects against atherosclerosis, whereas ROS results in atherosclerosis development by causing a rapid decrease of the anti-inflammatory and anti-atherogenic activities of NO. While the effects of eNOS and nNOS are protective against the arteriosclerotic vascular lesion formation, the effect of iNOS may be proatherogenic. The endothelial dysfunction may precipitate the occurrence of acute unpredictable cardiovascular events, such as MI, stroke, and cardiovascular death. The eNOS-derived NO may be effective in preventing the progression of MI. Cardiac ischemia may cause a loss of eNOS activity, leading to coronary dysfunction. Acutely reperfused coronary arteries exhibit a reduced responsiveness to a variety of endothelium-dependent vasodilators. Myocardial I/R injury is significantly enhanced in eNOS-deficient animals compared with wild-type controls. An early ischemic preconditioning may be useful to accelerate the complete recovery

of endothelial function by preserving the level of eNOS and stimulating the basal production of NO. An important component of HF is the loss of peripheral and coronary vascular eNOS activity: the increased oxidative stress resulting from under-perfusion of the tissues leads to the down-regulation of eNOS and bioavailability of NO. The dynamic changes in myocardial NO production with the development of HF represent a shift from a spatially and temporally regulated (by eNOS or nNOS) to a deregulated and excessive release of NO (mostly by iNOS). Attenuation of endogenous NO formation induced myocardial hypertrophy. In eNOS null mice, a pressure-overload induced severer LV dysfunction, LVH, and myocardial fibrosis than in wild-type mice. iNOS-derived NO has detrimental effects on the myocardium.

In UUO, the expression of eNOS was significantly decreased in the affected kidney. The endothelium-derived NO plays an important role in regulating the angiogenesis and slowing the interstitial fibrosis in the obstructed kidney. The renal lesion formation caused by UUO was noted in wild-type, singly NOS null, and triply NOS null mice, suggesting the critical protective effect of the NO system against pathological renal remodeling. NDI results from an inability to adequately concentrate the urine despite normal or elevated plasma concentrations of VP. VP may increase the expression of nNOS and eNOS in water-deprived rats. SNP and L-arginine are able to shift the localization of AQP2 from the cytoplasm to the apical side of collecting duct principal cells in a cGMP-dependent manner.

Conventionally, HF and renal dysfunction have been recognized as comorbidities, in which a highly complex interplay exists between the two organs. The renal and vascular expression of eNOS and iNOS decreased in rats with chronic renal failure. The availability of NO may play a critical role in preserving the cardiac function in CKD. In the CKD model of subtotal-nephrectomized rats, treatment with NOS inhibitors decreased systemic NO production and induced LV systolic dysfunction (renocardiac syndrome).

ACKNOWLEDGEMENTS

This study was supported by a grant from Chonnam National University Hospital Biomedical Research Institute (CRI13903-21).

CONFLICT OF INTEREST STATEMENT

None declared.

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