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Angiotensin II, nitric oxide, and end-organ damage in hypertension

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Angiotensin II, nitric oxide, and end-organ damage in hypertension. The adaptive changes that accompany hypertension and involve the kidney, heart, and vessels, namely, muscle hypertrophy/hyperplasia, endothelial dysfunction and extracellular matrix increase can, in fact, be maladaptive and eventually lead to end-organ disease, such as renal failure, heart failure, and coronary disease. However, these changes vary markedly between individuals with similar levels of hypertension. Nitric oxide (NO), an endogenous vasodilator and inhibitor of vascular smooth muscle and mesangial cell growth, is synthesized in the endothelium by a constitutive NO synthase (NOS). NO antagonizes the effects of angiotensin II on vascular tone and growth and also down-regulates the synthesis of angiotensin converting enzyme (ACE) and angiotensin II type 1 (AT-1) receptors. In hypertension, the physiologic response to the increased shear stress and cyclic strain is to upregulate NOS activity in endothelial cells. Upregulation of vascular NOS activity is a homeostatic adaptation to the increased hemodynamic workload that may help in preventing end-organ damage. Indeed, hypertension-prone salt-sensitive rats manifest a decrease (instead of an increase) in vascular NOS activity when hypertensive; these rats develop severe vascular hypertrophy, left ventricular hypertrophy, and renal injury. Studies in hypertensive humans suggest that, independent of the effects of salt on blood pressure, salt sensitivity may be a marker for susceptibility to the development of endothelial dysfunction as well as cardiovascular and renal injury. We hypothesize that in hypertension, recognition of markers of cardiovascular susceptibility to injury and the understanding of the pathophysiological mechanisms involved may open new opportunities for therapeutic intervention. In this context, only those antihypertensive agents that lower blood pressure and concomitantly restore the homeostatic balance of vasoactive agents such as angiotensin II and NO within the vessel wall would be effective in preventing or arresting end-organ disease.

Epidemiological studies have demonstrated that in hypertensive patients, increased serum creatinine [1], proteinuria [2] and microalbuminuria [3] are independent predictors of an increased cardiovascular morbidity/mortality due to left ventricular hypertrophy (LVH)/heart failure and coronary artery disease [1]. This suggests that end-organ damage in hypertension is diffuse, affecting all organs. Most studies show that the excess morbidity and mortality related to hypertension are progressive over the entire range of systolic and diastolic blood pressures. However, end organ damage varies markedly between individuals with similar levels of hypertension [4, 5]. For example, specific complications like LVH and chronic renal failure [6], have been shown to be more common in blacks than in whites, and in salt sensitive hypertensives independent of ethnicity [7, 8]. In patients with end-stage renal failure who are receiving hemodialysis, the incidence of myocardial ischemia/infarction approaches 20 times that in the general population [9]; in these patients the prevalence of cardiac death is higher during the first few years of dialysis, suggesting that cardiac disease is pre-existent and not acquired during chronic hemodialysis. In the aggregate these studies suggest that factors may be present that can both decrease or promote the susceptibility of individuals to hypertension and its complications. Therefore, the need to identify these factors and the subsets of patients who are at higher risk for development of end-organ disease is of paramount importance.

In this context, recent studies have shown that a deletion polymorphism of the angiotensin converting enzyme (ACE) gene is associated with target organ damage in hypertension. Specifically, the D allele of the ACE gene has been associated with microalbuminuria, LVH, and coronary artery disease, as well as with renal complications in insulin-dependent diabetes [10, 11]. Our laboratory has had a long standing interest in studying the relationship between endothelium dysfunction and cardiovascular injury in hypertension [12–14]. The endothelium plays a crucial role in the regulation of vascular tone by producing vasodilator and vasoconstrictor substances. Nitric oxide (NO) is one of the most important and well characterized endogenous vasodilators. NO is produced in endothelial cells by the enzyme nitric oxide synthase (NOS) [15], which can be activated by neurohumoral substances such as acetylcholine (Ach) and substance P, as well as by mechanical stimuli

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such as shear stress and cyclic strain [16]. NO has other important functions in the vessel wall, which include inhibition of platelet aggregation and inhibition of adhesion molecule expression, as well as prevention of vascular smooth muscle and mesangial cell proliferation [17]. Studies comparing endothelial NOS knock-out mice to wild mice showed that the NOS knock-out mice develop a more marked increase in vessel wall thickness due to vascular smooth muscle hyperplasia, in response to hemodynamically-mediated vascular injury [5]. Hence, NO acts as an antiatherogenic, antiproliferative, and antithrombotic factor that modulates vascular as well as glomerular remodeling in response to injury [17].

Superoxide anion is produced by the endothelium in response to various stimuli including oxidized lipoproteins, hyperglycemia [18] and ischemia [19]. This small molecule rapidly reacts and inactivates NO to form the highly reactive intermediate peroxynitrite (ONOO).

In hypercholesterolemia, measurements of superoxide anion levels in aortic segments of cholesterol-fed rabbits revealed that the production of superoxide anion is increased approximately threefold compared to vascular tissue obtained from normocholesterolemic animals [20]. This is also associated with impaired NO-dependent vascular relaxation, despite suggestive evidence of an increased production of NO. These finding suggest the possibility that, at least in earlier stages of hypercholesterolemia, the production of nitric oxide is unaltered, but is destroyed by superoxide anion. Furthermore, chronic NOS inhibition using subpressor doses of L-NAME in cholesterol-fed rabbits results in a dramatic increase in neointima formation in the thoracic aorta when compared with rabbits that consumed the cholesterol diet alone [21]. This supports the notion that the loss of NO and more important imbalance between NO and superoxide anion production may contribute to the development of atherosclerosis.

Studies done in our laboratory showed that hypertension prone, Dahl salt sensitive (DS) rats fed high cholesterol/vitamin E and selenium deficient diet do not develop hypertension; however, they exhibit significantly impaired endothelium dependent relaxation [22]. In the aggregate these studies suggest that NO has a more important role in modulating vascular remodeling in response to injury than in regulating blood pressure.

INTERACTION BETWEEN NITRIC OXIDE AND ANGIOTENSIN II

Angiotensin II has multiple effects on the cardiovascular system. These include vasoconstriction, promotion of renal sodium and water retention and therefore expansion of the plasma volume, induction of vascular smooth muscle growth, and modulation of myocardial hypertrophy and fibrosis [23]. Angiotensin II also plays an important role in the regulation of glomerular filtration rate (GFR) and renal blood flow by predominantly constricting the efferent and the afferent glomerular arterioles [24]. Angiotensin II has been found to modulate growth factors such as PDGF and TGF-β, which have been implicated in the pathological remodeling of the glomerulus in response to injury [25, 26]. It also has been reported that angiotensin II activates NADH/NADPH oxidase in vascular smooth muscle [27] and, according to more recent reports, in mesangial cells [28], and leads to the cells' protracted synthesis of superoxide anion NO, which has been shown to inhibit the response of mesangial cells to growth stimulating signals that are driven by angiotensin II that result in mesangial cell hypertrophy and/or hyperplasia as well as in increased matrix production [17].

It is now clear that angiotensin II can be synthesized at a variety of sites [29], including the kidney, vascular endothelium, adrenal gland and brain. In this context a concept of paracrine-autocrine functions of the renin-angiotensin system (RAS) in the regulation of cardiovascular and renal function has been developed. Since both angiotensin II and NO are synthesized and released locally, the antagonistic interaction of these two agents is important in the regulation of renal physiology and renal pathology. NO downregulates the synthesis of ACE [30] and of angiotensin II type-1 receptors (AT-1) in vascular tissue [31]. Chronic NO synthesis inhibition results in glomerular and tubulointerstitial injury [12] as well as coronary vascular remodeling, LVH and hypertension. This suggests that decreased vascular NO bioactivity due to endothelial dysfunction, as seen in hypertension, may promote vascular remodeling due to the combined deficit of NO and the local excess (absolute or relative) of angiotensin II.

NITRIC OXIDE AND RENAL HEMODYNAMICS

The pressures and flow that determine single nephron GFR (SNGFR) are controlled by the tone of afferent and efferent arterioles [17]. The ratio of the tone of these resistances determines the glomerular blood pressure and the overall level of tone in these vessels controls glomerular plasma flow. The glomerular capillary ultrafiltration coefficient, Kf, is another variable that can directly influence SNGFR. Changes in ultrafiltration may occur via alterations in tone of glomerular mesangial cells which result in alterations in glomerular filtration surface [17]. NO inhibits mesangial contraction induced by angiotensin II [17].

Intrarenal NO synthesis blockade at levels that do not change systemic arterial blood pressure results in a small rise in afferent arteriolar resistance, a small decrease in the glomerular ultrafiltration coefficient, and in single nephron GFR [32]. However, glomerular capillary pressure and efferent arteriolar resistance do not change unless the systemic administration of higher doses of NOS inhibitors results in a significant increase in systemic arterial blood pressure. In juxtamedullary nephrons, both afferent and efferent arterioles are under the tonic control of NO [33],

whereas in cortical nephrons, the afferent arteriole is predominantly under the tonic control of NO [32].

Studies of the relationship between angiotensin II and NO on renal blood flow shows that NOS inhibition decreases both cortical and papillary blood flow, and that AT-1 receptor blockade abolishes the effect of NOS inhibition on the cortical circulation, but has minor effects on the medullary blood flow [34]. These results suggest that NO is an important modulator of the vasoconstrictor influence of angiotensin II in the renal cortical circulation, but not in the medullary region.

Nitric oxide also contributes to the regulation of renal hemodynamics by participating in the control of the tubuloglomerular feedback (TGF) response and by modulating renin release from the juxtaglomerular cells [35].

INTERACTION OF NITRIC OXIDE WITH ENDOTHELIN

The endothelin (ET) family comprises three 21-amino acid peptides (ET-1, ET-2 and ET-3) [36]. ET-1 is the major renal ET isoform. ET receptors comprises two types of receptors, ET-A and ET-B [37, 38].

Most endothelial cells express only ET-B receptors, and activation of these receptors induces production of PGI_2 and NO, which counteract the vasoconstrictor effect of ET-1 [39]. Stimulation of the ET-A receptor, which is widely distributed in vascular smooth muscle cells, mediates most of the vasoconstrictor response to endothelins [40]. ET-1 causes mesangial cell contraction and induces mesangial cell mitogenesis [41].

The vast majority of ET-1 is derived from endothelial cells where many agents including thrombin, angiotensin II, inflammatory cytokines like IL-1 and TNF stimulate the endothelial cell to synthesize and release ET-1 [42]. On the other hand NO, bradykinin, PGE_2, PGI_2, atrial natriuretic peptide and high levels of shear stress are known to inhibit endothelial cell ET-1 production [42]. These factors appear to inhibit ET-1 release through stimulation of endothelial cell NO and/or cGMP production.

In porcine aorta, NO synthesis inhibition augments the release of ET-1, while 8-bromo cGMP has an inhibitory effect, suggesting that NO inhibits ET production via cGMP dependent mechanism [43]. Furthermore, the ET-A and ET-B receptor antagonist bosentan has recently been shown to attenuate the pressor response to NOS inhibition [44]. Human and animal studies have suggested that there is a feedback mechanism between ET-1 and NO synthesis that acts reciprocally to regulate vascular tone [44].

In hypertensive DS rats, NOS is down-regulated in the aorta and kidney [12]. In these rats, contraction of aorta to ET-1 is attenuated, suggesting that vascular ET-1 receptors are down-regulated, due to an increased local ET-1 synthesis linked to decreased NO production [12]. Moreover, urinary excretion of ET-1 is markedly increased in hypertensive DS rats given high dietary salt but not in Dahl salt-resistant rats [13]. This finding supports the notion that hypertension when accompanied by decreased NO synthesis promotes up-regulation of vascular and renal ET-1 synthesis.

NITRIC OXIDE AND HYPERTENSION

The pivotal role of the kidney in the development of arterial hypertension was noted through the connection between hypertension and renal disease, in which the rise in blood pressure is in part due to the kidney's impaired ability to excrete salt and water [45]. In hypertensive strains of rats, renal cross transplantation experiments between hypertensive and normotensive counterparts demonstrated that hypertension "follows the kidney" [46].

NO plays an important role in the regulation of medullary blood flow, and changes in the medullary flow can reset the pressure-natriuresis relationship, promote sodium retention and contribute to the development of hypertension [47]. The pressure natriuresis relationship plays a role in opposing incremental increases in blood pressure, where an increase in blood pressure is compensated by an increase in renal excretion of water and salt. Therefore, impaired NO synthesis, resulting in abnormal regulation of renal blood flow and sodium handling, may aggravate salt sensitive hypertension.

Abnormal endothelial function has been reported in several experimental models of hypertension, including spontaneous hypertensive rats (SHR) [48], DS rats [49], and deoxycorticosterone acetate (DOCA) salt hypertensive rats [51]. In SHR, the impaired endothelium-dependent relaxation to Ach is normalized by indomethacin, and this suggests that in the SHR synthesis of vasoconstrictor(s) derived from cycloxygenase plays an important role in modulating abnormal vascular tone [51]. In DS and DOCA-salt rats, indomethacin is ineffective, suggesting that in DS and DOCA-salt rats, impaired endothelial function is secondary to decreased production of NO.

Clinical and experimental data have demonstrated that the physiologic response to an increase in cyclic strain, as that imposed by hypertension, is to up-regulate vascular constitutive NOS activity [16]. Hayakawa and Raij have recently used age-matched SHR and DS rats with hypertension of similar severity and duration to investigate the relationship between hypertension and vascular NOS activity [12]. Aortic calcium dependent NOS activity measured by the conversion of [^{14}C] L-arginine to [^{14}C] L-citrulline was increased 106% in SHR but reduced by 73% in DS rats compared with their normotensive counterparts (Fig. 1). Hence, increased NOS activity in SHR suggests that SHR but not DS rats are able to mount a normal physiologic response to increased blood pressure, namely, an increase in NOS activity.

In DS rats, antihypertensive therapy consisting of ACE inhibitor and a diuretic concomitantly prevented hypertension, as well as the fall in NOS [13]. These studies support

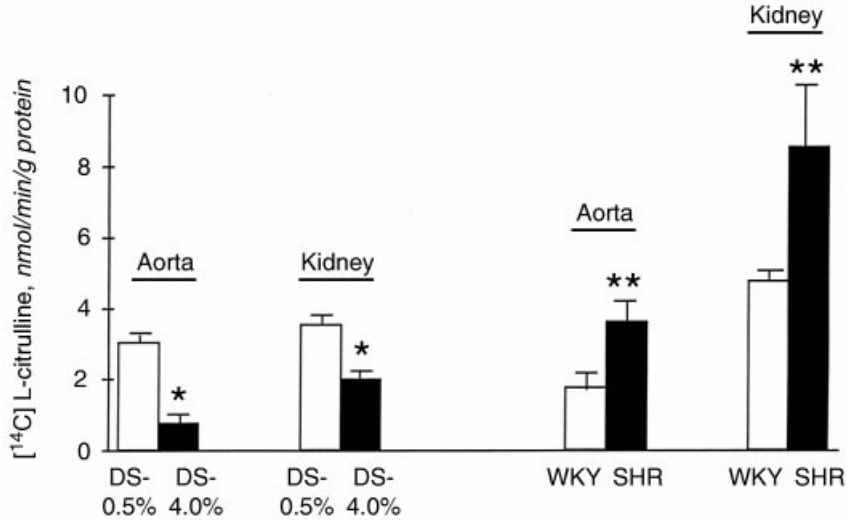

Fig. 1. Constitutive nitric oxide synthase (cNOS) in aortas and kidneys from normotensive Dahl salt-sensitive (DS) and Wistar-Kyoto (WKY) rats and hypertensive DS and spontaneous hypertensive rats (SHR). Systolic blood pressure (SBP) mm Hg was: DS, 0.5%, 133 ± 3; DS, 4.0%, 211 ± 7; WKY, 137 ± 3; and SHR, 219 ± 12. $^{*}P < 0.5$ vs. DS 0.5%; $^{**}P < 0.05$ vs. WKY. Values are mean ± SE (From [12]). Dahl rats were from the Brookhaven strain.

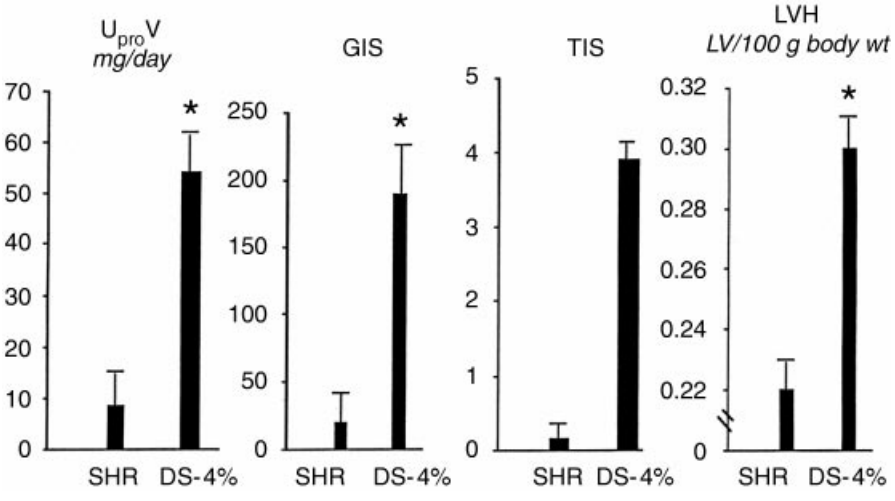

Fig. 2. Urinary protein excretion ($U_{pro}V$), glomerular injury score (GIS), tubular injury score (TIS), and left ventricular hypertrophy (LVH) in hypertensive DS 4.0% (SBP 211 ± 7 mm Hg) and SHR (SBP 219 ± 12 mm Hg), matched for SBP and duration of hypertension. $^{*}P < 0.05$ versus SHR. Values are mean ± SE. (From [12–14]). Dahl rats were from the Brookhaven strain.

the notion that in DS rats, the fall in NOS activity is a consequence and not a cause of hypertension.

LINK BETWEEN NITRIC OXIDE SYNTHASE ACTIVITY AND RENAL, VASCULAR AND CARDIAC INJURY

Comparative studies of SHR and hypertensive DS rats suggest a link between NOS activity, vascular remodeling, and end-organ injury (Fig. 2). In these studies, aortic hypertrophy did not occur and LVH increased only 15% in SHR [12], whereas in hypertensive DS rats the aorta and left ventricle hypertrophied 36% and 88%, respectively. A significantly negative correlation between NOS activity and aortic and LVH was also noted [12–14]. Furthermore, in the kidney, increased NOS activity in SHR was accompanied by minimal glomerular and tubulointerstitial disease as well as minimal urinary protein excretion. In hypertensive DS rats, however, renal NOS activity fell markedly, and severe glomerular injury, heavy proteinuria, and marked tubulointerstitial disease occurred [14].

In conclusion, recent animal studies suggest that in hypertension, NOS activity is linked with end-organ disease and that impaired NOS activity may be more commonly seen in salt-sensitive models of hypertension [12–14]. Studies in humans have suggested a similar scenario: salt sensitive hypertensive patients are more prone to the development of hypertensive end-organ disease, particularly LVH and renal disease [7, 8]. Aging is characterized by increased prevalence of hypertension, salt sensitivity [52] and decreased endothelium-dependent relaxation mediated by NO [53].

In view of these associations and the finding described, it is tempting to speculate that 1) vascular NOS activity (upregulation or downregulation) in response to hypertension may be genetically determined and 2) abnormalities in vascular NOS responses may at least partially explain the

different rates of occurrence of end-organ disease in humans with hypertension of similar severity [2, 54, 55]. We further speculate that in elderly patients the increased susceptibility to the development of hypertensive end-organ damage may be linked, at least in part, to the "physiologic" decrease in endothelial NO bioactivity that occurs with aging.

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APPENDIX

Abbreviations are: ACE, angiotensin converting enzyme; Ach, acetylcholine; AT-1, angiotensin II type 1; DOCA, deoxycorticosterone acetate; DS, Dahl salt sensitive; ET, endothelin; ET-A, endothelin type A; ET-B, endothelin type B; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; NO, nitric oxide; NOS, nitric oxide synthase; PDGF, platelet-derived growth factor; SHR, spontaneous hypertensive rats; SNGFR, single nephron glomerular filtration rate; TGF-β, transforming growth factor β.

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