Hypertension in Black Patients
An Emerging Role of the Endothelin System in Salt-Sensitive Hypertension
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Abstract—The prevalence of essential hypertension in blacks is much higher than that in whites. In addition, the pathogenesis of hypertension appears to be different in black patients. For example, black patients present with a salt-sensitive hypertension characterized by low renin levels. Racial differences in renal physiology and socioeconomic factors have been suggested as possible causes of this difference, but reasons for this difference remain unclear. Endothelial cells are important in the regulation of vascular tonus and homeostasis, in part through the secretion of vasoactive substances. One of these factors, endothelin-1 (ET-1), is a 21 amino acid residue peptide with potent vasopressor actions. In addition to its contractile effects, it has been shown to stimulate mitogenesis in a number of cell types. Moreover, ET-1 displays modulatory effects on the endocrine system, including stimulation of angiotensin II and aldosterone production and inhibition of antidiuretic hormone in the kidney. Recent data from several laboratories indicate that ET-1 is overexpressed in the vasculature in several salt-sensitive models of experimental hypertension. Moreover, circulating plasma ET-1 levels are significantly increased in black hypertensives compared with white hypertensives. Thus, the ET system might be particularly important in the development or maintenance of hypertension in this population. (Hypertension. 2000;36:62-67.)

Key Words: endothelin ■ hypertension, essential ■ blacks ■ sodium, dietary ■ race

Epidemiological studies have established that black Americans have an increased prevalence of essential hypertension compared with white Americans.1–4 Furthermore, the disease onset is earlier, and the consequences of hypertension, which include heart failure, myocardial infarction, stroke, and renal failure, are more pronounced in black patients.1,5 These racial differences in the development and clinical course of hypertension have been attributed to environmental and physiological factors.1,5 One hypothesis is that the development and progression of hypertension in blacks are related to abnormal hemodynamic reactivity characterized by increased peripheral vascular resistance in response to external stimuli, including physical and mental stress.1,6 Although the mechanism for increased peripheral vascular resistance has not been elucidated, vasoactive substances produced by endothelial cells such as endothelin-1 (ET-1) and NO are possible candidates to contribute to the vascular reactivity in response to mental stress.7–9 An increase in ET-1 levels, the most potent vasoconstrictor peptide with growth-promoting properties,10 a decrease in NO production, or both would shift the balance in favor of vasoconstriction. Moreover, recent studies suggest that ET-1 and its receptors are also involved in the regulation of sodium and water reabsorption and excretion and may contribute to the development or maintenance of salt-sensitive hypertension.11,12 Interestingly, black patients with essential hypertension have been reported to exhibit elevated plasma ET-1 levels compared with white hypertensive patients.13 The purpose of this review was to briefly summarize the current understanding of the physiological basis of pathogenesis of hypertension in blacks, to examine the vasoactive and renal effects of the ET system, and to discuss how this system may contribute to the development and maintenance of hypertension in blacks.

Pathogenesis of Hypertension
Racial Differences in Sympathetic Reactivity
It has been proposed that blacks experience chronic sympathetic system activation due to more recurrent exposure to social and environmental factors14 (Figure 1). Consistent with this hypothesis, a number of studies have demonstrated that black Americans display greater cardiovascular reactivity to a number of physical and mental stressors. For example, Murphy et al15 reported that black children and adolescents exhibit significantly higher blood pressure increase during a video game challenge. Similarly, Dysart et al16 and Treiber et al17 demonstrated that black children with a family history of essential hypertension manifest greater increases in total peripheral resistance, leading to greater increases in blood pressure in response to cold pressor test and the mental stress of playing a video game. Another group found that black children tended to have augmented pressor responses compared with white children during isometric hand-grip exercise.
and orthostatic testing. Using microneurography, Calhoun et al measured the muscle sympathetic activity of the peroneal nerve at rest and during cold pressor testing and provided direct evidence that blacks exhibit increased peripheral sympathetic nervous system activity compared with whites. Furthermore, several groups have shown that heightened blood pressure reactivity to laboratory stress is an independent predictor of primary hypertension. On the basis of these studies, repeated stress-induced sympathetic activation has been proposed to initiate a cycle of increased vascular resistance and vascular hypertrophy that results in the development of hypertension. Therefore, environmental stressors are likely to enhance sympathetic reactivity and to contribute to the early development and severe progression of hypertension in black Americans.

**Racial Differences in Salt Sensitivity**

In general terms, salt sensitivity is defined as an increase in blood pressure in response to relatively high sodium intake. Both normotensive and hypertensive black individuals are known to be more salt sensitive than white Americans. For example, when black normotensive individuals and patients with borderline hypertension on a salt-restricted diet were allowed to return to their regular diet, 27% of the normotensives and 50% of the hypertensive subjects displayed an increase of >5% in their mean arterial blood pressure. However, these percentages were only 15% and 24% in white normotensive individuals and borderline hypertensives, respectively. Falkner and Kushner studied the vaso-reactive response to several factors in the aortic rings obtained from salt-induced hypertensive rats and demonstrated that hypertension induced by salt loading was associated with increased sensitivity to norepinephrine, enhanced Ca entry through receptor-operated channels, and impairment of ATPase activity. On the basis of these observations, Fray and Douglas proposed that the pathogenesis of hypertension can be divided into 3 phases. The first phase involves an increase in stress response factors such as catecholamines that leads to increased total peripheral resistance. In phase II, genetic factors such as salt sensitivity come into play and lead to intravascular volume overload with heightened vascular reactivity. The last phase (phase III) is characterized by established hypertension.

**The Endothelin System**

The ETs are a family of 3 distinct 21-residue peptides, ET-1, ET-2, and ET-3, that are produced from precursor proteins via multiple cleavage steps (Figure 2). Prepro-ET is initially cleaved by a dibasic-specific endopeptidase and a carboxypeptidase to yield an inactive intermediate, termed big ET, which is further processed by endothelin-converting enzyme (ECE) to generate the active peptide. Various factors, including insulin, thrombin, angiotensin II (Ang II), vasopressin, low shear stress, and ET-1 itself, stimulate ET production at the transcriptional level. ET-1, the major isopeptide synthesized by endothelial cells, is a potent vaso-
constrictor and is secreted abuminally toward the underlying smooth muscle.\textsuperscript{27} (Figure 2). Therefore, circulating ET-1 is believed to be the result of spillover from the vascular wall. In addition to its potent vasoconstrictor effects, ET-1 has been shown to enhance mitogenesis in various cell lines, such as vascular and airway smooth muscle cells and fibroblasts.\textsuperscript{27}

The mature peptide exerts its diverse effects via 2 distinct G protein–coupled receptor subtypes (Figure 2). The ET\textsubscript{A} receptor subtype binds ET-1 and ET-2 with higher affinity than ET-3.\textsuperscript{28} The ET\textsubscript{B} receptor subtype displays similar affinities for all ET isoforms.\textsuperscript{28} Both receptors are distributed in various tissues and cells in different proportions. ET\textsubscript{A} receptors, which as localized mainly on smooth muscle cells of blood vessels, are believed to be involved in the vasoconstrictive response to ET-1.\textsuperscript{27,28} The ability of vascular smooth muscle cells to produce bioactive ET-1 has suggested that ET-1 might be involved in the contraction and growth of these cells in a paracrine and an autocrine manner.\textsuperscript{29} The role of ET\textsubscript{B} receptors in smooth muscle contraction is more complex. For instance, ET\textsubscript{B} receptors located on endothelial cells mediate vasodilation via the release of NO. This receptor subtype can also exert vasoconstriction when located on the smooth muscle cells.\textsuperscript{28} Thus, the net contractile effect of ET-1 depends mainly on the relative density of ET\textsubscript{A} receptors on smooth muscle cells and of ET\textsubscript{B} receptors on endothelial cells. ET\textsubscript{B} receptors are also involved in the clearance of circulating ET-1,\textsuperscript{30,31} as well as in sodium and water reabsorption from distal tubules, as discussed later.

**ET and Vascular Reactivity**

The intravenous administration of ET-1 causes a rapid and transient vasodilatation followed by a sustained increase in blood pressure.\textsuperscript{30} The pressor response is due to increased total peripheral resistance with no change in heart rate and cardiac output and is blocked by the administration of ET\textsubscript{A} receptor antagonists.\textsuperscript{28,32} In addition to its direct vasoconstrictor effect, ET-1 amplifies the contractile response to other vasoactive agents, including norepinephrine and serotonin.\textsuperscript{31} Reciprocally, norepinephrine and serotonin can also potentiate the vasoconstrictor response to ET-1.\textsuperscript{28} These findings further demonstrate that ET-1 plays an important role in the regulation of vascular reactivity. In healthy individuals, the administration of a mixed ET\textsubscript{A}/ET\textsubscript{B} receptor antagonist increases the forearm blood flow and causes a small decrease in blood pressure, providing further evidence that ET-1 is involved in the regulation of vascular tone.\textsuperscript{34}

**ET and Renal Effects**

ET-1 has 2 main effects on kidney function, renal vasoconstriction and increased sodium and water excretion, which indicate distinct sites of action (for a review, see Kohan\textsuperscript{35}). ET-1 is a potent constrictor of both afferent and efferent arterioles and causes decreased renal blood flow and glomerular filtration rate, resulting in reduced urine flow and sodium excretion.\textsuperscript{27,35} Both receptor subtypes have been shown to contribute to renal vasoconstriction.\textsuperscript{35} and receptor subtype distribution shows a species difference. For example, the ET\textsubscript{A} subtype is responsible for renal vasoconstriction in humans and dogs,\textsuperscript{27} whereas in rats, ET\textsubscript{B} receptors mediate the same effect.\textsuperscript{52} However, the activation of ET\textsubscript{B} receptors on the distal tubules causes opposite effects and mediates the natriuretic and diuretic actions of ET-1.\textsuperscript{35}

Recent studies that involve ET\textsubscript{B} knockout mice provided further evidence that disruption of the gene encoding this receptor results in hypertension.\textsuperscript{11} Because the knock-out of ET\textsubscript{B} results in a genetic disorder called aganglionic megacolon, the role of this receptor in blood pressure regulation was further evaluated in “rescued” ET\textsubscript{B}–deficient mice.\textsuperscript{36} In this model, the expression of the receptor in the gastrointestinal tract was corrected with the result that these transgenic mice exhibited a normal phenotype and did not possess ET\textsubscript{B} receptors in any tissue other than the gut. When these animals were put on a high-salt diet, they developed hypertension, and the elevation of blood pressure could be prevented by the use of amiloride, a highly selective inhibitor of the epithelial sodium channel of the distal tubules.\textsuperscript{36} ET-1 also blocks reabsorption of water in the collecting duct by inhibiting the effects of antidiuretic hormone.\textsuperscript{26,35} On the basis of these findings, the current working hypothesis is that under normal conditions, the binding of ET-1 to the ET\textsubscript{B} receptor on the epithelial cells inhibits the epithelial sodium channel and promotes natriuresis and diuresis as depicted in Figure 3. In the rescued ET\textsubscript{B}–deficient mouse model, excess salt intake upregulates renal ET-1 production, and the lack of ET\textsubscript{B} receptor–mediated inhibition of the sodium channels results in excess sodium and water reabsorption and, ultimately, hypertension.

**The ET System in Experimental and Clinical Hypertension**

Because of its potent vasoconstrictor and mitogenic properties, ET-1 has been suggested to as being involved in the
pathogenesis of hypertension. It has been shown that the continuous infusion of ET-1, as well as overexpression of the PPET-1 gene in animal models, resulted in sustained hypertension. The circulating levels of ET-1 in the hypertensive animal models have been consistent, and it is now known that the ET system is activated in salt-dependent models of hypertension, including the deoxycorticosterone acetate (DOCA)-salt hypertensive rat and DOCA-salt–treated spontaneously hypertensive rats (for a review, see Schiffrin37). In these models, plasma levels of ET-1 are elevated and the expression of ET-1 in the vascular endothelium is enhanced.38 Consistent with these findings, ET receptor antagonists lower blood pressure in these models. In other hypertensive animal models, including spontaneously hypertensive rats, ET-1 concentrations are not elevated unless severe hypertension associated with renal impairment is present.38

In humans, several groups reported an elevation in plasma ET-1 levels in hypertensive patients,39 and a careful analysis of patient characteristics revealed that increased circulating levels were secondary to the impairment of renal clearance.27 Our laboratory reported that black hypertensive individuals have higher plasma ET-1 concentrations than white hypertensives and black normotensives.3 It appears that the ET system in human hypertension is similar to the animal models of hypertension and is turned on in salt-sensitive hypertension. Although plasma ET-1 levels are not elevated in all forms of hypertension, a mixed ET_A/ET_B receptor antagonist can lower blood pressure in individuals with mild hypertension.40

Vascular reactivity to ET-1 in the hypertensive state is also altered. In animal models as well as in patients with essential hypertension, the efficacy of ET-1 in resistance arteries is reduced, and this phenomenon has been attributed to the downregulation of ET receptors. On the other hand, ET-1–mediated constriction in the venous system is enhanced in hypertensive patients. To avoid the effect of vascular hypertrophy on vasoreactivity, Haynes and Webb27 and Haynes et al34 studied the responses to the local infusion of ET-1 into hand veins and found that maximal contraction in response to ET-1 was significantly greater in the hypertensive group than in the normotensive patients. Furthermore, ET-1 potentiated sympathetically mediated vasoconstriction in hypertensive patients, and a positive correlation was noted between ET-1–induced vasoconstriction and blood pressure. Because the venous system may contribute to the high cardiac output observed in early phases of hypertension, it has been suggested that ET-1 plays a role at this stage of the disease.

Growth-promoting properties of ET-1 may also play an important role in hypertension. In models associated with an activated ET system, there is substantial vascular hypertrophy, and the chronic administration of ET receptor antagonists in DOCA-salt–sensitive rats reduces vascular proliferation.41 In DOCA-salt–treated spontaneously hypertensive rats, another model that is characterized by malignant hypertension, ET-1 expression in the arteries and glomeruli is enhanced, suggesting that proliferative actions of ET-1 may play a role in fibrinoid necrosis and renal failure in this system.42 Even in models in which the ET system is not activated, such as spontaneously hypertensive rats, long-term treatment with an ET receptor antagonist improves renal function.43 Recently, Schiffrin et al44 extended these studies to human hypertension and demonstrated that the PPET-1 gene is overexpressed in small arteries obtained from gluteal subcutaneous biopsy samples from patients with moderate to severe hypertension. These findings provide strong evidence that ET antagonism may prove beneficial in the treatment of at least the complications of hypertension.

Black and the ET System

Plasma ET-1 Levels

Evans et al45 reported that in healthy individuals between the ages of 28 and 35 years, black men have significantly higher levels of ET-1 than white men. Interestingly, they did not detect any differences in ET-1 concentrations between black and white woman. In contrast, our group investigated the circulating ET-1 levels in hypertensive patients and found a difference.13 Both female and male black hypertensive patients had significantly higher ET-1 levels than white hypertensive patients. This study revealed that the magnitude of this difference between the black normotensive and hypertensive group was 8-fold.13 These striking differences suggested that ET-1 might be a contributory factor to the development, maintenance, and complications of hypertension in this population.

In another study, to assess the effect of rapid blood pressure control on plasma ET-1 levels, black patients with uncontrolled hypertension were followed for a 1-month period after antihypertensive treatment was initiated.46 Plasma ET-1 concentrations that were relatively high at the beginning of the study were dramatically reduced in a manner parallel to the reduction in blood pressure. This study provided indirect evidence that ET-1 levels may rise as a consequence of hypertension and contribute to the high incidence of hypertension-related complications in blacks.

The ET System and Vascular Reactivity

In a recent study, Treiber et al7 investigated plasma ET-1 levels at rest and in response to acute stress in white and black adolescents with family histories of essential hypertension. Both video game challenge and forehead cold stimulation resulted in a higher increase in ET-1 concentrations in blacks than in whites. Moreover, black individuals manifested higher diastolic blood pressure and total peripheral resistance than whites, and changes in ET-1 levels mirrored the changes in hemodynamic parameters. Although this study did not provide evidence that ET-1 was the causal factor in increased peripheral resistance, it clearly demonstrated racial differences in ET-1 levels in response to stress and lay the groundwork for future studies to investigate the role of ET-1 in the abnormal hemodynamic reactivity observed in the black population.

The distribution of ET receptors on peripheral vasculature also shows racial differences.47 A recent study reported that the total ET receptor density was higher in white patients and that they possessed only the ET_A subtype on vascular smooth muscle cells. Black patients had both receptor subtypes on vascular smooth muscle cells, yet the total number of ET_B receptors was lower than in white patients. This decrease in
ET\(_{a}\) ratio of endothelial to smooth muscle cells suggested a shift in favor of vasoconstriction-promoting receptors. However, the effect of this difference on vasomotor activity and whether the low receptor density is due to receptor down-regulation remain to be determined. Nevertheless, these findings provided evidence that in addition to ET-1 expression, ET receptors are also differentially regulated in blacks.

**Conclusions and Future Directions**

Despite substantial clinical and laboratory investigation, the reason or reasons for the increased prevalence of hypertension in blacks remain unknown. There clearly are socioeconomic and psychosocial factors involved. There also is accumulating evidence that the pathophysiologic basis of hypertension in blacks is different than that in whites. Hypertension is characterized with an abnormal hemodynamic reactivity and increased salt sensitivity. Plasma levels of potent vasoactive peptide ET-1 are significantly higher in blacks in response to acute stress and in the hypertensive states than in whites. Given the fact that ET-1 induces long-lasting vasoconstriction and modulates the sympathetic system–mediated contractility, it is likely that ET-1 contributes to the abnormal vascular reactivity in blacks. In the peripheral venous circulation, black patients have significantly lower numbers of ET\(_{a}\) receptors. Future studies are necessary to determine the effect or effects of these differences in receptor subtype distribution on ET-1–mediated contractility. Given that blacks exhibit an increased sympathetic system activity, how the vasomotor activity is modulated by the ET-1 and catecholamines in this population remains to be resolved. Moreover, studies are needed to investigate whether these differences in the receptor subtype distribution exist in healthy individuals and in other vascular beds. If the receptor subtype difference is true in the kidney epithelial cells where ET\(_{a}\) receptors are involved in natriuresis and diuresis, the ET system may play an important role in the salt-sensitive component of high blood pressure in blacks. Therefore, a careful consideration of the ET system in blacks and longitudinal studies that investigate the role of ET-1 in the development and complications of hypertension are warranted. Agents that modulate the ET system (ie, ET receptor antagonists, ECE inhibitors, or both) may prove beneficial to reduce the long-term complications of hypertension as well as in the treatment of hypertension in this population.

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**References**


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