Differences in Blacks and Whites With Essential Hypertension: Biochemistry and Endocrine

State of the Art Lecture

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Epidemiological studies have demonstrated racial and geographical differences in both incidence and severity of essential hypertension. In the United States, the prevalence of essential hypertension is far greater in blacks.\textsuperscript{1-4} This difference is further accentuated by vital statistics data on mortality. Blacks have a threefold greater mortality from hypertensive disease than whites. This disproportionate mortality increases to more than sixfold greater in blacks in the age range of 34–54 years.\textsuperscript{5} Thus, the morbidity consequences of hypertensive disease are several times greater in blacks, particularly in early to middle adulthood.\textsuperscript{6}

A vast body of investigations has demonstrated the multiple dimensions of blood pressure regulation. A remarkable finding in these studies is the clinical and biochemical heterogeneity of essential hypertension. It is well accepted that not all patients with essential hypertension have the same underlying pathophysiology. Profiles of endocrine or metabolic function have been developed to characterize different groups of patients with hypertension. Some of the prominent endocrine or physiological expressions in hypertensive patients have been used to develop a subclassification of hypertension. These expressions include renin-angiotensin,\textsuperscript{7} endocrine modulation,\textsuperscript{8} and calcium metabolism.\textsuperscript{9} Some of these variations of biologic function have also been identified among normotensive relatives of hypertensive patients, indicating that these functional patterns of hypertension are operational before the onset of elevated blood pressure. Not only are there different and distinguishable patterns in the endocrine-biochemical profile of hypertensive patients, but values in different groups of patients can deviate in opposite directions from average normotensive values. For example, low-renin hypertension appears to be a disorder distinctly different from high-renin hypertension.\textsuperscript{7} Calcium metabolism is another area of paradox in which some hypertensive patients appear to have a shift in calcium metabolism indicative of a calcium deficit, whereas other patients appear to have calcium excess.\textsuperscript{9} Investigations that now distinguish clinical populations by race and age have shown that blacks with hypertension exhibit variations in endocrine regulation that differ from both normotensive subjects, generally, and hypertensive whites.

Sodium Sensitivity

There are several investigations of sodium sensitivity that have shown that blacks respond to shifts in sodium balance more frequently than whites.\textsuperscript{10-12} In extensive studies of sodium loading and sodium depletion, Weinberger et al\textsuperscript{13} have demonstrated a greater prevalence of sodium sensitivity in both normotensive and hypertensive blacks. In blacks who demonstrated a pressure response to a sodium load, there was a delay in renal excretion of sodium. These observations correlate with lower plasma renin levels and a blunted response to furosemide-stimulated plasma renin activity in blacks.\textsuperscript{14-16}

Sodium sensitivity as defined in clinical investigations appears to be related to an impaired ability to excrete a sodium load. Sowers et al\textsuperscript{17} investigated, in normotensive and hypertensive blacks, the capacity to generate natriuretic substances such as dopamine, prostaglandin E\textsubscript{2} (PGE\textsubscript{2}), and atrial natriuretic factor. Both normotensive and hypertensive blacks exhibited sensitivity to sodium by an increase in blood pressure after a change from low sodium (40 mmol/day) to high sodium (180 mmol/day) dietary intake. Plasma aldosterone, urinary norepinephrine, and PGE\textsubscript{2} were comparable in the two groups at both levels of sodium intake. Plasma atrial natriuretic factor increased with increasing sodium intake only in the hypertensive group. The hypertensive blacks exhibited lower dopamine excretion compared with normotensive blacks for both levels of sodium intake. These authors proposed that decreased renal production of dopamine might contribute to the sodium sensitivity and might also be a pathological factor in the development of hypertension in blacks.

Investigations on the renal kallikrein system have also demonstrated racial differences. Zinner et al\textsuperscript{18} reported lower levels of urinary kallikrein concentr-
ition in black children than in white children. Levy et al measured urinary kallikrein in normotensive and hypertensive subjects, including both blacks and whites, during usual diet and again after sodium restriction. They reported significantly lower levels of urinary kallikrein in blacks than in whites. With sodium restriction, urinary kallikrein excretion increased significantly in all groups except hypertensive blacks. It was the hypertensive blacks who also exhibited a decrease in renal blood flow with sodium restriction. The variations in dopamine and kallikrein reported in blacks might contribute to a system that exhibits both sodium sensitivity and renal vasoconstriction. This pattern is consistent with volume expansion and earlier nephrosclerosis in black hypertensive patients.

**Cation Transport**

Genetic variations of the sodium transport systems are also related to the endocrine variations observed in blacks. Canessa and coworkers have demonstrated that the sodium-lithium exchange and the sodium-potassium-chloride cotransport systems display genetic differences in their expression in humans, and in particular, in hypertensive patients. These sodium transport systems are expressed in red blood cells, and more importantly, they are also expressed in target tissues of the hypertensive process such as vascular smooth muscle, kidney epithelial cells, and adrenal glomerular cells. In hypertensive blacks, and also in young blacks with a family history of hypertension, the most distinct alteration occurs in sodium-potassium-chloride cotransport, which has significantly lower activity in blacks than in whites.

Canessa et al have also demonstrated that abnormalities of sodium-potassium-chloride cotransport are predictors of sodium sensitivity in young blacks, both normotensive and hypertensive. In young blacks with borderline hypertension, intracellular sodium concentration is increased and the sodium pump is lower compared with whites.

The investigations of the sodium transport systems indicate that some of the transport phenotypes might be genetically transmitted, and it has been suggested that expression of these variations in sodium transport might predict the onset of clinical hypertension. The transport phenotypes, due to their effect on sodium flux at a cellular level, can relate to the other endocrine functions and participate in the characteristic renal sodium retention and high volume state of black hypertension.

**Vascular Injury**

Hypertensive target organ injury to the kidney occurs with greater frequency in hypertensive blacks than in hypertensive whites. Progression toward renal insufficiency has also been described in some hypertensive blacks despite good control of blood pressure. As reviewed by Dustan and coworkers, there are differences in the micropathology of hypertensive nephrosclerosis in blacks compared with whites. In blacks, there is a constellation of renal vascular pathology, altered renal hemodynamics, and sodium retention with its attendant variations in endocrine parameters. This suggests that either the impact of high volume, or some other biochemical defect imposes greater injury in the renal vasculature, possibly even at lower pressure levels.

The morbidity of essential hypertension is related to the vascular consequences. Similar vascular consequences occur with diabetes and obesity. These three diseases not only share a common outcome, but also overlap in occurrence, with prevalence in all three disorders greater in blacks.

**Insulin Resistance**

Epidemiological and clinical studies have recently addressed the overlap of essential hypertension with non-insulin-dependent diabetes mellitus (NIDDM) and obesity. NIDDM and obesity are characterized by hyperinsulinemia, which in itself is regarded as a cardiovascular disease risk factor. Several recent reports have described the linkage of hyperinsulinemia to the clustering of essential hypertension, NIDDM, and obesity. Data are also emerging that indicate that hyperinsulinemia or insulin resistance correlates with essential hypertension, independent of NIDDM or obesity. Manicardi et al compared the insulin response to an oral glucose load in obese hypertensive and obese normotensive men. Obese hypertensive patients had plasma insulin levels twice as high as the obese normotensive subjects, indicating more severe insulin resistance. Modan et al investigated essential hypertension and glucose intolerance in a large Israeli population. Their analysis revealed a significant independent effect of insulin levels on blood pressure when adjusted for body mass index, age, sex, and glucose tolerance. In a rigorous experimental study, Ferrannini et al used the euglycemic hyperinsulinemic clamp technique to study insulin resistance in lean, middle-aged adult hypertensive patients with normal glucose tolerance. Compared with age-matched and weight-matched normotensive controls, the hypertensive patients exhibited pronounced impairment of glucose uptake in response to the insulin infusion. Their data provide substantial evidence that essential hypertension is associated with insulin resistance independent of obesity or carbohydrate intolerance. These reports have emerged from investigations conducted largely on white populations. To address the question of insulin resistance in blacks, Faiikner et al studied insulin-stimulated glucose uptake in healthy lean young adult black males by using the euglycemic hyperinsulinemic clamp procedure. Compared with normotensive subjects, the borderline hypertensive subjects exhibited a reduction in insulin-stimulated glucose uptake, consistent with relative insulin resistance. The borderline hypertensive subjects also had a significantly higher fasting plasma insulin concentration than the normotensive...
subjects despite no difference in adipose mass. In preceding studies on this black population, the investigators have already demonstrated the presence of both a lower sodium-potassium-chloride cotransport and a significant correlation of low cotransport with sodium sensitivity. Transport studies by Lewitter and Canessa have also demonstrated that these borderline hypertensive blacks, with insulin resistance and higher fasting plasma insulin, also have a higher intracellular sodium concentration and a lower sodium pump. What remains to be determined is whether, in these young blacks, sodium sensitivity is mediated by transport variations that are driven by higher insulin levels.

Guyton et al. have proposed that the kidney functions as the final common pathway of blood pressure regulation by its control of salt and water excretion in both essential hypertension and the normotensive state. The physiological effects of insulin can contribute to blood pressure regulation through sodium and volume regulation. DeFronzo and coworkers demonstrated by closed-clamp technique in dogs that small increments in insulin levels stimulated increased tubular reabsorption of sodium in the distal nephron. This effect occurred at physiological insulin levels. In another study on six normal males, DeFronzo et al. demonstrated that during euglycemic hyperinsulinemia, there is no change in glomerular filtration rate or renal plasma flow, but there is a reduction in urine sodium excretion and an increase in free water clearance, again indicating that the effect of insulin on sodium excretion is enhanced sodium reabsorption in the distal nephron. Rocchini et al. also demonstrated the relation of insulin resistance and sodium sensitivity in a study on obese adolescents. The mean blood pressure decrease after a change from a high salt diet to a low salt diet was 12 mm Hg. After weight reduction with a concurrent decrease in plasma insulin concentration, the blood pressure response to the dietary salt intake maneuvers diminished, indicating a loss of sodium sensitivity with reduced plasma insulin levels. Thus, insulin resistance in the peripheral tissues in hypertensive men, as demonstrated by Ferrannini and by Falkner results in hyperinsulinemia; chronically, these higher insulin levels can direct increased tubular sodium reabsorption and a volume-dependent increase in blood pressure.

Adrenergic Activity

Another area of investigation has been the sympathetic nervous system. There is a correlation of stress-induced enhanced adrenergic activity in subjects with essential hypertension and in young people with a family history of essential hypertension. Based on the experimental design of these studies, it has been assumed that the hyperresponsiveness has been related to greater \( \beta \)-adrenergic activity. Many of the clinical studies on neurogenic-cardiovascular interaction, however, have used racially mixed populations. Fredrickson compared racial differences in cardiovascular reactivity to mental stress in patients with essential hypertension. Although the sample of blacks was small, he observed that, compared with whites, blacks had less cardiac sympathomimetic responses but had greater vascular responses to mental stress. Light et al. have investigated the cardiovascular response to active coping stressors in college age men. Blacks were compared with whites in both normotensive and marginally hypertensive groups. Hypertensive men demonstrated a greater response than normotensive men. The blood pressure response was greatest in the black hypertensive men but without an attendant increase in heart rate. The investigators propose that in blacks, stress-mediated adrenergic stimulation might have a greater effect on peripheral vascular resistance. In another recent investigation, Dimsdale et al. investigated vascular sensitivity to infused norepinephrine in blacks and whites under conditions of low and high dietary salt intake. During the infusion, hypertensive subjects had a higher blood pressure at each norepinephrine dosage, but the slopes of the dose-response curves were the same for normotensive subjects and hypertensive subjects. On a high salt intake, however, black hypertensive subjects had an augmented blood pressure response to infused norepinephrine, whereas white hypertensive subjects had a reduced dose response to the same infusion. This report, which demonstrated augmented \( \alpha \)-receptor sensitivity in blacks, also delineated a peripheral vascular variation in hypertension in blacks that emerges under a high salt condition.

An alteration in sympathetic nervous system activity might also be involved in insulin resistance. Long-term insulin release has been shown to be stimulated by \( \beta \)-mediated sympathetic activity (which is regarded to be higher in essential hypertension). It had been suggested that the peripheral uptake of glucose would decrease with increasing \( \beta \)-receptor-mediated sympathetic activity, resulting in decreased insulin sensitivity. More recently, however, Rowe et al. used the hyperinsulinemic euglycemic clamp technique to demonstrate a significant increase in plasma norepinephrine levels in response to euglycemic hyperinsulinemia. Cardiovascular measurements demonstrated a concurrent increase in blood pressure. This study indicates that elevated levels of plasma insulin can increase sympathetic nervous system activity in the absence of changes in blood glucose.

Alternatively, augmented sympathetic activity can induce insulin resistance. Diebert and DeFronzo infused stress levels of epinephrine during the euglycemic insulin clamp procedure and demonstrated a reduction in insulin-stimulated glucose uptake. Naturalistic investigations to explore the interrelation between environmental stress, insulin-directed glucose metabolism, and blood pressure have not been conducted but could be a productive area of study regarding hypertension in blacks.

The role of insulin resistance in the shared pathophysiology of obesity, NIDDM, and essential hyper-


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Differences in blacks and whites with essential hypertension: biochemistry and endocrine. State of the art lecture.

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