Reflections in Hypertension
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Muscular Hypertension: Is Creatine Kinase Responsible for Hypertension in Blacks?

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The search for a genetic basis of the increased prevalence of hypertension in African Americans has gone on for many years and has for the most part been disappointing. A previous discussion in this column argued that environmental causes are of greater importance.[1] A recent series of papers has suggested a new and probably genetic mechanism, based on the finding that the blood levels of creatine kinase are closely correlated with the blood pressure (BP) and are higher in black Africans than in other groups. The key paper, which was published in *Circulation* in 2006 by Brewster and colleagues,[2] studied a random sample of people living in Amsterdam, which included 503 white Europeans, 580 black Africans, and 292 South Asians. Black African individuals had the highest creatine kinase (CK) (149 IU/L) and the highest BP (128/84 mm Hg) levels, while the white European persons had the lowest for both (88 IU/L and 124/79 mm Hg). The distribution of CK was skewed, but there was a significant relationship between the log CK tertiles and BP, which was independent of demographic factors and ethnicity. In other words, the higher CK level might be causally related to the higher BP.

The measurement of serum CK is one that is very familiar to all physicians, although not for evaluating patients with hypertension. Traditionally, we have used CK measurement to detect damage to either cardiac muscle (eg, in myocardial infarction) or skeletal muscle (eg, in myositis). If the CK level is high, we look at the isoenzyme distribution, because an increase in the MB band indicates that the CK comes from damaged cardiac muscle. We have also been taught that someone who exercised recently is likely to have a high CK level. (In my younger days I once ran the Boston Marathon, and on the day after the race, my CK level was 10,000 IU/L, with a strongly positive MB band). In the Dutch study mentioned above, investigators did not measure the CK isoenzymes but quoted other studies which have shown that the distribution of isoenzymes is the same in blacks and whites, despite the generally higher CK levels in blacks.[3,4] CK has been described as the "central regulatory enzyme of cellular energy metabolism"[5] on the grounds that it catalyzes the transfer of a high-energy phosphate group from phosphocreatine to adenosine diphosphate, to generate adenosine triphosphate. It is expressed in high amounts in cells that have high-energy demands such as muscle (including skeletal, cardiac, and smooth muscle), brain, and kidney tubules.

THE CK THEORY OF BLACK HYPERTENSION

The hypothesis advanced by Brewster and colleagues[5] to explain the increased incidence of hypertension in blacks on the basis of the increased serum CK level, which mostly comes from skeletal muscle, assumes that CK is also increased in smooth muscle and cardiac muscle, although there appears to be no evidence that this occurs in humans. In spontaneously hypertensive rats, however, the level

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Table. Effects of Different Types of Muscle Fibers and Relations to Disease

Fiber Type	I	IIa	IIb
Twitch type	Slow	Fast	Fast
Metabolism	Oxidative	Oxidative-glycolytic	Glycolytic
Major storage fuel	Triglycerides	Phosphocreatine, glycogen	Phosphocreatine, glycogen
Insulin sensitivity	Sensitive	Resistant	Resistant
Vascularity	High	Low	Low
Frequency in blacks	Low	High	High
Frequency in obesity	Low		High
Frequency in type 2 diabetes mellitus			High
Frequency in hypertension			High

of CK in the aorta and left ventricle is increased.[2] Thus it is suggested that increased CK in smooth muscle leads to increased vasoconstriction and vascular reactivity and increased cardiac contractility. These characteristics might make blacks more likely to become hypertensive when exposed to environmental stress. It is also proposed that high CK levels in the kidney (again not demonstrated) would lead to increased renal vascular resistance and increased sodium retention.

THE ROLE OF SKELETAL MUSCLE

Another key observation in this area that was not addressed in the CK hypothesis is that there is a racial difference between the types of skeletal muscle fibers. There are 3 general types, often referred to as the slow-twitch (type I) and fast-twitch (types IIa and IIb) fibers (Table). The slow-twitch fibers tend to be more densely vascularized and are metabolically oxidative, while the type IIa fast-twitch fibers are both glycolytic and oxidative and the type IIb are more glycolytic.[6] The important difference for the current discussion is that phosphocreatine is one of the major forms of stored energy in the fast-twitch fibers (the other being glycogen), while triglycerides are the principal energy source in the slow-twitch fibers. In the vastus lateralis muscle of the leg (the muscle most commonly biopsied for studies of fiber types), the proportion of type I fibers may vary from 13% to 98%.[6] The fast-twitch fibers are better for sprinting, and the slow-twitch for endurance exercise. Thus most people have about 50% of slow-twitch fibers in the gastrocnemius muscle, while sprinters may have 25% and distance runners 70%.[7] The extent to which training alters the relative proportion of the different fiber types is controversial, although the oxidative function of the fibers can be dramatically changed[7] and the capillary density can also increase.[8] There are studies which have reported that endurance training can reduce the proportion of type I fibers, although the degree of change appears to be relatively small.[9] The best estimate is that genetic factors account for 45% of the variance, environmental factors for 40%, and sampling and technical variance for the remaining 15%.[9] A study comparing sedentary blacks and whites found that blacks had 33% of type 1 fibers, while whites had 41%, and there were also marked differences in the CK concentrations in the muscles of the 2 groups, being more than 50% higher in the black group. It has been suggested that this different distribution may be part of the reason why so many of the world's top sprinters are black.[10]

MUSCLE TYPES AND THE METABOLIC SYNDROME

Although insulin resistance is recognized as a major component of the metabolic syndrome and type 2 diabetes, the role of skeletal muscle receives surprisingly little attention. Skeletal muscle accounts for about 75% of insulin-stimulated glucose uptake and is the major site of insulin resistance.[11] The importance of insulin resistance in the early stages of the metabolic syndrome was demonstrated in a study[12] of young lean patients who were divided into insulin-sensitive and insulin-resistant groups. It found that after a carbohydrate meal, insulin-resistant patients showed a 60% smaller glycogen synthesis in their skeletal muscles than insulin-sensitive patients, and also showed increased synthesis of triglycerides in the liver, which was associated with increased plasma triglycerides and lower high-density lipoprotein cholesterol. The authors suggested that skeletal muscle insulin resistance precedes hepatic insulin resistance, and that this may be more important than abdominal obesity, which was not present in these patients.

The importance of individual differences in muscle fiber types has been shown in several studies, which have noted a correlation between muscle fiber type and obesity, such that patients with fewer type I fibers are more likely to be obese.[6,13] A study of lean and obese women[6] found that the obese

women had fewer type I fibers than the lean women. Here it is worth noting that type I fibers are more insulin-sensitive than type II fibers, so that people with fewer type I fibers are more likely to develop insulin resistance. The importance of this finding was underscored by also looking at patients who had undergone gastric bypass surgery and correlating the muscle fiber distribution with the amount of weight lost after the surgery. There was a surprisingly strong correlation (0.72; $P<.005$) between the percentage of excess weight lost and percentage of type I fibers. Since there is no reason to suspect that obesity will affect muscle fiber type, these findings suggest that people who are born with fewer type I fibers, such as blacks, are more likely to be insulin-resistant and hence more likely to develop obesity, type 2 diabetes, and hypertension.

There may be hemodynamic consequences of the differences in muscle fiber types. The insulin-resistant fast-twitch fibers have a relatively meager capillary supply. Lillioja and colleagues[14] found a positive correlation of stimulated glucose uptake with capillary density and the percentage of slow-twitch fibers. Julius and colleagues[11] have suggested that in hypertension, the BP-induced restriction of the microcirculation of muscles limits nutritional flow and hence glucose uptake and exacerbates insulin resistance.

MUSCLE TYPES AND HYPERTENSION

There is some evidence that muscle fiber composition may be related to BP. This was first shown in 1979[15] in a study of 22 normotensive and 19 untreated hypertensive patients with intra-arterial pressure. In both groups there was a negative correlation between BP and the vascular resistance of the leg with the percentage of slow-twitch fibers. This is consistent with the poorer blood supply and higher resistance of the fast-twitch type II fibers contributing to the higher BP. Another even smaller study of 7 normotensive and 8 hypertensive patients[16] found correlations between BP and the percentage of type IIb fast-twitch fibers. Another aspect of this research relates to BP during exercise. Several studies have shown that normotensive individuals who develop very high systolic pressures during exercise may be at increased risk of developing hypertension.[17,18] Houmard and associates[19] studied 35 sedentary normotensive men and found that the systolic pressure during exercise was significantly correlated with the percentage of type IIb fibers in both the vastus lateralis and gastrocnemius muscles. Body fat (determined by hydrostatic weighing) was also correlated with the percentage of type IIb fibers. A study of 17 hypertensive and 17 normotensive patients found that the hypertensive patients had a tendency to have more fast-twitch fibers and that the BP response to isometric exercise (but not to a cold pressor test) was significantly related to the proportion of fast-twitch fibers.[20] Whether any of this relates to ethnic differences or serum CK levels has not been investigated.

CONCLUSIONS

The CK findings are certainly worth pursuing, but at the present time we do not know whether there is any causal relationship between high CK and BP. Thus it would be of interest to know whether CK falls when BP is lowered. The current version of the hypothesis focuses on possible but unproven changes in cardiac and smooth muscle and completely ignores the marked ethnic differences in muscle fiber types. The first demonstration that there may be a relationship between muscle fiber types and hypertension was made nearly 30 years ago, but has largely been ignored, although what few other studies have been performed supported the finding. The fact that these differences are also related to obesity and type 2 diabetes makes them even more important. Perhaps the reason for the neglect of this field is that biopsy of skeletal muscle is invasive and not something that is traditionally performed by cardiovascular investigators. Muscular hypertension is not a recognized term, and probably never will be, but genetically determined variations in muscle fiber composition could well be of considerable importance in furthering our understanding of the deadly combination of hypertension, obesity, and type 2 diabetes, and why black Americans are more susceptible.

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