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Hypertension: Heavy Metals, Useful Cations and Melanin as a Possible Repository

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Abstract — Popular belief has often attributed the disproportionate occurrence of hypertension in blacks to the increased social stresses faced by the minority population. Evidence now points to a more biologically relevant explanation of black hypertension, an increase in levels of heavy metals. Preferentially bound to melanin, cadmium, lead, and copper have implications not only in the etiology of black hypertension, but in the etiology of all hypertension. Of course, hypertension is heterogeneous by nature and cannot be attributed solely to any single cause. However, the indictment of the heavy metals, as well as a deficiency of other cations such as calcium, magnesium, and potassium, warrants a more nutritional approach and less reliance on current pharmacological therapy in selected cases. Melanin should be investigated as a storage bank for useful cations. If real, such a cation reservoir would explain the heat tolerance capacity of blacks and other dark-skinned tropical races.

Introduction

Attention has been continually focused on the role of stress in the development and aggravation of hypertension. Many articles in lay publications such as Time (1) and The Wall Street Journal (2) have gone so far as to implicate social stresses and the pressures of being a minority in America as a primary cause of the disproportionate representation of hypertension among blacks. Certainly, blacks suffer the brunt of hypertension in the United States. The statistics are indeed shocking. Blacks are twice as likely as whites to suffer from heart failure, twelve to eighteen times as likely to suffer from kidney failure, and have the world's second highest death rate from stroke (just behind the much older Japanese) (2). Unfortunately, these articles have overlooked the possible metabolic causes of hypertension, concentrating too heavily on soft sociological data. This article does not contend that stress does not exacerbate the symptoms of hypertension; that point is well documented. Stress, however, is probably not the underlying cause for the increased incidence of hypertension in blacks, nor the underlying cause for its prevalence in any population.

The Heavy Metals

Schroeder (3) awakened interest in the effects of metallic cations with his original studies of cadmium-induced hypertension in rats. Perhaps the greatest contribution of this work was to concentrate the interest of research in the area of heavy metals and their relationship to hypertension. Subsequent studies have both supported (4) and contradicted (5) Schroeder's original findings, and raised questions concerning the susceptibility of certain animal strains or species to cadmium intoxication. At this date, Schroeder's hypothesis has not been disproven and therefore, must be kept in mind. Perry (6) additionally illustrated that cadmium-induced hypertension can be inhibited by selenium. A study of youth in Mississippi by Mederios and Pellum (7) showed that blacks had significantly higher concentrations of hair cadmium than whites. Although only a single correlation, herein lies a possible answer to the hypertension problem in the black population. Smoking was also reported by Schroeder (8) to increase cadmium levels in the body.

The Hanes II study (9), with data compiled between 1976 and 1980, also linked hypertension with elevated levels of lead in men and women between the ages of 21 and 55. In the elderly, however, the relationship was found to be insignificant. Perhaps the lead-poisoned individuals died too early to achieve geriatric status. The hypertensive effects of lead were apparent well below the "accepted toxic levels" and remained significant when the data were corrected for other known hypertension-precipitating factors. Similar to their findings concerning cadmium, Medeiros and Pellum (7) also reported increased concentrations of hair lead in blacks with respect to whites. Recent studies, most importantly a large survey conducted as a part of the British Regional Heart Study, have failed to reveal any correlation between lead and blood pressure (10). Thus, although not conclusive, here again is a metallic cation with a possible link to hypertension, especially in blacks.

Manganese is a third heavy metal implicated as a potential cause of hypertension. Aston (11) reported that oral doses of manganese have been shown to elevate blood pressure, especially in patients over forty years of age. Similarly hydralazine, a manganese chelator, reduces blood pressure and has been the subject of numerous studies (12, 13). We find at the Brain Bio Center that both copper and manganese raise blood pressure, while zinc lowers blood pressure.

A much stronger association to black hypertension can be found in a fourth heavy metal ion, copper, which as a heavy metal poison is more widespread than cadmium or lead. As early as 1974, the World Health Organization (14) warned that high copper levels in the tissues are positively correlated with cardiovascular diseases and hypertension. This relationship is well documented in both laboratory animals and humans. Lui and Medeiros (15, 16) have repeatedly shown that rats placed on high copper diets have significantly higher systolic blood pressures than those with low copper intakes. Ahmed and Sackner (17) have demonstrated that a similar correlation exists with sheep receiving infusions of copper sulfate. Most of the hypertensive patients we see at the Princeton Brain Bio Center exhibit elevated serum copper as well as depressed serum zinc levels.

This inverse relationship between copper and zinc can be logically explained if one realizes that zinc, as well as vitamin C, inhibits the intestinal absorption of copper while promoting its excretion. This reduction in copper levels subsequently reduces blood pressure. The positive correlation of the copper/zinc ratio to blood pressure was supported by a hair analysis study of youths by Medeiros and Brown (18) which revealed that high copper levels were positively associated with blood pressure, while high zinc levels were negatively correlated. Bremner et al. (19) reported up to a 40% reduction in liver copper in zinc-supplemented sheep (420 mg/kg) and several reports have documented copper deficiency anemia in patients suffering from zinc intoxication (20, 21). Studies of chickens (22), rabbits (23), guinea pigs (24) and monkeys (25) as well as Finley and Cerklewski's (26) illustrative study of young men have illustrated a significant reduction in serum copper activity following ascorbic acid supplementation. Selenium is also antagonistic to the toxic effects of copper as well as cadmium (27). Dougherty and Hoekstra (28) have shown that selenium and vitamin E protect against the toxic peroxidative activity of elevated copper.

Although much of the research is relatively recent, we maintain that the high copper/low zinc ratio can be a major factor in hypertension.

Melanin: The Key

Melanin may be an important factor in the hypertension preponderance with respect to blacks. Melanin, the natural pigment which gives skin its color, is found in increasing concen-

trations as the skin becomes darker. During the summer months, the amount of melanin increases due to the tanning effects of the sun. The black population and ethnic groups of tropical origin carry a higher and more varied melanin burden than most caucasians. The numerous free carboxyl groups on the melanin polymer are responsible for an electrostatic attraction that draws and binds heavy metals (29). Other postulated binding sites for metallic cations include hydroxyl groups and negatively-charged semiquinones (30). The melanin molecule itself has riboflavin, tetrapyrrole, purine, pteridine, beta carotene, and ubiquinone modalities as well as at least five acidic groups (31), all of which have some chelating potential with respect to heavy metals. Larsson and Tjalve (32) determined that copper and lead are preferentially bound, both in vitro and in vivo, compared to other monovalent and divalent cations. Manganese was also shown to have an affinity for melanin, although not nearly as great as with lead and copper. Affinity was expressed as the percentage of-paraquat remaining bound to melanin following exposure to a 10^{-2} M metal ion solution. Lead yielded only 0.6% of paraquat remaining while copper allowed 4.2% of the paraquat to remain. All other monovalent and divalent cations allowed greater than 10% of paraquat to remain with manganese corresponding to 17.7% of paraquat. Lindquist and Ullberg (33) observed extraordinary body retention of pharmacological agents with a high affinity for melanin. Years after a single dose injection traces of these chemicals were detected in the melanin. Although to our knowledge no studies have been done on this depot effect, it would seem that melanin retention may be characteristic of the heavy metals as well.

We postulate that in a healthy individual, melanin may serve as a slowly mobilized reserve of more populous and useful cations, such as calcium, potassium, sodium, and zinc. This cation reserve would be vast if one considers the volume represented by the skin and may possibly explain why darker skinned peoples are more tolerant of hot climates. Simply imagine a large cation reserve and its effect upon heat dissipation and sweating. The binding of these ions to melanin would prevent a disruption in the body's osmotic balance. However, when the mineral balance is disrupted by dietary or physiological causes, the increased concentrations of copper and lead, combined with their greater affinity for melanin, leads to the displacement of the more favorable cations (zinc, calcium). Additionally, the darker the skin, the greater the levels of copper and lead in such imbalances, and subsequently the greater the risk of hypertension. This hypothesis was confirmed by Creason and his colleagues (34) in the analysis of whole blood samples of two thousand male military recruits. Blacks consistently show higher levels of serum copper and lead as compared to whites. Additionally, the study revealed that smoking raises the copper concentrations of the body. Two studies, one of 433 black subjects by McClean et al. (35) and another of 5570 Brazilian subjects by Barbosa et al. (36) have documented significant correlations between systolic and diastolic blood pressures and percentage of black African admixture. Epidemiologic studies carried out in Detroit by Hardburg and his colleagues (37) revealed an astonishing relationship. Darker skin color in blacks, as rated by trained nurse interviewers, was linearly related to blood pressure. Although one can argue the subjectiveness of the measurement, the distinctness of the relationship cannot be disregarded. Hardburg (29), without the benefit of recent studies relating copper, lead and manganese to melanin, again attributed the skin color-hypertension correlation to social stress.

A subsequent study by Hardburg (38) of the residents of Maupiti Island in French Polynesia found no correlation between skin color and blood pressure, but one would have to question the population's exposure to heavy metal intoxicants on this underdeveloped island. Their diet of manioc, arrowroot, breadfruit, and taro hardly pose a threat from heavy metals, and it seems few homes have copper plumbing. This exception to the skin color-hypertension correlation is supported at a physiological level by a compilation done by Wasserman (30) studying the elemental composition of various melanoproteins. The developing nations, such as the Bantu and East Indians, have significantly less manganese and copper attached to their melanin pigment as follows in the table:

	Sulfur (%)	*Mn (ppm)*	*Cu (ppm)*	*Fe (ppm)*
Bantu	1.9	6.9	30	992
Indian	2.9	7.0	51	332
Cape Coloured	3.0	10.0	334	1721
Caucasian	3.2	14.0	203	941
Japanese	1.6	6.0	139	—

This increase in copper and manganese with industrialization could be an important factor raising blood pressure. The high iron levels suggest that iron intoxication, also implicated in hypertension, may also be a factor more than likely due to the use of iron cookware.

Method of Intoxication

The major role of ingestion and intoxication of the heavy metal cations appears to be via drinking water. Plumbing systems constructed with copper pipes and lead-soldered joints are common, rapidly replacing the older galvanized (zinc) steel systems. These soft, easily dissolved metals combined with the acidity of the water can lead to astronomically high levels of heavy metals being unwittingly consumed in tap water. All physicians should be distinctly aware of such heavy metal intoxications, especially if the drinking water in their area is unusually soft. Well water is usually acid. Numerous cases of copper poisoning from tap water have been published (40, 41, 42), but perhaps one of the best documentations was reported by Spitany and his coworkers (43). The case involved a Vermont family whose home was fed by a municipal water supply from the end of a terminal main consisting of 1 1/2 inch type K copper pipe. The water was slightly acid (pH = 5.8) and considered soft. This soft, acidic water combined with stagnation due to their terminal position on the main caused copper levels of the water to rise to 7.8 mg/L, significantly higher than the accepted standard of 1.0 mg/L. Members of the family exhibited symptoms of acute copper poisoning, gastrointestinal illness and emesis, due to a consistent high copper intake.

Other Cations Implicated

The complexity of hypertension precludes the possibility that all cases could be attributed to levels of cadmium, lead, and copper. The heterogeneity of hypertension is evidenced by the large number of conflicting studies continually being published. Numerous reports have correlated calcium-deficient diets with hypertension; some patients showing marked improvements when treated with calcium supplements (44, 45). Epidemiologic studies, however, have been inconsistent in attempting to relate hypocalcemia and hypertension. A current hypothesis forwarded by McCarron and Parrott-Garcia (46) atttributes the effect of calcium to the proper operation of smooth muscle vasculature. They contend that adequate calcium, necessary for any muscle contraction, is required for vasodilation and reduced peripheral resistance. Vasodilation is a common body response to elevated blood pressure. Calcium, like zinc (27), is a known antidote to heavy metal poisons. Certainly, additional study is necessary to determine the relevance of the many factors.

Further studies have linked hypomagnesemia to hypertension in both laboratory animals (47) and humans (48). Resnick (48) postulates that a reciprocal relationship exists between magnesium and calcium. When magnesium is low, a state of hypercalcemia may exist, increasing the excitability of vascular smooth muscle cells and contributing to vasoconstriction. Thus, it seems that calcium can have pathogenic repercussions in either elevated or lowered states. Again, epidemiologic data to support Resnick are inconsistent, accenting the need for further research. Other cations consistently identified in hypertension include potassium and sodium as reflected by the therapeutically common high potassium-low sodium diet.

Conclusions

The evidence pointing to a possible connection between hypertension and cadmium and an even stronger connection with lead and copper validates a survey of these body levels when confronted with a black patient presenting hypertensive symptoms. At the Princeton Brain Bio Center, all of our hypertensive patients are continually screened for heavy metal levels. The effects of elevated cadmium and copper are antagonized by selenium. Vitamin C and zinc inhibit the absorption of copper while promoting its excretion. The identification of calcium, magnesium, potassium and sodium as factors simply illustrates the complexity of hypertension and the body's regulatory mechanism controlling blood pressure. Certainly a host of variables may influence the cardiovascular, nervous, or renal systems. The fact that research is shifting to cations in search of causative agents of hypertension in conjunction with the numerous side effects of current drug therapy seemingly warrants a less pharmacological, more dietary approach clinically. At the Brain Bio Center numerous successes have been documented, using mineral supplementation as a primary

approach, while implementing diuretics, vasodialators, and angiotension-converting enzyme inhibitors as reserve methods.

The pertinent factor in the discussion of cations, hypertensions, and blacks appears to be the pigment melanin. Studies by Larsson and Tjalve (23), revealing melanin as a natural cation-binding agent, especially of the heavy metals, seems to have profound implications. Combine this information with research linking elevated levels of cadmium, lead, manganese, and copper to hypertension and the etiology of a major form of black hypertension evolves. Of course, this may also apply to whites, but the risk and variability of the effects would not be as great due to decreased melanin. Simply stated, heavy metal cations of cadmium, lead, manganese, and especially copper appear to be a precipitating factor if present in high levels. Melanin will preferentually bind these ions and retain them in the body, thus excluding them from normal excretory mechanisms. The body predisposes itself to hypertension by building this large heavy metal reserve. This hypothesis backed by biological facts seems to contain much more validity than those which attribute hypertension differences between races solely to stress factors.

It cannot be disputed that stress may be a secondary and exacerbating cause of black hypertension, however, in light of these recent scientific correlations, it seems unlikely that it is the major causative factor. The melanin-bound cation pool could also explain other physiological differences between caucasians and the darker-skinner tropical peoples. In a healthy individual it seems likely that this cation storage pool would be filled with the more prominent minerals such as sodium, potassium, magnesium, calcium, and zinc. The survival advantages of such a large cation pool become obvious in the hotter climates. Osmotically inactive when bound, these cations could be mobilized by the body in times of need and effectively limit dehydration. Also, the effects from the loss of salts due to sweating would be minor because of the large reserve. Certainly, this also implies that should a cation imbalance be perpetuated by some physiological mechanism its effects would be potentiated by the melanin-bound reserve.

The prevalance of hypertension in blacks may be one illustration of such an effect. Copper and lead, which have higher affinities for melanin, may be entering the body and displacing the usually more populous cations in the melanin pool, thus predisposing the individual to hypertension. Although more research is required to adequately support this hypothesis, it may explain a number of racial disparities. Studies of the ion balances in patients suffering from pigment-producing malignant melanomes may provide insight. Additional studies of dark-skinned, tropical peoples, such as South Americans, Cubans, and Puerto Ricans as well as studies following any ion or hypertensive changes in whites as they tan, may substantiate or refute the apparent central role of melanin.

Appendix

A recommended treatment regime, which would correct many of the cation imbalances hereto discussed, would be:

Vitamin C	1.0 g, AM & PM
Zinc	30 mg, AM & PM
*Inositol	2 of 650 mg, AM & PM
Low sodium diet	
Magnesia	2 of 400 mg, AM & PM
Calcium	500 mg, AM & PM
Potassium	daily from salt substitutes
Molybdenum	500 mcg, AM & PM
Selenium	200 mcg, AM & PM
Daily exercise & reducing diet	

* Inositol is a mild natural sedative and diuretic.

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