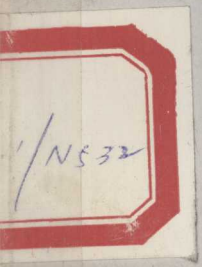
NUTRITIONAL FACTORS IN HYPERTENSION

SECTION A: SELECTED NUTRIENTS



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NUTRITIONAL FACTORS IN HYPERTENSION

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Preface

In the U.S., hypertension is a public health problem of enormous magnitude. There is now substantial evidence to suggest that diet has a major influence on the prevention and treatment of hypertension. Nutrition intervention, currently recommended as part of the treatment for established hypertension, may help with prevention as well.

Of the many dietary factors that may affect blood pressure, obesity, sodium, and alcohol have been well substantiated. There is also considerable research on the effects of other dietary factors that include calcium, potassium, magnesium, linoleic acid, caffeine, omega 3-fatty acids, and dietary fat and fiber.

This volume can be divided into two parts. The first six chapters serve as an overview of nutritional influences on the pathophysiology of hypertension. Included are topics related to the epidemiology of nutrition and hypertension, effects of alcohol and hypertension, nutritional issues related to childhood hypertension, and a dietary approach to the management of hypertension. The last six chapters deal with the issue of the role of calcium in hypertension. Dr. McCarron's pioneering work has led many investigators to pursue this area. There is increasing evidence that dietary calcium and regulation of overall calcium metabolism may be a pathological link in the genesis of hypertension in many individuals.

There is rapid growth of knowledge and interest in the area of nutrition and hypertension. We hope that some of the questions and problems posed in these chapters may soon by resolved.

Barbara Levine
Leon Ellenbogen

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Section A:

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SELECTED NUTRIENTS

Nutritional Factors in Hypertension
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1 Nutritional Influences on the Pathophysiology of Hypertension

Thomas G. Pickering, M.D., D. Phil.

INTRODUCTION

Essential hypertension is most probably the end result of the interaction of a number of factors, both environmental and genetic. Of the environmental factors, two of the three that have received the most attention (sodium intake, weight gain, and psychosocial stress) are nutritional in origin. The role of weight gain is well accepted, while the other two remain highly controversial as etiological factors. At the present time, the evidence would favor the view that these factors may contribute to the development of hypertension in a minority of individuals who are particularly susceptible to their influence. This susceptibility is currently being studied most intensively for the role of sodium intake, and may be genetically determined.

This chapter will review the mechanism by which the two major nutritional influences on blood pressure, obesity and sodium intake, may exert their effects. The pathophysiological role of other nutritional factors such as potassium, divalent cations, and alcohol are reviewed elsewhere.

PATHOPHYSIOLOGY OF OBESITY AND HYPERTENSION

Numerous epidemiological studies have documented the association between obesity and hypertension [13], and there is also abundant evidence that

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weight loss can lower blood pressure in such patients, as exemplified by the recent study of MacMahon et al. [47].

Hemodynamic Factors

The principal hemodynamic changes associated with obesity are an increased cardiac output and blood volume, according to some investigators [51], although others have reported both of these to be normal [58]. In this context, the basal metabolic rate is of great interest: on the one hand, a decreased metabolic rate might be a possible cause of obesity; on the other, an increased cardiac output might be expected if the metabolic rate was increased. The consensus is that it is raised little if at all [29]. When cardiac output is elevated, it may be attributed to an increased preload [20,32]. Left ventricular hypertrophy is relatively common. (Messerli et al., 1984) [50].

In patients who have both hypertension and obesity, the main change is that peripheral resistance is elevated in addition to cardiac output [50].

Hormonal Factors

There appears to be no consistent differences in plasma renin or aldosterone between normal weight and obese subjects, whether or not they are hypertensive, although plasma catecholamines tend to be elvated [7,66,68]. A more consistent link between obesity and blood pressure may be hyperinsulinemia: Three studies have shown correlations between serum insulin and blood pressure in obese subjects [5,42,48]. Such hyperinsulinemia could contribute to the elevation of pressure by at least two mechanisms: first, insulin has a sodium-retaining effect on the kidney and second, it may raise plasma norepinephrine and other indices of sympathetic nervous activity [64]. These effects are independent of blood glucose levels.

CARDIOVASCULAR AND HORMONAL EFFECTS OF CHANGES IN CALORIC INTAKE

Fasting lowers blood pressure, and this is associated with diminished plasma catecholamines [25,31,82]. Conversely, overfeeding sucrose to spontaneously hypertensive rats raises blood pressure [81] and sympathetic nervous activity increased fat intake has similar effects, whereas protein does not [37]. One of the most striking features of fasting is a natriuresis, which continues for about 5 days, when it is followed by sodium retention. Plasma renin activity initially falls during fasting, while aldosterone rises transiently [69]. Studies of more gradual and prolonged weight loss have demonstrated reductions of both renin and aldosterone, which occur independently of changs of sodium intake [74].

Since both caloric restriction and sodium restriction may lower blood

pressure, and usually the two go hand in hand, it has been questioned which mechanism is more important in this regard. Fagerberg et al. [21] randomized obese hypertensive men to receive for 10 weeks a diet that was restricted in either calories but not sodium, or one that was restricted in both. Blood pressure fell with the latter, but not the former, suggesting that sodium restriction was the most important component. Plasma norepinephrine showed a greater decrease when both sodium and calories were restricted. Reactivity to infused norepinephrine was increased when calories alone were restricted, but not when both calories and sodium were. These findings led Fagerberg to suggest that although sympathetic nervous activity fell in both cases, increased vascular reactivity may have prevented the blood pressure from falling in the former case.

HEMODYNAMIC CHANGES ASSOCIATED WITH CHANGES IN SODIUM INTAKE

Normotensive Subjects

A number of studies have investigated the hemodynamic effects of changing sodium intake in normal subjects. Abboud [1] and Kirkendall et al. [34] found that going from a low (10 mEq/day) to a high (410 mEq/day) sodium intake did not raise arterial pressure, because there was a decrease of forearm vascular resistance occurring as a result of vasodilation. Similarly, Sullivan and Ratts [70] found that increasing sodium intake from 10 to 200 mEq/day decreased peripheral resistance but raised cardiac output, again with no change of arterial pressure. Finally, Luft et al. [44] found that raising sodium intake from 10 to 300 mEq/day did not increase blood pressure, although there was a modest increase at very high levels of sodium intake (800 to 1500 mEq/day). This was due to an increased cardiac output, but peripheral resistance was again lower.

Several mechanisms may be responsible for these changes. Central venous pressure increases with sodium loading, which would tend to increase cardiac output. The vasodilation might occur as a reflex mediated by stimulation of low-pressure baroreceptors [83]. In addition, the activity of the renin-angiotensin system will be reduced.

Hypertensive Subjects

In contrast to the vasodilator effects of a high sodium intake in normal subjects, Mark et al. [49] found that increasing sodium intake from 10 to 410 mEq/day in subjects with borderline hypertension tended to increase both arterial pressure and forearm vascular resistance. These results were confirmed by Koolen and Van Brummelen [35], who showed that the reflex

vasoconstrictor response to lower-body negative pressure (mediated by low-pressure receptors) was enhanced by the high sodium diet in hypertensives, but they also observed a decreased maximal vasodilator capacity (during reactive hyperemia) in sodium-sensitive individuals (i.e., those whose blood pressure varied according to their sodium intake). This finding would suggest that there were structural changes in the arteries occurring with sodium loading, and that the vasoconstriction is not necessarily all mediated neurally.

EFFECTS OF SODIUM INTAKE ON THE SYMPATHETIC NERVOUS SYSTEM

The relationship between sodium intake and sympathetic nervous function is a complex one. A number of studies have indicated that dietary or diuretic-induced sodium depletion can increase plasma catecholamines, which are commonly thought to reflect sympathetic nervous activity [45,76,78]. Conversely, sodium loading has variously been reported to result in a reduction of plasma catecholamines [45], no change [36], or an increase [55]. The latter group reported that the relationship between norepinephrine and sodium intake was U-shaped, with increases of norepinephrine occurring at both extremes of sodium intake. Plasma epinephrine was unaffected by changes of sodium intake.

These apparently conflicting reports on the response to sodium loading may to some extent be attributable to differences in the responses of different subjects. Thus, Koolen and Van Brummelen [35] found that sodium depletion increased plasma norepinephrine in both sodium-sensitive and sodium-resistant hypertensive subjects, but sodium loading produced different effects. Initially, both groups showed a decrease, but after two weeks plasma norepinephrine remained low in the sodium-resistant subjects, but increased to above basal levels in the sodium-sensitive subjects, in whom there was also a significant correlation between the change of blood pressure and of norepinephrine. A temporal component of these relationships was also demonstrated by Volpe [76a], who found that the increased norepinephrine occurring during sodium depletion persisted only for 1 to 2 weeks.

Studies of the effects of sodium depletion on other indices of sympathetic nervous activity have given a very different picture. For example, Ljundqvist [40] found that sodium depletion causes a depletion of norepinephrine from adrenergic nerve terminals in the rat, and Rocchini et al. [63] demonstrated a diminished pressor response to carotid artery occlusion in sodium-depleted dogs. Finally, Takeshita and Ferrario [72] found that sympathetic nerve activity measured directly in the renal nerves of sodium-depleted dogs was diminished in comparison to sodium-replete dogs. Brosnihan et al. [8] re-

ported that sodium depletion causes changes of plasma catecholamines in dogs that are the same as observed in man, namely an increase of norepinephrine without any change of epinephrine. They also found that the concentration of norepinephrine in the cerebrospinal fluid was increased, which they attributed to an increased activity of brain stem noradrenergic neurons. This would be consistent with a decreased central sympathetic outflow, since norepinephrine injected into the brainstem lowers blood pressure [17]. These animal studies would therefore suggest that sodium depletion reduces sympathetic nervous activity.

Human studies of sympathetic responsiveness as a function of sodium intake are few. Ambrosioni et al [2] observed that sodium restriction has relatively little effect on the basal blood pressure in young subjects with borderline hypertension, but the pressor response to stress (dynamic and isometric exercise, and mental arithmetic) was diminished. Similar conclusions were reached by Falkner et al. [22], who found that sodium loading increased the pressor response to mental arithmetic. In contrast, in normal subjects Volpe et al. found that the response to isometric exercise was transiently increased during sodium restriction.

In normotensive subjects, sodium loading increases the pressor sensitivity to infused norepinephrine [59].

If the interpretation of animal studies is correct, why should a decreased level of sympathetic nerve activity during dietary sodium restriction be associated with an increased plasma norepinephrine? A possible explanation is that the increased angiotensin, which also occurs in response to sodium depletion, stimulates the adrenals to release norepinephrine. This effect has been demonstrated experimentally in response to hemorrhage [23]; however, in man, Nicholls et al. [55] did not observe any increase of plasma catecholamines in response to an angiotensin infusion.

At the other end of the spectrum, animal experiments have indicated that sodium loading tends to increase sympathetic activity, and that the sympathetic nervous system plays an important role in mediating experimental models of hypertension that have traditionally been regarded as being sodium-dependent. These include DOCA-salt hypertension [62], one-kidney, one-clip renovascular hypertension [77], and the subtotally nephrectomized rat on a high-salt diet [19]. Gavras [26] has recently proposed the hypothesis that sodium exerts its hypertensive effect by a central effect on adrenergic neurons.

It does not necessarily follow that the interpretation of the animal data that sympathetic activity is diminished by sodium depletion applies to man, because it is conceivable that the assumption of the upright posture necessitates a dual defense mechanism maintaining blood pressure during sodium depletion, and that both the sympathetic nervous system and the renin-angiotensin system are activated.