Non-modulating Hypertension
A Subset of Sodium-Sensitive Hypertension

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A major difficulty in determining the mechanisms responsible for human hypertension is the great variety of systems involved in regulating blood pressure and our tendency to assume that these mechanisms are similar in all hypertensive patients. Even when patients are separated into those whose blood pressure is or is not sensitive to the level of sodium intake, it is often assumed that all "salt-sensitive" hypertensive patients have similar defects. However, an accumulating body of evidence suggests this is not the case, and at least six different mechanisms have been proposed to account for a substantial change in blood pressure when a patient's salt intake is modified (Table 1). This article will review one of these subgroups—non-modulators.

Role of Aldosterone and Renal Vasculature in Sodium Homeostasis

Changes in the level of aldosterone and in renal blood flow have profound effects on renal sodium handling. The absence of aldosterone, that is, Addison's disease, clearly leads to a state of decreased renal conservation of sodium, whereas an aldosterone excess, that is, primary aldosteronism, leads to increased renal sodium conservation, at least acutely. Evidence has accumulated that the renal vasculature also participates in modifying renal sodium handling. For example, when sodium intake is restricted and the renin-angiotensin system is activated, renal blood flow is reduced and sodium concentration is enhanced. Under conditions of a low sodium intake, if a competitive antagonist to angiotensin II or converting enzyme inhibitors are administered, renal blood flow is increased in a dose-related fashion, with a concomitant increase in sodium excretion, documenting that angiotensin II contributes to sodium handling by the kidney. Intriguingly, not only do these two factors play a critical role in modifying sodium homeostasis, but also their level of responsiveness to angiotensin II is modified by the level of sodium intake in a reciprocal fashion. Sodium restriction enhances the adrenal but reduces the renal vasculature (and the general vasculature) response to angiotensin II; sodium loading produces the opposite effect.

Because administration of converting enzyme inhibitors or angiotensin II antagonists acutely modifies the responsiveness of the vascular system to infused angiotensin II when the endogenous renin-angiotensin system is activated (i.e., sodium restriction), it is likely that a change in the angiotensin receptor itself is likely to mediate the changing responsiveness of the vascular system when sodium intake is modified. However, the mediator of the change in aldosterone responsiveness is less clear.

At least two possibilities exist. Either the change in sensitivity is secondary to a change in a postreceptor event, or it is receptor mediated. In the rat glomerulosa cell, angiotensin II receptors have been reported to be increased with sodium restriction or chronic infusion of angiotensin II. However, binding studies using primate adrenal tissue have documented a reduction in the number of receptors when the animal is sodium restricted. Further evidence that the angiotensin II receptor is not a major participant in this event has been the documentation that reducing plasma angiotensin II with a converting enzyme inhibitor does not modify the adrenal response to angiotensin II in normal subjects although it does change the renal vascular response to angiotensin II. Thus, how the adrenal gland "knows" what the level of sodium intake is requires further investigation.

Non-modulating Essential Hypertension

With a clearer understanding of the normal relation among the adrenal and renal vasculature, changes in sodium intake, and responsiveness to angiotensin II, it became feasible to evaluate potential abnormalities in this relation in patients with essential hypertension. Two observations in the 1970s led to the formulation of the concept of the subset of patients with hypertension, termed "non-modulators." First, in normal subjects renal blood flow increases when dietary sodium intake is increased. However, in some patients with essential hypertension, no change was observed. Second, some hypertensive patients do not increase their aldosterone output in response to acute volume depletion in a manner similar to that observed in normotensive subjects. Because the response of both the adrenal and the renal blood supplies with shifts in total body

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sodium or effective blood volume is primarily determined by angiotensin II, the data suggested that the underlying difficulty was an abnormality in the interaction of these tissues with angiotensin II. Indeed, one study suggested that these two defects were occurring in the same patient and that they might be related to an abnormality in the way the renal vasculature and adrenal sensitivity to angiotensin II change with sodium intake. This hypothesis was directly tested in a group of normal and high renin essential hypertensive patients. The patients were divided into normal or abnormal responders, based on their renal vascular response to a 3 ng/kg/min infusion of angiotensin II on a 200 meq sodium intake. Normal subjects have a reduction of at least 105 ml/min/1.73 m². However, nearly half of the hypertensive subjects had a smaller decrement. The abnormal responders had three major characteristics distinguishing them from normal subjects free of a family history of hypertension and the normal-responding hypertensive patients. First, not only was their renal vascular response to angiotensin II reduced on a high salt diet, but also the level of sodium intake did not change the responsiveness at all. Second, sodium intake also did not change the adrenal response to angiotensin II. Finally, with chronic sodium loading there was no increase in renal blood flow, a finding in sharp contrast to what was observed in normotensive subjects and modulating hypertensive patients. Thus, these data strongly suggest that there is a subgroup of patients with hypertension in whom sodium intake no longer modulates target tissue responsiveness to angiotensin II. It is the failure of this sodium-mediated modulation that resulted in coingage of the term non-modulators.

There are several additional characteristics that partially distinguish non-modulators from other hypertensive patients (Table 2). Importantly, not all may be present in each non-modulator. First, when subjects are sodium restricted and placed in the upright position, the plasma renin activity and angiotensin II levels tend to be higher and the plasma aldosterone levels tend to be lower in non-modulators; thus, a lower change in aldosterone/change in plasma renin activity ratio results. Second, both angiotensin II and acute sodium chloride infusion have a reduced ability to suppress plasma renin activity in the sodium-restricted non-modulator. Third, plasma dopamine levels are increased in non-modulators, particularly on a low sodium intake, and dopamine excretion is fixed regardless of the level of sodium intake. Fourth, sodium-lithium countertransport in red blood cells is significantly elevated in non-modulators. Fifth, non-modulators have a decreased ability to handle a sodium load. Finally, plasma norepinephrine levels are increased in non-modulators, particularly in response to sodium restriction and upright posture.

Non-modulators, however, do not differ from other essential hypertensive patients in age, duration of hypertension, sodium or potassium balance, renal function, cardiac output, gender, or plasma volume. There also appear to be no clinical differences in the severity of the hypertension as judged by electrocardiograms, physical examination, or admission blood pressures.

Thus, there are 10 different characteristics associated with the non-modulating phenotype (Table 2). However, only three of them have demonstrated sufficient specificity and sensitivity to be useful in the identification of these patients. The most precise way of identifying non-modulators is to determine the increment in plasma aldosterone in response to a 3 ng/kg/min infusion of angiotensin II when subjects are in balance on a low (10 meq) sodium intake. Nearly as precise is the increment in p-aminohippuric acid clearance (renal blood flow), when using plasma rather than urine clearance techniques, in patients changing from a 10 to a 200 meq sodium intake. The final technique is the assessment of the decrement in renal blood flow in response to a 3 ng/kg/min infusion of angiotensin II when the subject is in balance on a high (200 meq) sodium intake. None of the other characteristics listed in Table 2 have sufficient specificity to allow identification of these patients.
What is the concordance between the adrenal and renal blood flow criterion for identifying non-modulators? When the responses in 34 patients who have received angiotensin II infusions both on a low and on a high sodium intake were examined, the concordance was extremely high.\textsuperscript{14,15} Eighty-four percent of the patients were identified as modulators or non-modulators by both the adrenal and the renal vascular responses to angiotensin II. Thus, it is reasonable to assume that using only one of the three procedures outlined above is necessary to identify a non-modulator. However, of critical importance, as mentioned earlier, the level of sodium intake markedly influences the responsiveness of both these target tissues to angiotensin II. Thus, sodium balance needs to be carefully controlled to prevent misclassification.

Heritability of the Non-modulation Trait

One of the initial questions addressed in the study of non-modulators was "Are they a discrete group or are the abnormalities simply part of a continuum of responsiveness different at the extremes from that observed in normotensive subjects?" The accumulated evidence strongly suggests that non-modulation reflects a discrete subgroup.\textsuperscript{23} One of the first techniques to separate patients into modulators and non-modulators was to measure their aldosterone secretory response to acute volume depletion induced by a diuretic after sodium restriction. By use of this technique in 46 normal and high renin hypertensive patients, the responses could be separated into two distinct subgroups: in one, comprising 54\% of the subjects, the increment in aldosterone secretion was similar to that observed in normotensive subjects; in the other, little, if any, increase in aldosterone secretion occurred. Reanalysis of previously published data\textsuperscript{23} using maximum-likelihood analysis established that the probability was highly significant that this distribution reflected a bimodal versus a unimodal distribution ($p<0.00001$).

Confirmation of this observation has occurred with the assessment of adrenal responses to infused angiotensin II in 157 sodium-restricted normal and high renin hypertensive subjects and 46 normotensive subjects.\textsuperscript{23} Again, reanalysis of these data indicate that the responses in the hypertensive but not the normotensive patients are bimodal.\textsuperscript{23} The non-modulators do not increase renal blood flow, thereby enhancing the ability of the kidney to excrete sodium. However, of critical importance, as mentioned earlier, the level of sodium intake markedly influences the responsiveness of both these target tissues to angiotensin II. Thus, sodium balance needs to be carefully controlled to prevent misclassification.

Relation Between Non-modulation and Hypertension

In normal subjects an increase in sodium intake produces an increase in renal blood flow, thereby enhancing the ability of the kidney to excrete sodium. The non-modulators do not increase renal blood flow when sodium intake is increased; therefore, one would predict that they would retain sodium. This sodium retention could underlie their elevated blood pressure. The validity of this hypothesis has been demonstrated in a number of ways. First, the time necessary to achieve sodium balance is distinctly increased in non-modulators; this increase strongly suggests an expanded sodium space. Thus, the halftime of disappearance of sodium from the urine when subjects are placed on a 10 meq sodium diet is approximately 50\% longer (36 hours) in non-modulators than in normotensive subjects or modulators.\textsuperscript{20} Second, when non-modulators are given an acute sodium load they fail to excrete it as rapidly as do modulating hypertensive patients.\textsuperscript{19} Finally, when non-modulators are chronically sodium loaded (for 5 days after achieving balance on a low salt diet), they take longer to reestablish high salt equilibrium, and when they do, the net accumulated sodium balance is nearly twice as great as in modulating hypertensive patients.\textsuperscript{20}

Thus, several lines of evidence suggest that, when compared with the rest of the normal and high renin essential hypertensive population, non-modulators fail to handle sodium loads appropriately. As has been described for other clinical states in which an abnormality in sodium handling has been described, that is, primary aldosteronism and bilateral renal artery stenosis, one would anticipate that these patients' blood pressures would be sensitive to the level of sodium intake. This has been documented acutely in response to sodium chloride infusion\textsuperscript{27,28} and with short-term oral salt loading (5 days on a high salt diet)\textsuperscript{25}; only in the non-modulator subgroup was a substantial (6 mm Hg) rise in blood pressure documented. In a preliminary study of 20 patients, sodium sensitivity was defined as a rise in mean blood pressure when sibling pairs with hypertension are analyzed for the presence or absence of the non-modulating phenotype, a high degree of concordance is observed ($p<0.0001$).\textsuperscript{26} Thus, the non-modulating phenotype aggregates in families, providing further evidence that this is an inherited abnormality.
pressure of 10 mm Hg after 2 weeks on a 250 meq salt diet. Eighty percent of the sodium-sensitive patients were non-modulators; there were no non-modulators in the sodium-resistant group.

Thus, the available evidence strongly suggests that when non-modulators increase their sodium intakes, they are unable to excrete it appropriately, presumably because of the defect in their renal hemodynamic responses to the sodium load. Because the frequency of non-modulation is approximately 40% in the normal and high renin essential hypertensive group, non-modulators probably account for all of the sodium-sensitive subjects in this subgroup and form the largest sodium-sensitive hypertensive subgroup.

What could account for the absence of an effect of sodium intake on tissue responsiveness to angiotensin II? Evidence accumulated so far strongly suggests that it is due to a difference in tissue angiotensin II levels. This is based primarily on the seminal observation that in non-modulators the defects in both the adrenal and renal vascular response to angiotensin II, the renal vascular response to sodium intake, and the kidney's ability to excrete a salt load are all corrected after the administration of converting enzyme inhibitors. In contrast, neither normotensive subjects nor modulating hypertensive patients change any of these parameters after administration of converting enzyme inhibitors. Because modulators and non-modulators have similar levels of circulating renin activity and angiotensin II, particularly on a high salt diet, abnormalities in locally produced angiotensin II are likely to underlie these defects. This provides a particularly appealing hypothesis to explain the abnormal renal blood flow and sodium handling in non-modulators. Thus, if there is an increase in the intrarenal angiotensin II production or an abnormality in the renal angiotensin II receptors, this could produce an apparent high local angiotensin II state, which would reduce the renal vascular response to exogenously administered angiotensin II and prevent an increase in renal blood flow when sodium intake is increased and thereby reduce the ability of the kidney to excrete a salt load.

What does this mean to the hypertensive patient? In part, the answer lies in the non-modulator's blood pressure response to converting enzyme inhibitors on a high salt diet. Under these circumstances, the "sodium-sensitive hypertensive," who should be particularly resistant to converting enzyme inhibitors, actually is particularly sensitive to them. Indeed, the fact that converting enzyme inhibitors correct the underlying defects in the non-modulators provides a reasonable explanation to what had been a puzzling observation. Most studies have documented that nearly 50% of the hypertensive population will show a substantial reduction in blood pressure when given a converting enzyme inhibitor on a high salt diet—a circumstance that would not logically favor a positive response. Observations noted above would suggest that responders to converting enzyme inhibitor monotherapy are non-modulators.

In conclusion, from the data cited in this review, the accumulated evidence suggests that essential hypertension is not a single disease entity, despite the fact that a number of features in these patients, including blood pressure itself, appear to form a continuum. Even patients whose blood pressures are sensitive to the level of sodium intake do not form a discrete group. However, in one of the sodium-sensitive hypertensive subsets, non-modulators, the intermediate phenotype that characterizes these patients is clearly bimodal. These patients have an abnormality related to locally produced angiotensin II or the angiotensin II receptor, which prevents them from changing their target tissue responsiveness to exogenous angiotensin II when sodium intake is modified and thus reduces their ability to excrete a sodium load. Paradoxically, converting enzyme inhibitors, which theoretically should be ineffective in these patients, are more effective than they are in the non-sodium-sensitive subgroups. Finally, preliminary data strongly suggest that the non-modulating trait is inherited.

Does this evolving theory account for all abnormalities in patients with essential hypertension? The answer is clearly no. It can be seen from the discussion cited above that there are a variety of underlying mechanisms resulting in an increase in blood pressure even in the sodium-sensitive subgroup. Detailed investigations of the fundamental mechanisms producing sodium-sensitivity in them and in those non-sodium-sensitive subjects with increased vasoconstrictor activity are still required.

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