Plasma Norepinephrine Variations with Dietary Sodium Intake

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SUMMARY Plasma catecholamine and renin activity levels were measured across a range of dietary sodium intakes (10-300 mEq/day) in 20 normal male volunteers. Supine plasma norepinephrine levels presented a triphasic pattern in relation to urine sodium, whereas epinephrine levels were not significantly altered by sodium intake, and renin showed the well-known hyperbolic relationship to urine sodium excretion. Highest supine norepinephrine values occurred at low salt intakes, the lowest when sodium excretion was between 100 and 180 mEq/day, and intermediate when sodium excretion was greater than 180 mEq/day. These findings show that sodium intake is an important consideration in the interpretation of plasma norepinephrine levels. (Hypertension 2: 29–32, 1980)

KEY WORDS norepinephrine • diet sodium • hypertension

PLASMA norepinephrine levels are considered to reflect the activity of the autonomic nervous system, but until recently the methods available for their measurement have been restricted to only a handful of specialized research laboratories. The introduction of radioenzymatic assay has simplified and improved the measurement of plasma catecholamines. The widespread use of newly available commercial kits is anticipated in both clinical and research fields. Since many laboratories will now be able to carry out plasma catecholamine determinations, it is essential that normal ranges be defined under standardized conditions. It is already well known that such factors as body posture, smoking, "stress," age, and some medications influence sympathetic activity. The present study documents that dietary sodium intake is another important factor in determining plasma norepinephrine levels in normal male volunteers.

Methods

We measured plasma norepinephrine, epinephrine, and plasma renin activity (PRA) in 20 healthy men aged 20–45 years who were on "normal," low, and high sodium diets, as a baseline for later comparison with hypertensive patients. The protocol was approved by the University of Michigan Hospital's Human Use Committee, and each subject gave his informed consent before initiation of the study. The volunteers were interviewed and examined to ensure that there was no family history of hypertension and that blood pressure in the sitting position was less than 140/90 mm Hg. Strict instructions were given on how to collect 24-hour urines, and a Clinical Research Center dietitian outlined a detailed regime of foods for purchase to achieve a low salt (10–105 mEq/day) and "normal" salt (105–180 mEq/day) intake. For the high salt regime, sodium chloride capsules (0.5 g, nine per day) were taken along with the "normal" salt diet. Each of the three diets was taken for 4 days, with a 2- to 5-day washout period of unrestricted intake between any two regimens. Smoking, caffeine, and vigorous exercise were avoided during these periods of controlled salt intake.
Blood for hormone measurements was drawn on the morning of the fifth day at the completion of each diet. At this time the volunteers entered the Clinical Research Center by 7:45 a.m. after a 12-hour fast, bringing a 24-hour urine specimen from the final day of the diet, for sodium and creatinine measurement. At 8 a.m., a 20-gauge butterfly needle was inserted into a forearm vein of each volunteer to obtain blood samples for measurement of norepinephrine, epinephrine, and PRA. All subjects remained supine for 1 hour when the first sample was drawn, and then 15 of the 20 volunteers were allowed to walk about for another hour. At 10 a.m., a second venous sample was drawn.

Since the dietary regime of hypertensive patients was to begin with low sodium intake (as a safety precaution), the dietary pattern of the initial 12 volunteers was also of this sequence: low, high, then "normal" salt intake. Later volunteers received their diets beginning with either the "normal" or high salt intake.

Plasma norepinephrine and epinephrine were measured by the radioenzymatic method of Peuler and Johnson, and PRA was measured by radioimmunoassay using New England Nuclear kits. All samples from any one volunteer were analyzed for both catecholamines and renin in a single assay run by a technician who had no knowledge of the dietary sodium sequence.

Results

All 20 subjects completed the trial. One additional volunteer was eliminated from the study as his urine creatinine and sodium excretion indicated inaccuracy in urine collection and in controlling dietary sodium intake.

Supine norepinephrine showed a triphasic pattern when plotted against 24-hour urine sodium (fig. 1). The highest values (672 ± 52.7 pg/ml, mean ± SEM) were seen when the subjects took the low sodium diet, whereas the lowest values (239 ± 15.3 pg/ml) occurred in association with the "normal" salt diet. Intermediate values of norepinephrine (449 ± 33 pg/ml) were observed when dietary sodium intake was high. Supine epinephrine levels (fig. 1) were, in general, higher for the low salt (113 ± 15.6 pg/ml, mean ± SEM) and high salt (102 ± 12.8 pg/ml) diets compared to the normal sodium intake (59 ± 6.5 pg/ml), but the differences failed to reach levels of statistical significance. Plasma renin activity showed the well-known hyperbolic relationship to urine sodium, with highest values occurring at low urine sodium levels (fig. 1).

Because the initial pattern of sodium diets (12 subjects) was in the set sequence of low, high, then "normal," it was important to determine whether the changes in plasma norepinephrine levels (fig. 1) were dictated by salt intake or by the sequence of the diets. Analysis of variance shows that norepinephrine levels were not influenced by sequence of diet in these 20 subjects. That is, there were no significant differences in norepinephrine levels for subjects who received their low salt diet first as compared to those who took the low salt diet second or third, as was also the case for normal and high sodium diets. In contrast to this non-significance of diet sequence, the differences in the mean norepinephrine values by levels of salt intake (low, "normal," and high) were significant statistically (p < 0.001) by repeated measures analysis. Furthermore, the triphasic pattern of supine norepinephrine levels for subjects following the dietary sequence of low, "normal," and high sodium diets was confirmed.
observed in the initial volunteers receiving a set sequence (fig. 2, upper) was also clearly seen in the eight subjects whose diet sequence was altered (fig. 2, lower).

Upright norepinephrine values, measured on three occasions in 15 of the 20 subjects (755 ± 50.4 pg/ml, mean ± SEM) were higher than supine values drawn 1 hour before, in all but one instance. The triphasic pattern observed in the supine position disappeared with upright posture. Upright plasma epinephrine values (119.6 ± 9.1 pg/ml) likewise showed no relationship to urine sodium. Epinephrine values of ambulants increased in 34 and fell in 11 instances.

Discussion

Circulating norepinephrine reflects the activity of the sympathetic nervous system, although clearly its concentration in plasma represents a balance between release (from nerve endings and adrenal medulla) and clearance by reuptake, metabolism, and excretion. Circulating epinephrine is an indicator of adrenal medullary activity.

Methological improvements in recent years have made it possible for large numbers of laboratories to measure plasma catecholamines at picogram levels of sensitivity. Attention to details of body posture, age, smoking, caffeine intake, the stress of venipuncture, and ingestion of medications is essential for accurate interpretation of plasma catecholamines. There is also some evidence that dietary sodium intake influences plasma norepinephrine levels, although the effect of diet sequence has not been separated from the effect of salt intake per se. Further, to our knowledge there has been no systematic study of plasma catecholamine levels across different salt intakes within the physiological range that has eliminated possible effects of diet sequence.

Our current study shows that supine plasma norepinephrine levels are altered by different sodium intakes within the 10-300 mEq/day range, at least in the short term. The highest levels were seen when dietary sodium was most restricted, and lowest levels occurred when urine sodium excretion was in the 100-180 mEq/day range. Intermediate norepinephrine values were seen with higher salt intakes. It remains to be seen whether this pattern holds true for more chronic changes in dietary sodium intake. This triphasic relationship of norepinephrine to urine sodium might theoretically be explained by the sequence of the diets and the blood sampling, since Peuler and Johnson showed that norepinephrine levels in an individual were usually lower in a second venipuncture specimen compared to the first. We excluded a major sequence effect by demonstrating the same triphasic relationship of supine norepinephrine levels to dietary sodium content despite a varied sequence of salt intakes.

These data complement the findings of two other groups who reported urine and plasma norepinephrine levels in normal volunteers to be highest when dietary sodium was restricted (10 mEq/day) compared to when sodium intake was increased. In neither of these studies, however, was attention paid to the sequence of the various sodium diets. Our results define a pattern of supine plasma norepinephrine levels to dietary sodium content despite a varied sequence of salt intakes.

Our study does not define the mechanisms or the physiological importance of the plasma catecholamine changes we observed. We might speculate, however, that activation of the sympathetic nervous system during sodium restriction and with upright posture is a homeostatic mechanism preventing hypotension, and the plasma norepinephrine increments under these two circumstances most likely represent augmented norepinephrine release (rather than changes in reuptake or metabolism) from nerve endings. It is conceivable that the increased norepinephrine levels we observed with the high salt diet is akin to the augmentation in sympathetic activity documented in DOCA-salt hypertensive rats and

FIGURE 2. Upper: Supine fasting plasma norepinephrine levels in 12 volunteers on the fixed regime of sodium diets (low, high, then "normal" salt). For one volunteer, the sample for norepinephrine while on the "normal" salt diet was lost; his two other values are represented by open circles. Lower: The pattern for eight volunteers whose diet sequence began with either the "normal" or high salt diet.
might explain in part the rise in blood pressure when dietary sodium is increased in normal humans. If this is so, the increased norepinephrine values we saw during periods of high salt intake most likely represent accelerated release from nerve endings. Formal studies of release, reuptake, and metabolism of norepinephrine are required to confirm or refute these speculations.

Whatever the underlying mechanisms, our data have important implications in the interpretation of norepinephrine levels for both research and clinical circumstances. For example, there is considerable disagreement in the literature as to whether plasma norepinephrine levels are normal or elevated in essential hypertensive patients. An objective assessment of dietary sodium intake has been provided in only a few of such reports, which makes accurate interpretation of data difficult.

Probably the most common clinical application for plasma norepinephrine measurements will be in the diagnosis of pheochromocytoma. The results above indicate that, when this diagnosis is being entertained, discrimination between normal and abnormally elevated plasma norepinephrine would be most likely obtained by a sodium intake in the range of 100-180 mEq/day. Certainly, a severely sodium-restricted diet or diuretic treatment should be avoided; in the short term, both elevate norepinephrine levels toward those seen in pheochromocytoma patients.

Just as a 24-hour urine sodium measurement is required for interpretation of plasma renin levels, we also recommend it as a necessary accompaniment to plasma norepinephrine determination, at least when there are short-term alterations in diet compared to the normal home intake.

In conclusion, the present study in healthy men emphasizes that dietary sodium intake must be considered as well as body posture, age, smoking, caffeine intake, “stress,” and medications when interpreting plasma norepinephrine levels.

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References

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