Pressor Effects of Epinephrine, Norepinephrine and Desoxycorticosterone Acetate (DCA) Weakened by Sodium Withdrawal

By W. Raab, M.D., R. J. Humphreys, M.D., N. Makous, M.D., R. DeGrandpré, M.D., Ph.D., and W. Gigee, R.N., A.B.

Recent findings suggest an important role of the sodium ion, intracellularly deposited by the adrenal mineralocorticoids, as the physicochemical mediator between the pressor actions of the mineralocorticoids and of the adrenosympathogenic neurohormones. The following observations show that the pressor effectiveness of both the pressor neurohormones and desoxycorticosterone acetate depends on the availability of sodium. This supports the theory that vascular pressor responsiveness and tonus is determined jointly by the sodium-depositing corticoids as sensitizers and the adrenosympathogenic neurohormones as the physiologic stimulators of the vascular contractile elements.

An important role of the local action of electrolytes in the maintenance of vascular tone was postulated by Loeb and Swingle 10 years ago. In the meantime, it was found that the slow pressor effect of desoxycorticosterone acetate (DCA) is enhanced by sodium ingestion and weakened or abolished by sodium withdrawal. These observations suggested that the sodium ion is fundamentally involved in the pressor action of desoxycorticosterone and probably also of the natural mineralocorticoids. Furthermore, it has been shown in previous publications and confirmed by others that the pressor effects of injected or infused epinephrine and norepinephrine in man are potentiated by pretreatment with desoxycorticosterone. On the other hand, in adrenalectomized animals and in hypoadrenocortical human subjects, the pressure ceilings after epinephrine injection proved to be lowered.

It appeared possible, therefore: (a) that adrenal mineralocorticoid activity might be an important factor in determining the degree of cardiovascular pressor responsiveness to the adrenosympathogenic catecholamines (epinephrine, norepinephrine) by virtue of its influence on electrolyte balance, and (b) that the pressor effect of desoxycorticosterone itself might be due to an increase of vascular contractile reactivity to intrinsic catecholamine (norepinephrine) action as a result of intracellular sodium deposition.

The following experiments were carried out in order to study the influence of dietary salt withdrawal (a) upon the pressor responses to infused epinephrine and norepinephrine, and (b) upon the epinephrine- and norepinephrine-potentiating action of desoxycorticosterone.

Methods

In four patients (three moderately, one markedly hypertensive), all of whom had been hospitalized for weeks or months prior to the beginning of the experiments, the average pressor effects of intravenously infused epinephrine and norepinephrine (0.1 or 0.2 or 0.3 μg per kilogram per minute for five minutes each) were recorded with the same technic as published elsewhere. Thereupon, the patients were placed on a sodium-poor, rice-fruit diet, containing 180 mg. of sodium per day. During certain periods of this regime, desoxycorticosterone was administered intramuscularly in daily doses of

* Three of the patients were located at the Vermont State Hospital in Waterbury. We want to express our thanks to the Superintendent, Dr. Rupert Chittick, for the permission to work there, and to the hospital staff for efficient assistance.
10 mg.† (corresponding to the dosage and duration of administration which had regularly intensified the pressor catecholamine effect in another series of experiments). The experimental periods were concluded with the resumption of a normal diet with or without desoxycorticosterone. During all phases of these procedures, repetitions of the epinephrine and norepinephrine infusions were carried out with the same dosages as at the beginning.

Sodium and potassium in serum and urine were determined with a flame photometer. In the cases of two patients who were incontinent and two others who were mentally disturbed it was not always possible to collect complete 24-hour specimens. Consequently, the urine electrolytes were expressed in these cases in milliequivalents per liter and the readings represent only an approximate, indirect measure of the total daily excretion. These tests served mainly the purpose of checking the reliability of the patient’s dietary discipline. In one case, the sodium assay in the urine revealed the temporary surreptitious ingestion of extra salt.

RESULTS

The systolic and diastolic blood pressure data, represented in figures 1 through 4, indicate: (a) resting levels in recumbent position after preparatory rest periods (no sedatives); (b) pressor responses to infused epinephrine and norepinephrine, that is, the absolute pressure deviations from the respective resting levels; (c) pressure ceilings, that is, the pressure levels, reached under the influence of epinephrine or norepinephrine infusion. Each value for (b) and (c), appearing in figures 1 through 4, represents the average of five readings, taken during a five-minute infusion period. (For explanation of graphs, see legend to fig. 1.)

During sodium withdrawal, the systolic resting pressure level was decreased in all four cases. Administration of desoxycorticosterone during the period of sodium deprivation failed to raise the blood pressure, except in one instance (fig. 3). With resumption of a normal diet, the systolic pressure levels (without or with desoxycorticosterone) tended to return toward their original height with individually different speeds. The diastolic pressure levels behaved generally in a similar fashion but within narrower ranges.

† We are indebted to Ciba Laboratories, Inc., for a generous supply of Percorten (desoxycorticosterone acetate).

The absolute systolic and, less regularly, the diastolic pressor responses to infused epinephrine and norepinephrine were weakened or occasionally abolished during salt withdrawal.

![Graph showing blood pressure levels](image)

FIG. 1. Case 1. Resting blood pressure is shown by the upper limit of each shaded area where a black area is superimposed, and by the top line where a white area is superimposed. Absolute increments of the blood pressure during epinephrine and norepinephrine infusions are represented by black areas, absolute decreases of the blood pressure by white areas. Each graphically symbolized blood pressure response to infused epinephrine or norepinephrine represents the average of five readings made during a five-minute infusion period.

The systolic and, less markedly, the diastolic pressor ceilings were lowered throughout. Administration of desoxycorticosterone during salt withdrawal failed to increase the pressor effects of epinephrine and norepinephrine. Resumption of a normal diet, without or with desoxycorticosterone, was followed by a grad-
irregularly and without any recognizable relationship to blood pressure levels and pressor responses. The serum potassium level was not significantly affected by the salt-poor diet. Desoxycorticosterone administered during salt withdrawal, did not depress the serum potassium concentration.

In one case, not reported in this series, the intake of a diet containing a larger amount (400 mg.) of sodium per day caused a moderate decline of the resting blood pressure, but only an insignificant lowering of the catecholamine-induced pressure ceilings. Desoxycorticosterone restored both to the pre-experimental levels.

**Discussion**

The salient points among the findings obtained are the following: (a) the absolute pressor effects (predominantly systolic) of epinephrine and norepinephrine, and even more so their ceiling effects, were significantly diminished or abolished by intake of an almost sodium-free rice-fruit diet; (b) during sodium withdrawal, desoxycorticosterone failed to intensify the pressor effects of epinephrine and norepinephrine, in contrast to its normally potentiating action upon these effects.

These observations suggest that the presence of a certain amount of sodium in the body is
necessary to maintain full cardiovascular pressor responsiveness to both adrenosympathogenic neurohormonal stimuli and desoxycorticosterone (adrenal mineralocorticoids?). Desoxycorticosterone intensifies the pressor effectiveness of the adrenosympathogenic catecholamines during normal salt intake,\textsuperscript{2,13-15} probably by retaining sodium in the body, and particularly by its specific ability to augment the intracellular sodium concentration.\textsuperscript{20-26}

The results obtained during intake of the rice-fruit diet are ascribed to the lack of sodium and not to other peculiarities of this diet, since its blood pressure-lowering action could be duplicated by various mixed diet forms, provided that their sodium content was low.\textsuperscript{9,27-31}

The fact that in one case a somewhat higher sodium intake (400 mg. per day) failed to produce a striking effect on the pressor reactions seems to indicate that sodium restriction must be extreme to alter the vascular reactivity significantly.

The slowness of the return to pre-rice diet reactions after resumption of a normal salt intake in three out of the four cases may possibly be explained as the result of a temporary adrenal cortical functional insufficiency, caused by the preceding periods of desoxycorticosterone administration.

Neither the phenomenon of a potentiating effect of catecholamine pressor effectiveness by desoxycorticosterone nor the opposite weakening effect of salt withdrawal would be of any particular interest if these findings did not open a new outlook on the fundamentals of integrated nervous and hormonal blood pressure regulation. It appears conceivable that the interplay between the intrinsic sympathogenic pressor catecholamines (mainly norepinephrine) and adrenal mineralocorticoids maintains, elevates, or depresses the blood pressure level whereby sodium seems to act as the physicochemical mediator. It has recently been shown that the contractile power of muscular elements depends on their electric membrane potentials and that the latter in turn are determined by the gradient between intra- and extracellular electrolyte concentrations.\textsuperscript{32, 33} The significance of desoxycorticosterone for muscular activity by its apparent action on cell membranes and intracellular electrolyte distribution was demonstrated specifically concerning the heart muscle.\textsuperscript{35} Furthermore, epinephrine and norepinephrine have been recognized as depolarizing agents.\textsuperscript{34-38}

These important findings are likely to facilitate the understanding of hypertensive and hypotensive mechanisms on a physicochemical basis. A tentative interpretation of the integrated role of catecholamines, mineralocorticoids and sodium in the origin of hypertension and in the mechanism of action of successful therapeutic procedures, such as sympathectomy, salt-poor diet and adrenalectomy, will be presented elsewhere.\textsuperscript{37}

**Summary**

During intake of a practically sodium-free diet, the following effects were observed in four hypertensive patients: (a) the resting blood pressure declined; (b) the pressor effectiveness of infused epinephrine and norepinephrine was significantly weakened or abolished; (c) desoxycorticosterone failed to intensify the pressor effects of epinephrine and norepinephrine in contrast to its normally potentiating action.

Brief reference is made to the conceivably integrated role of adrenosympathogenic catecholamines, mineralocorticoids and the sodium ion in the neurosecretory and hormonal system of blood pressure regulation.

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