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J Clin Invest. 1967;46(4):599-605. <https://doi.org/10.1172/JCI105561>.

Research Article

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We suggest that both upright posture and sodium depletion lead to decreases in effective plasma volume and increases in sympathetic nervous system activity. This increase in sympathetic activity is then responsible for an increase in renal afferent arteriolar constriction, leading to an increase in renin secretion and, ultimately, an increase in aldosterone secretion.

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Role of the Sympathetic Nervous System in Regulating Renin and Aldosterone Production in Man *

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Summary. Several lines of evidence have been developed indicating that the sympathetic nervous system may play a role in mediating the renal and adrenocortical secretory responses to upright posture and sodium deprivation. Despite concurrent increases in arterial blood pressure, the plasma renin activity of normal subjects increased both in response to the infusion of catecholamines (norepinephrine: epinephrine, 10:1) and in response to stimulation of the sympathetic nervous system by cold. Aldosterone excretion was also increased by catecholamine infusion. In normal subjects the stimuli of upright posture and of sodium depletion both resulted in increases in urinary catecholamines, plasma renin activity, and urinary aldosterone. A patient with severe autonomic insufficiency did not experience normal elevations of urinary catecholamines, plasma renin activity, or urinary aldosterone in response to upright posture or sodium deprivation, despite a substantial fall in arterial blood pressure. When orthostatic hypotension was prevented by infusion of catecholamines, however, increases in plasma renin activity and in aldosterone excretion were observed.

We suggest that both upright posture and sodium depletion lead to decreases in effective plasma volume and increases in sympathetic nervous system activity. This increase in sympathetic activity is then responsible for an increase in renal afferent arteriolar constriction, leading to an increase in renin secretion and, ultimately, an increase in aldosterone secretion.

Introduction

A decade ago it was known that the secretion of aldosterone is governed in part by hemodynamic factors (1-3), but the mechanism through which such factors influence adrenocortical activity remained obscure. An important connection between the circulation and the adrenal cortex was established when angiotensin was discovered to

stimulate aldosterone secretion (4-6), for it had previously been shown that conditions which compromise the renal circulation can stimulate the secretion of renin and thereby increase the production of angiotensin (7). It thus became possible to think in terms of a hierarchy of functional dependents regulating aldosterone secretion: A decrease in effective blood volume results in an increase in the production of renin and angiotensin, which leads to an increase in aldosterone secretion.

Our study represents an attempt to understand the mechanism through which subtle changes in circulatory dynamics may lead to increased production of renin. Previous studies have shown that gross decreases in the perfusion pressure of the kidneys result in increased renin secretion (7,

* Submitted for publication July 19, 1966; accepted December 22, 1966.

These studies were supported in part by the following grants-in-aid from the National Institutes of Health: 5-K6-AM-3782, 8MOI-FR-95, TI-AM-5092, and 5-ROI-AM-05318.

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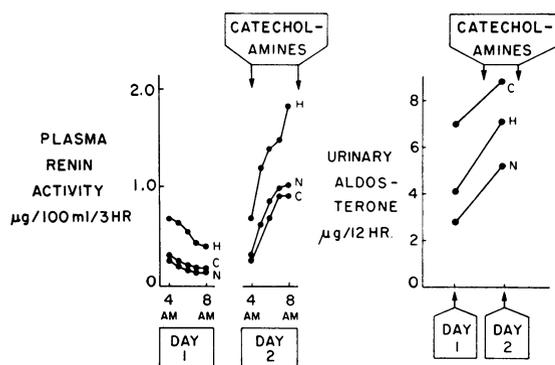


FIG. 1. CHANGES IN PLASMA RENIN ACTIVITY AND OF ALDOSTERONE EXCRETION IN THREE NORMAL SUBJECTS (H, N, AND C) WHO RECEIVED 4-HOUR INFUSIONS OF NOREPINEPHRINE:EPINEPHRINE (10:1) AT RATES SUFFICIENT TO ELEVATE SYSTOLIC BLOOD PRESSURE BY 25 MM HG ABOVE CONTROL LEVELS. All subjects received constant 100-mEq sodium diets. They were recumbent from 9 p.m. on the day preceding the study until 4 p.m. on the day of the study. Control days (day 1) preceded or followed the day of infusion (day 2).

8), but increased secretion of renin has also been shown to occur after the assumption of upright posture without a gross change in arterial blood pressure (9, 10). Such facile adjustment of the blood pressure to changes in posture is possible because the sympathetic nervous system regulates the tone of small blood vessels, thus bringing about an increase in peripheral resistance upon assumption of upright posture. It was postulated that small arteries and arterioles of the kidney may participate in this vasoconstrictor response and that this may be an important link in the chain of events through which upright posture brings about an increase in renin production. Direct evidence that sympathetic nervous activity can increase the production of renin has been shown in the recent studies of Vander (11) and Wathen and associates (12) in the dog.

Evaluation of the state of the renal vasculature was not feasible in our present clinical study, but we were able to develop several lines of evidence suggesting that the sympathetic nervous system plays a role in the regulation of renin production and, indirectly, of aldosterone production.

In normal subjects and in a patient with severe autonomic insufficiency, we measured urinary catecholamines, plasma renin activity, and urinary aldosterone during adaptation to upright

posture and to sodium deprivation. In addition, we evaluated the effects of catecholamine infusions on plasma renin activity and on urinary aldosterone. In an effort to stimulate endogenous sympathetic nervous activity without resorting to postural or dietary manipulations, we performed "cold pressor tests" in normal subjects and observed the ensuing changes in plasma renin activity. In several of the experiments in which arterial blood pressure and sympathetic nervous activity could be assumed to be exerting opposing effects on renin production, we found that changes in plasma renin activity were correlated more closely with changes in sympathetic nervous activity than with changes in central arterial blood pressure.

Methods

Clinical

Twenty normal subjects, 15 male and 5 female, all between 21 and 35 years of age, participated in these studies.

Several studies were also performed on a 68-year-old man (R.M.) with severe autonomic insufficiency, macroglobulinemia, and amyloidosis. His blood pressure during recumbency was 115/70, but when he was upright, it fell to 70/40 mm Hg. Despite this, he was capable of standing and walking for prolonged periods. Regardless of blood pressure changes, his heart rate was fixed at about 70 beats per minute. Other manifestations of autonomic insufficiency included impotency of 20 years' duration and impaired sweating. His urinary catecholamine excretion was low, and his blood pressure was more sensitive than that of normal subjects to an infusion of norepinephrine and epinephrine. His urinary 17-hydroxycorticosteroids were normal both under basal conditions and in response to exogenous corticotropin.

In all studies, diet, posture, and time of day were strictly controlled. Before any experiment, each subject was maintained for at least 5 days on a constant diet containing 100, 30, or 10 mEq of sodium per day. When recumbent, the subjects were permitted to lie in any position, provided it was horizontal, but not to raise themselves on their elbows or sit up; they ate, drank, and voided lying flat in bed. When upright, the subjects sat, stood, or walked, but never lay down.

Laboratory

Plasma renin activity was determined by a modification (10) of the method of Boucher, Veyrat, de Champlain, and Genest (13, 14) with 15 to 20 ml of venous blood.

Urinary aldosterone was measured by the method of Kliman and Peterson (15). Aldosterone secretion rates were determined by an isotope dilution method described previously (16).

TABLE I
Responses to upright posture in 18 normal subjects and in a patient with autonomic insufficiency

Normal subjects	Dietary sodium mEq/day	Urinary catecholamines		Plasma renin activity			Urinary aldosterone		
		Recumbent (4 a.m.- 8 a.m.)	Upright (8 a.m.- noon)	Recumbent (8 a.m.)	Upright (10 a.m.)	(Noon)	Recumbent (4 a.m.- 8 a.m.)	Upright (8 a.m.- noon)	
		$\mu\text{g}/\text{hour}$	$\mu\text{g}/\text{hour}$	$\text{ng angiotensin}/3 \text{ hours}/100 \text{ ml}$			$\mu\text{g}/\text{hour}$		
1. J.C.	100	2.0	3.8	324	855	1,484			
2. N.N.	100	2.1	3.9	234	1,003	833			
3. F.D.	100	1.8	2.6	215	670	440			
4. J.C.	30	0.9	3.4	789	1,789	2,447			
5. F.D.	30	1.5	2.5	627	2,416	1,578			
6. T.B.	10	2.5	3.4	391	806	1,475			
7. J.S.	10	2.1	2.9	423	604	738			
8. J.C.	10	3.3	5.0	789	1,310	1,230			
9. J.D.	10	1.5	3.8	418	1,415	1,650	1.0	1.3	
10. R.W.	10	1.4	3.1	484	1,211	916	1.8	2.1	
11. J.S.	10	3.8	6.6	504	1,351	1,313	0.55	0.63	
12. L.S.	100			349	973	739	0.26	0.90	
13. J.Y.	100						0.28	0.50	
14. L.Y.	100						0.33	0.54	
15. N.S.	100						0.13	0.25	
16. J.D.	100						0.38	0.60	
17. N.M.	100						0.14	0.38	
18. J.D.	100						0.14	0.26	
Subject R.M. (autonomic insufficiency)	100	Day 1	1.0	0.9	29	29	27	0.10	0.09
	100	Day 2*	1.1	2.2	22	100	221	0.10	0.28

* Catecholamines were infused intravenously on day 2 (see text).

Urinary catecholamines were measured by the method of Von Euler and Lishajko (17).

Results

Effects of norepinephrine: epinephrine infusion on renin and aldosterone (Figure 1). After suitable control studies, three normal subjects received iv infusions of norepinephrine and epinephrine (10 parts to 1) from 4 to 8 a.m. The rates of the infusions were adjusted every few minutes to maintain the systolic blood pressure 25 mm Hg above control levels. Dietary sodium was 100 mEq per day in each case. All three subjects were recumbent from 9 p.m. on the day preceding the infusion until the completion of the aldosterone study at 4 p.m. on the day of the infusion. Plasma renin activity was measured every hour during the infusion, and aldosterone excretion was measured from 4 a.m. until 4 p.m. In each case, the infusion of catecholamines was accompanied by distinct increases in both plasma renin activity and urinary aldosterone.

Effect of "cold pressor test" on plasma renin activity (Figure 2). In an effort to stimulate endogenous sympathetic activity, three healthy individuals repeatedly immersed their hands in ice water for 90 minutes. In response to the cold

pressor test, there was in each case a sustained but variable elevation of the blood pressure throughout the 90-minute experimental period. In each case there was also a distinct increase in plasma renin activity.

Responses to upright posture in normal subjects and in a patient with autonomic insufficiency

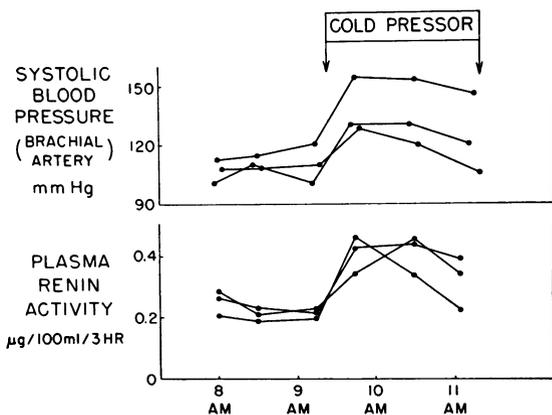


FIG. 2. CHANGES IN ARTERIAL BLOOD PRESSURE AND PLASMA RENIN ACTIVITY IN RESPONSE TO REPEATED IMMERSION OF HANDS IN ICE WATER. The three normal subjects received constant 100-mEq sodium diets and were recumbent from 9 p.m. on the previous day until the completion of the study.

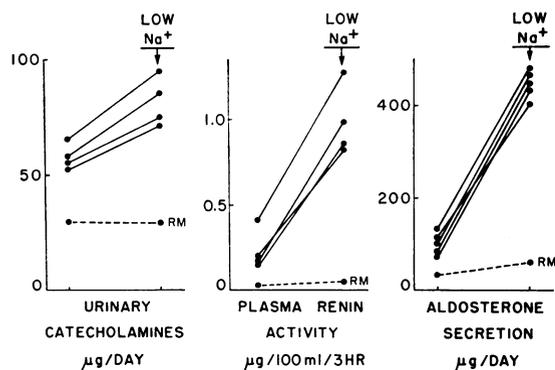


FIG. 3. RESPONSE OF URINARY CATECHOLAMINES, PLASMA RENIN ACTIVITY (MEASURED AT 8 A.M., SUBJECTS RECUMBENT SINCE 9 P.M.), AND ALDOSTERONE SECRETION RATES OF NORMAL SUBJECTS TO A LOW SODIUM DIET. The measurements shown on the left were made after the subjects had been maintained on constant 100-mEq sodium diets for 5 days; those shown on the right were made after they had been maintained for 5 days on constant 10-mEq sodium diets. A patient with severe autonomic insufficiency is represented by the broken lines.

(Table I). When normal subjects are continuously recumbent, they have relatively stable plasma renin activity and urinary aldosterone from 4 a.m. until noon (10, 18). This portion of the day was used, therefore, to study the effects of upright posture. All subjects had been recumbent since 10 p.m. on the previous day. Control observations were made during recumbency from 4 to 8 a.m.; then the effects of upright posture were observed from 8 a.m. until noon. The assumption of upright posture by normal subjects consistently led to increases in urinary catecholamines, plasma renin activity, and urinary aldosterone.

In contrast, a patient with autonomic insufficiency (R.M.) had low levels of urinary catecholamines, plasma renin activity, and urinary aldosterone during recumbency and did not show increases in any of these measurements in response to upright posture. However, when this patient was given an iv infusion of catecholamines (10 parts norepinephrine and 1 part epinephrine) at a rate just sufficient to prevent postural hypotension, he exhibited clear-cut increases in plasma renin activity and urinary aldosterone.

Responses to sodium deprivation in normal subjects and in a patient with autonomic insufficiency (Figure 3). When four normal subjects were

given low sodium diets (10 mEq per day) for 5 days, they all showed increases in urinary catecholamines, plasma renin activity, and urinary aldosterone. By the fifth day on the low sodium diet, sodium excretion was less than 15 mEq per day in every case.

In contrast, the patient with autonomic insufficiency (R.M.) failed to adjust normally to sodium deprivation. After 5 days on a low sodium diet, this patient still had subnormal catecholamine excretion, subnormal plasma renin activity, and subnormal urinary aldosterone. He failed to conserve sodium (urinary sodium on the fifth day of the diet was 81 mEq) and he developed mild azotemia.

Discussion

The autonomic nervous system works with such facility in bringing about cardiovascular adjustments to postural changes that one is hardly aware of how profound these adjustments are until he observes the postural syncope of patients with sympathetic nervous system disorders. The change from recumbency to upright posture in normal individuals tends to result in pooling of fluid in the lower extremities, which leads to decreases in venous return and cardiac output. The autonomic nervous system responds with an increase in sympathetic activity, which leads to cardiac acceleration, venoconstriction, increased peripheral resistance (19), increased myocardial contractility, increased plasma norepinephrine (20, 21), and increased urinary catecholamines (22). This instantaneous sympathetic response maintains the arterial blood pressure and prevents cerebral ischemia during upright posture.

Meanwhile, more sluggish mechanisms come into play to expand extracellular fluid volume and thus support the blood pressure in yet another way. In response to upright posture there is an increase in the production of renin by the kidney (9, 10). Renin catalyzes the formation of angiotensin (23). Angiotensin stimulates the adrenocortical secretion of aldosterone (4-6), which promotes the conservation of sodium by the kidneys. Conservation of sodium leads to expansion of extracellular volume and supports the arterial blood pressure. The present study offers evidence that the sympathetic nervous system, in addition to mediating the instantaneous adaptation of the

cardiovascular system to upright posture, also plays an important role in mediating the more sluggish renin-aldosterone response to upright posture.

If the hierarchy of functional dependents (upright posture → pooling of fluid in the lower extremities → increased sympathetic nervous activity → increased renin → increased aldosterone) is interrupted at some point, the derivative functions fail. For example, if the lower extremities are firmly bandaged before the assumption of upright posture, then pooling of fluid in the lower extremities is prevented, and the assumption of upright posture fails to result in increased plasma renin activity (10) or increased urinary aldosterone (24). Or if some disease of the sympathetic nervous system results in severe autonomic insufficiency, then the pooling of fluid in the lower extremities fails to result in increased plasma renin activity or urinary aldosterone. This interruption in the hierarchy of functional dependents can be circumvented by the infusion of exogenous norepinephrine and epinephrine.

In some respects, sodium depletion resembles the assumption of upright posture. If severe enough, it results in the reduction of effective blood volume (25), increased catecholamine excretion (26, 27), increased plasma renin activity (28-30), and increased secretion of aldosterone (31, 32). Since the last two effects fail to occur in some patients with autonomic insufficiency (2, 33, 34), we suggest that the sympathetic nervous system is a member in this hierarchy of functional dependents.

Our study draws attention to the possible importance of the caliber of the small arteries or arterioles of the kidney in regulating renin production. In three of the conditions described in this paper, plasma renin activity changed in the opposite direction from that which would have been predicted if the blood pressure in the renal artery were the key determinant of renin secretion. Other things being equal, a fall in central arterial pressure should lead to an increase in renin production, and a rise in central arterial pressure should lead to a decrease in renin production (8). Yet, in the patient with autonomic dysfunction, postural hypotension failed to bring about a rise in plasma renin activity, but correc-

tion of postural hypotension by catecholamine infusions did result in increased renin activity. If a fall in central blood pressure per se were the major stimulus to renin production, then patients with autonomic insufficiency should have large increases in plasma renin activity when standing upright and experiencing postural hypotension. It is postulated that the catecholamine infusion in autonomic insufficiency caused some degree of generalized arteriolar constriction including that of the renal vasculature, and this may have been of crucial importance in stimulating the secretion of renin. Conversely, the two maneuvers that elevated the central arterial pressure of our normal subjects, the infusion of catecholamines and the immersion of the hands in ice water, actually brought about increases in plasma renin activity. Again it would appear that sympathetic nervous activity, possibly by causing renal arteriolar constriction, is more important than central arterial blood pressure per se in regulating renin production by the kidneys.

The observation that exogenous catecholamines can stimulate renin and aldosterone secretion is not without precedent. In the anesthetized dog, Vander (11) and Wathen and associates (12) have shown a stimulatory effect of infused epinephrine and norepinephrine on the secretion of renin. Vander (11) also found renin secretion to be elevated after stimulation of the renal nerves, and previous experiments in the rat have shown that denervation of the kidney results in decreases in renin content of the kidney (35) and in the degree of granularity of the juxtaglomerular cells (36).

Extrapolation beyond the observations and conclusions of the present studies should be undertaken with caution. Data tabulated in publications by Laragh and associates (4, 37) suggest that norepinephrine infusions can stimulate aldosterone secretion in human subjects receiving constant liberal salt diets; their data were not consistent, however, for all subjects on various levels of dietary sodium. It may be that exogenous catecholamines given over more prolonged periods or to subjects on restricted sodium intake would have different effects from those found in the present study. We have observed a patient with a pheochromocytoma producing enough catecholamines to cause chronic

hypertension who had normal plasma renin activity.

Several investigators (2, 33, 34) have described patients with autonomic insufficiency who responded abnormally to sodium deprivation with respect to sodium excretion and aldosterone secretion (or excretion). Their studies did not include measurements of plasma renin activity, but it seems probable that this function might have been impaired in their patients as it was in ours. We have encountered some patients with clinical manifestations of autonomic insufficiency who have less clear-cut deficiencies of catecholamines, renin, and aldosterone than the patient described in this report. It is possible that these patients had retained enough function of their renal sympathetic nerves to enable them to adjust in a qualitatively normal fashion to conditions that stimulate renin production. Such a hypothesis is, however, difficult to test.

Addendum

Since the submission of this paper, Bunag, Page, and McCubbin have reported that in dogs neural stimuli are capable of causing release of renin in the absence of gross change in renal perfusion pressure or flow (38).

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