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Effects of Valine-5 Angiotensin II on Excretion of Water and Salt in Primary and Secondary Hypertension.* (26804)

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Intravenous administration of angiotensin in hypertensive subjects promotes an increased excretion of water and salt(1). In contrast, a similar infusion in normal subjects usually results in sodium retention and antidiuresis(2). Whether angiotensin causes natriuresis in subjects with hypertension by acting directly on the kidney, or by some other mechanism is not clear. Since hypertensives seem to ingest more salt than normotensives (3), it may well be that this dietary factor conditions their response to angiotensin.

The present study deals with the effects of intravenous angiotensin under conditions of high and low salt intake on renal excretion of sodium, potassium and water in subjects with hypertension due to primary aldosteronism, advanced essential hypertension and chronic glomerulonephritis.

Material and methods. Six subjects were studied. One (H.M.) had primary aldosteronism, 2 (H.F., O.J.) advanced essential hypertension, and 3 (S.J., B.E., R.D.) chronic glomerulonephritis. Resting diastolic blood pressure ranged between 110 and 130 mm Hg in H.M., H.F. and O.J., and from 90 to 100 mm Hg in S.J., B.E. and R.D. Degree of renal disease varied from severe (S.J., B.E., R.D., H.F.) to moderate (O.J.) or no impairment (H.M.). None of the subjects presented symptoms or signs of congestive heart failure.

All subjects were maintained on a fixed Na (30 to 90 mEq/day) and K (50 to 90 mEq/day) intake for one to 6 weeks. Daily urines were measured and samples of the individual diets saved. After establishing Na retention (urinary Na 20 to 80 mEq/day below intake for at least 10 days) in H.M., H.F. and O.J., and Na depletion (urinary Na exceeding intake by 20 to 30 mEq/day for 2 weeks) in S.J., B.E. and R.D. an intravenous infusion of 300 cc of 5% D/W was given over 6 to 24 hours. On the following day, 100 to 200 μg of synthetic valine-5 angiotensin II (angiotensin II)† diluted in 300 cc 5% D/W was administered intravenously during 6 to 24 hours.

In one of the subjects (R.D.) on each of the following 2 days the effects of intravenous aldosterone‡ alone, 0.5 mg diluted in 300 cc 5% D/W, and in combination with angiotensin II were also studied.

Observations similar to the above were repeated in the subject with primary aldosteronism (H.M.) after removal of an adrenal cortical adenoma, in one subject (O.J.) with advanced hypertension after 3 weeks of reduced Na intake (20 mEq/day), and in 2 subjects (B.E., R.D.) with chronic glomerulonephritis after Na depletion had been corrected by provision of additional salt in tablet form (65 and 100 mEq Na/day).

All subjects were kept recumbent throughout the infusions. Blood pressure was determined at 5 to 30 minute intervals during administration of angiotensin II, and less frequently during infusion of 5% D/W. Blood was drawn before and at termination of infusions.

Pooled diet samples and urines were analyzed for sodium and potassium by flame

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† Hypertensin Ciba, lot E6429

‡ d-aldosterone Ciba, lot E6403.

TABLE I. Effects of I.V. Angiotensin II on Urinary Excretory Function in Primary Aldosteronism and Essential Hypertension. Values of urine volume (V), sodium (U_{Na}), potassium (U_K), osmolality (U_{Osm}), urine sodium to potassium ratio (U_{Na}/U_K), endogenous creatinine clearance (C_{Cr}) and blood pressure (BP).

Subject	Intake (meq/day)	Reg.	V (l/day)	U_{Na} (meq/l)	$U_{Na} \times V$ (meq/day)	U_K (meq/l)	$U_K \times V$ (meq/day)	U_{Na}/U_K	U_{Osm} (mOsm/l)	C_{Cr} (ml/min.)	BP (mm Hg)	Angiotensin (μg/min.)
H.M.						Before adrenalectomy						
	Na 50	C	1.40	18	25	37	52	.48	333	81.0	190/120	
	K 65	Angiot.	2.70	49	134	30	82	1.64	280	96.0	246/155	.4
		R	1.74	23	41	29	50	.82	286	92.0	196/100	
H.F.	Na 90	C	.89	12	11	54	48	.23	423	11.0	215/124	
	K 60	Angiot.	1.00	28	38	56	56	.68	408	10.0	248/136	.4
O.J.	Na 40	C	1.23	17	21	45	56	.37	584	46.2	220/120	
	K 90	Angiot.	1.91	39	74	40	77	.96	476	46.3	240/130	.4
H.M.						After adrenalectomy						
	Na 60	C	1.60	76	121	32	52	2.32	416	90.0	180/110	
	K 75	Angiot.	1.60	55	88	42	67	1.51	419	91.5	214/130	.5
O.J.	Na 20	C	1.91	22	43	32	62	.70	303	49.7	220/117	
	K 90	Angiot.	1.92	4	8	28	55	.14	320	49.7	230/122	.4

Reg. = regimen; C = control; Angiot. = angiotensin II; R = recovery.

TABLE II. Effects of I.V. Angiotensin II on Urinary Excretory Function in Chronic Glomerulonephritis. Values of urine volume (V), sodium (U_{Na}), potassium (U_K), osmolality (U_{Osm}), urine sodium to potassium ratio (U_{Na}/U_K), endogenous creatinine clearance (C_{Cr}) and blood pressure (BP).

Subject	Intake (meq/day)	Reg.	V (l/day)	U_{Na} (meq/l)	$U_{Na} \times V$ (meq/day)	U_K (meq/l)	$U_K \times V$ (meq/day)	U_{Na}/U_K	U_{Osm} (mOsm/l)	C_{Cr} (ml/min.)	BP (mm Hg)	Angiotensin (μg/min.)
S.J.	Na 30	C	1.60	38	61	32	51	1.20	115	16.0	140/90	
	K 50	Angiot.	1.50	34	51	41	61	.83	118	16.0	150/98	.4
B.E.	Na 60	C	2.10	38	80	19	39	2.05	275	18.0	135/90	
	K 80	Angiot.	1.60	42	67	40	64	1.05	333	18.0	142/95	.6
R.D.	Na 30	C	2.00	29	58	15	30	1.93	194	7.0	162/80	
	K 80	Angiot.	1.95	29	56	15	29	1.93	186	7.2	194/100	.2
		d-aldost.	1.96	15	30	23	45	.67	186	7.6	167/88	
		Angiot. + d-aldost.	1.79	18	33	24	43	.77	187	6.5	197/100	.3
B.E.	Na 160	C	1.43	55	78	38	55	1.42	377	19.0	140/85	
	K 80	Angiot.	1.70	66	112	32	53	2.12	354	19.0	150/92	.6
R.D.	Na 95	C	1.34	36	48	24	33	1.45	208	6.1	180/90	
	K 80	Angiot.	1.41	43	61	25	35	1.74	227	6.3	215/105	.3

Reg. = regimen; C = control; Angiot. = angiotensin II; d-aldost. = d-aldosterone 0.5 mg.

photometry. Plasma and urine creatinine chromogen concentration was measured by the method of Bossnes and Taussky(4), and urine osmolality by the Fiske osmometer.

Results. In Tables I and II are listed the observed data relative to blood pressure (BP), 24-hour urine volume (V), urine sodium (U_{Na}), potassium (U_K), osmolality (U_{Osm}), urinary sodium to potassium ratio ($U_{Na/K}$) and endogenous creatinine clearance (C_{Cr}).

Effects of angiotensin II infusion in primary aldosteronism and advanced hypertension (Table I). 1. Administration of angiotensin II under conditions of Na retention promoted in H.M. (before adrenalectomy), H.F. and O.J. a mild to marked diuresis, a more than 2-fold increase in U_{Na}/L and a 3- to 5-fold rise in U_{Na}/day. In contrast, U_K/L did not change, while U_K/day increased from 12 to 16% and $U_{Na/K}$ more than 50% above control. C_{Cr} rose by 18% in H.M., but did not change in H.F. and O.J.

2. After Na depletion had been established in H.M. (3 weeks following adrenalectomy) and O.J. angiotensin II infusion did not alter V, though U_{Na}/L and U_{Na}/day decreased 18 and 33 mEq, respectively. U_K/L and U_K/day changed little, consequently $U_{Na/K}$ decreased markedly. C_{Cr} did not change in either subject.

Effects of angiotensin II infusion in chronic glomerulonephritis (Table II). 1. Administration of angiotensin II under conditions of Na depletion promoted a slight to moderate decrease of V in S.J. and B.E., but not in R.D. U_{Na}/L remained nearly unchanged in all the 3 subjects, while U_{Na}/day decreased 10 and 13 mEq in S.J. and B.E. U_K/L and U_K/day tended to rise in S.J. and B.E., while it did not change in R.D. $U_{Na/K}$ diminished by 10 to 50%, and C_{Cr} remained unchanged.

The infusion of aldosterone in R.D. caused a fall in U_{Na}/L and U_{Na}/day of about 50%, and a small rise in U_K/L and U_K/day. Consequently, $U_{Na/K}$ decreased markedly. When angiotensin II was added to the aldosterone infusion on the following day, no further decrease of U_{Na} or increase of U_K were found, though V and C_{Cr} fell by 8.7 and 14.6% respectively.

2. After a state of Na retention had been established in B.E. and R.D. administration of angiotensin II caused a slight to moderate rise in V, U_{Na}/L and U_{Na}/day. Since U_K/L and U_K/day were not affected by the infusion, $U_{Na/K}$ increased. C_{Cr} did not change in either subject.

Discussion. These observations show that under conditions of sodium retention angiotensin promotes natriuresis and diuresis in hypertensive subjects. By contrast, under conditions of sodium depletion angiotensin tends to cause a diminished excretion of salt and water. The results are in accord with observations made in the rat(5,6), and emphasize the role of sodium metabolism in renal response to angiotensin.

The fact that angiotensin caused exaggerated natriuresis in the 2 subjects with advanced hypertension (H.F., O.J.) as well as in those with chronic glomerulonephritis (S.J., B.E., R.D.) and in that with primary aldosteronism (H.M.) indicates that the phenomenon is not a specific feature of essential hypertension. Peart and Brown(7) have found that angiotensin-induced natriuresis could be abolished in hypertensives by lowering the blood pressure to normal levels. It is pertinent in this respect that 3 subjects of the present study (H.M., H.F., O.J.) having a diastolic blood pressure above 110 mm Hg exhibited the greatest natriuresis during infusion of angiotensin. Thus, the results suggest that renal response to angiotensin is related to the height of blood pressure and is conditioned by the state of sodium balance.

The mechanism of angiotensin-induced natriuresis in hypertensive subjects is obscure. Understanding of the phenomenon is further complicated by the complexity and variety of factors affecting the renal handling of sodium. Renin causes less renal vasoconstriction in the hypertensive than in the normotensive dog(8), and angiotensin in hypertensive subjects does not significantly affect glomerular filtration(7). In the patient with primary aldosteronism (H.M.) the natriuretic response to angiotensin before adrenalectomy was associated with a rise of endogenous creatinine clearance of 18%. This finding suggests that the natriuresis in this sub-

ject might have been due to an increased filtered sodium. However, there were no changes in endogenous creatinine clearance in the other subjects exhibiting natriuresis (H.F., O.J.), nor in those in whom sodium excretion decreased or did not change. One might speculate that angiotensin acts directly on the renal tubule causing a diminished reabsorption of sodium. However, this hypothesis is difficult to reconcile with the fact that adrenal secretion of aldosterone is elevated in hypertensives and is further increased by administration of angiotensin(2, 9). Another hypothesis might be that the natriuresis induced by angiotensin represents the effect described in the dog(10), wherein a rise in the kidney perfusion pressure causes increased sodium excretion without changing the glomerular filtration rate.

Summary. Angiotensin II was administered at rates of 0.3 to 0.6 μg per minute over 6 to 24 hours to 6 subjects with hypertension of various etiologies under conditions of positive and negative sodium balance. Angiotensin produced hypernatriuresis under condition of positive sodium balance. The effect was most marked in those subjects having a diastolic blood pressure above 110 mm Hg.

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Ovarian Weight Response to Varying Doses of Estrogens in Intact and Hypophysectomized Rats.* (26805)

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A dose-response relationship was demonstrated for injected diethylstilbestrol and ovarian weight stimulation in hypophysectomized immature rats after a 4-day treatment interval(1). A recent study has shown that the greatest increase in ovarian weight occurs after about 8 days of treatment with large doses of estrogen in both intact and hypophysectomized immature rats(2). The following experiments were carired out to evaluate ovarian weight response after 8 days of injection with varying doses of diethylstilbestrol or estradiol.

Materials and methods. Intact or hypophysectomized Sprague-Dawley rats, 23-25 days old, were utilized in groups of 5 animals each. Hypophysectomized rats were received on the second post-operative day from Hormone Assay Laboratories, Chicago, Ill. Cortisone acetate (2.5 mg) was administered upon arrival and estrogen injections were begun on the following day. Daily injections of 4, 20, 100, 500, or 1000 μg of either diethylstilbestrol or estradiol, dissolved in 0.1 cc peanut oil, were given for 8 days. Uninjected control animals were caged separately. The animals were asphyxiated with natural gas 24 hours after final injection. The ovaries were dissected free, weighed on a Roller-Smith torsion balance, and prepared for microscopic examination.

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