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BRIEF COMMUNICATION

Adrenalectomy Potentiates Drinking Induced by Renal Artery Constriction[1]

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ATKINSON, J. *Adrenalectomy potentiates drinking induced by renal artery constriction.* PHARMACOL BIOCHEM BEHAV 19(2) 373–378, 1983.—We have tested the hypothesis that the dipsogenic response to an increase in the circulating angiotensin level in the rat is mediated via release of cathecholamines from the adrenal medulla. Increases in circulating angiotensin levels were induced by unilateral renal artery constriction in animals which were uninephrectomized and/or adrenalectomized, twenty four hours previously. The dipsogenic response to renal artery constriction was not attenuated by prior adrenalectomy—there was, in fact, a slight potentiation. Adrenalectomy also potentiated the dipsogenic response to injection of hypersomotic saline. We conclude that drinking following renal artery constriction is not mediated by release of catecholamines from the adrenal medulla.

Adrenalectomy Drinking Renin-angiotensin Catecholamines

SOME of the effects of angiotensin are mediated by catecholamines. The pressor response to exogenous angiotensinamide is attenuated by adrenalectomy [10]. On the basis of this (and other results) we concluded that the pressor response to angiotensin is partially mediated by angiotensin-induced release of catecholamines from the adrenal medulla [10]. Unilateral renal artery constriction in the rat induces an increase in plasma renin level [3] and drinking [3]. The beta-adrenoreceptor antagonist, propranolol, attenuates this latter dipsogenic response [3]. This result suggests that angiotensin-induced drinking is, like the angiotensin-induced pressor response, partially mediated by the sympathetic nervous system. If this were so, it is to be expected that prior adrenalectomy (with mineralocorticoid substitution) would attenuate the dipsogenic response following renal artery constriction. On the other hand, if angiotensin were to stimulate release of catecholamines from sources other than the adrenal medulla, (for example, sympathetic nerve endings) then adrenalectomy would not alter this dipsogenic response, but generalized depletion of catecholamines with reserpine would.

This article describes experiments designed to test these hypotheses. In order to test whether adrenalectomy or catecholamine depletion procedures were having specific effects on angiotensinergic drinking (and to exclude any non-specific effects on other drinking behaviours), a dipsogenic stimulus thought to be independent of the renin-angiotensin system, an intravenous injection of hyperosmotic saline, was also administered to adrenalectomized or reserpine-pretreated rats.

EXPERIMENT 1

METHOD

Forty-eight female Sprague-Dawley rats of 195–205 g body weight were divided into 4 groups of 12 rats/group. The rats were treated as follows: Group 1. Left nephrectomy and total adrenalectomy under ether anesthesia followed by injection of 7 mg prednisolone base·kg^{-1} IP. Group 2. Left nephrectomy and sham adrenalectomy (consisting of manipulation of adrenal glands without removal. Group 3. Sham left nephrectomy (consisting of manipulation of left kidney without removal), total adrenalectomy and prednisolone injection. Group 4. Sham left nephrectomy and sham adrenalectomy.

All rats were then allowed 24 hr to recover during which time they received food and tap water ad lib.

The following day each group was split into two subgroups (n=6/subgroup); the first, (A), underwent right renal artery clipping. A solid silver clip of 0.2 mm i.d. was placed on the right renal artery under ether anesthesia. In the second subgroup, (B), the right renal artery was dissected free—but not clipped—under ether anesthesia.

The water intake of all rats was then measured every hour for 6 hours. At the end of this period the rats were sacrificed by decapitation. A blood sample was taken using heparin as anticoagulant (0.3 ml blood sample into a cooled tube containing 0.005 ml of a 0.1% solution of sodium heparin). The remaining kidney or kidneys were removed as were the adrenal glands (in groups 2 and 4).

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Plasma renin levels (ng AI·ml^{-1}·hr^{-1}) were determined as follows—all blood samples were centrifuged at 3000 g for 30 min at 4°C. Following centrifugation 0.05 ml aliquots of plasma were taken into cooled tubes containing 0.005 ml of a 1% solution of sodium edetate and samples were then frozen at −20°C awaiting incubation with a semi-purified rat plasma substrate (obtained by bleeding rats nephrectomized 24 hr previously). The angiotensin I generated for 1 hr at 40°C in the presence of angiotensin I converting enzyme inhibitors was measured by radioimmunoassay (for further details see [9].

Renal cortical renin levels (ng AI·mg cortex^{-1}·hr^{-1}) were determined as follows—100 mg of renal cortex were homogenized in 2 ml distilled water at 4°C. The homogenate was then centrifuged at 3000 g for 20 min at 4°C. The supernatant was diluted 1:1000 with a phosphate buffer containing 20 mM sodium edetate. An aliquot of 0.05 ml of diluted supernatant was then incubated with 0.4 ml of semi-purified rat plasma substrate and the amount of angiotensin I generated was determined by radioimmunoassay (for further details [9]).

Adrenal glands were decorticated and then stored at −80°C awaiting homogenization and determination of tyrosine hydroxylase activity (pmoles DOPA·min^{-1}) following a modification of the method of Nagatsu *et al.* [8]. The main modification of this method was a preliminary determination of the excess of tyrosine substrate required for the final determination.

Results were analysed according to multivariate analysis of variance techniques [11]. If significant F values were found, means were compared using a *t*-test based on the error mean square as variance estimate.

RESULTS

No significant differences were detected between the rats randomized into the various groups (or subgroups) for body weight, water or food intake before the initial operations of nephrectomy and/or adrenalectomy. Overall means were 200 g, 137 ml·kg^{-1}·24 hr^{-1} and 101 g·kg^{-1}·24 hr^{-1} respectively.

In all groups (1 to 4) there was a significant fall ($p<0.001$) in body weight, water and food intake during the 24 hr following the nephrectomy, adrenalectomy or sham operations. Overall means were 192 g, 99 ml·kg^{-1}·24 hr^{-1} and 54 g·kg^{-1}·24 hr^{-1} respectively. Adrenalectomy had a significant effect on food intake, significance of F=0.001, sham adrenalectomy (groups 2+4) mean 69, adrenalectomy (groups 1+3) mean 39 g·kg^{-1}·24 hr^{-1} $p<0.001$. There was no significant interaction between nephrectomy and adrenalectomy (significance of F=0.420). Apart from this there were no significant differences between groups for either body weight change or water intake during the 24 hr following the operation or sham operation.

On the day following the uninephrectomy and/or adrenalectomy, the right renal artery was either clipped or sham clipped as outlined in the Method section and water consumption was recorded every hour for 6 hours. The results are shown in Fig. 1. Right renal artery clipping produced an increase in water intake in all rats independent of whether they were uninephrectomized and/or adrenalectomized (groups 1 to 4 versus groups 5 to 8, overall effect of adrenalectomy, F=0.001). Water intake was greater in clipped, two-kidney, adrenalectomized rats (group 3) than in clipped, one-kidney, adrenalectomized rats (group 1). In non-adrenalectomized rats (groups 2, 4, 6 and 8), the presence (groups 4 and 8) or absence (groups 2 and 6) of the left kidney, had no effect on the amount of water drunk following clipping. In both one- and two-kidney rats, prior adrenalectomy increased the amount of water drunk between the 2nd and the 6th hours following right renal artery clipping (groups 1 and 3 versus groups 2 and 4). Adrenalectomy in either one- or two-kidney rats also increased water intake following sham-clipping (groups 5 and 7 versus groups 6 and 8, overall effect of adrenalectomy, F=0.001).

Both adrenalectomy and unilateral renal artery clipping increased significantly plasma renin level in blood samples taken 6 hr after clipping or sham-clipping operations (ad-

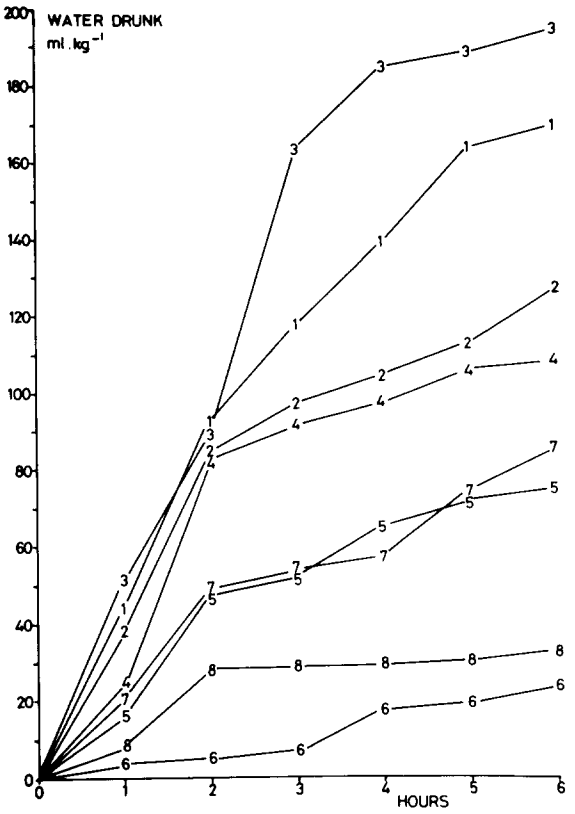

FIG. 1

WATER CONSUMPTION (ml·kg^{-1} FOR 6 HR) IN CLIPPED OR SHAM-CLIPPED RATS FOLLOWING UNINEPHRECTOMY AND/OR TOTAL ADRENALECTOMY

Groups are	Left Nephrectomy	Adrenalectomy	Clip
1	+	+	+
2	+	−	+
3	−	+	+
4	−	−	+
5	+	+	−
6	+	−	−
7	−	+	−
8	−	−	−

Coefficient of variation (estimated in this and the following analyses from the square root of the error mean square divided by the global mean)—80.2%.

t-Test variance (equals: $\sqrt{\text{error mean square} \times (1/6 + 1/6)}$=6.6.

TABLE 1

EFFECT OF NEPHRECTOMY, ADRENALECTOMY AND CLIPPING ON KIDNEY WET WEIGHT (mg) AND RENAL CORTEX RENIN LEVEL (RCRL ng AI·mg^{-1}·hr^{-1})

			Left Kidney		Right Kidney	
			Weight (mg)	RCRL (ng AI mg^{-1}·hr^{-1})	Weight (mg)	RCRL (ng AI mg^{-1}·hr^{-1})
Nephrectomy	Adrenalectomy	Clip	729	4292	970	2056
		Sham clip	754	4209	772	2990
	Sham adrenalectomy	Clip	763	4021	976	2481
		Sham clip	739	4556	817	3954
Sham nephrectomy	Adrenalectomy	Clip	732	4065	734	3048
		Sham clip	722	3410	753	2875
	Sham adrenalectomy	Clip	750	4312	782	3393
		Sham clip	727	3667	816	3375
$\sqrt{\text{Error mean square}} \times (1/6 + 1/6)$.			29	567	50	413
Coefficient of variation %.			6.8	23.1	10.5	23.8
Significance of F for: Nephrectomy			—	—	0.001	—
Adrenalectomy			—	—	—	0.008
Clip			—	—	0.005	0.015
Nephrectomy × adrenalectomy			—	—	—	—
Adrenalectomy × clip			—	—	—	—
Nephrectomy × clip			—	—	0.001	0.005
Nephrectomy × adrenalectomy × clip			—	—	—	—

renalectomy F=0.001, clipping F=0.001). The effect of adrenalectomy was proportionally greater than that of clipping and there was a significant interaction between the two (F=0.014). Although the effect of nephrectomy was not significant, there was a significant interaction between nephrectomy and clipping (F=0.001) and between nephrectomy, adrenalectomy and clipping (F=0.001). Plasma renin levels (ng AI·ml^{-1}·hr^{-1}) for nephrectomized, adrenalectomized rats after clipping or sham-clipping were 656 or 297; for nephrectomized, sham-adrenalectomized rats after clipping or sham-clipping were 116 and 19; for sham-nephrectomized, adrenalectomized rats after clipping or sham-clipping were 524 and 522, and for sham-nephrectomized, sham-adrenalectomized rats after clipping or sham-clipping were 71 and 17 (t-test variance=41).

There were no significant differences between groups as regards left kidney wet weight or renal cortex renin level (see Table 1). Clipping significantly increased right kidney wet weight and decreased renal cortical renin level in previously left nephrectomized rats. We have previously reported this phenomenon in uninephrectomized rats [3]. Adrenalectomy caused an overall decrease in right kidney renal cortex renin levels (there was a non-significant trend to decrease renal cortex renin levels in left kidneys also) (see Table 1). This decrease in kidney renal cortex renin levels may be due to depletion of renal renin stores following stimulation of plasma renin level by adrenalectomy.

Results for the wet weight, protein content and tyrosine hydroxylase activity of left and right adrenal medulla are shown in Table 2. While isolated variables gave statistically significant F values (for example, effect of adrenalectomy on wet weight and protein content of left adrenal medulla but not the right adrenal medulla) no general trends of physiological significance were discernible. In the experiment described above, the adrenalectomized rats were given a mineralocorticoid but were not given a saline solution to drink during recovery. Whether this latter factor could influence their water consumption on the day of the experiment was checked in Experiment 2.

EXPERIMENT 2

METHOD

Twenty female Sprague-Dawley rats of 180–200 g body weight were randomly assigned to one of the two following groups. Group 1. Bilateral adrenalectomy and left nephrectomy were carried out under ether anesthesia. Rats (n=10) were then injected with 7 mg prednisolone base·kg^{-1} IP and given 0.15 M NaCl to drink for the following 24 hr recuperation period. At all other times, rats were given tap water to drink. Group 2. Control rats (n=10) were not operated upon. They also received saline to drink.

At the end of the 24 hr recovery period, subgroups of rats were subjected to one of the two following procedures. (1) Right renal artery clipping. A solid silver clip of 0.2 mm i.d. was placed on the remaining right renal artery under ether anesthesia (see Experiment 1). (2) Sham-clipping. The right

TABLE 2

EFFECT OF NEPHRECTOMY, ADRENALECTOMY AND CLIPPING ON WET WEIGHT, PROTEIN CONTENT AND TYROSINE HYDROXYLASE ACTIVITY OF ADRENAL GLANDS

				Adrenal medulla					
				Left			Right		
			Groups	Wet Weight (mg)	Protein ($mg \cdot g^{-1}$)	Tyrosine Hydroxylase (pmoles DOPA mg protein^{-1} min^{-1})	Wet Weight	Protein	Tyrosine hydroxylase
Nephrectomy	Adrenalectomy	Clip	1	15.7	191	41.2	19.1	171	45.1
		Sham clip	5	17.8	181	53.8	14.1	172	60.0
	Sham Adrenalectomy	Clip	2	22.1	147	57.9	19.9	155	60.0
		Sham clip	6	25.0	151	44.4	21.5	160	45.6
Sham Nephrectomy	Adrenalectomy	Clip	3	16.8	153	51.3	14.7	170	57.5
		Sham clip	7	19.5	174	45.8	14.0	172	54.0
	Sham Adrenalectomy	Clip	4	26.4	141	39.9	21.3	155	48.6
		Sham clip	8	21.9	167	56.2	19.3	179	61.3
Coefficient of variation (%).				14.7	13.5	29.8	16.1	11.7	28.7
$\sqrt{\text{error mean square}} \times (1/6 + 1/6)$.				1.8	12.7	8.4	1.7	11.3	8.9
Significance of F for:									
Nephrectomy				—	—	—	—	—	—
Adrenalectomy				0.001	0.001	—	0.001	—	—
Clipping				—	—	—	—	—	—
Nephrectomy × adrenalectomy				—	0.037	—	—	—	—
Nephrectomy × clipping				—	0.039	—	—	—	—
Adrenalectomy × clipping				—	—	—	—	—	—
Nephrectomy × adrenalectomy × clipping				0.030	—	0.007	0.023	—	0.015

renal artery was dissected free (but not clipped) under ether anesthesia.

Following the operations water intake was measured for 6 hr. Results are given as means±SEM, and statistical significance is based on t-test.

RESULTS

Clipping of the right renal artery produced more drinking in adrenalectomized rats than in controls, as in Experiment 1 (see above). However overall drinking was less than in Experiment 1 in both subgroups and more variable: 35±10 versus 27±9 $ml \cdot kg^{-1}$ in 6 hr for controls. The effect of prior adrenalectomy was not statistically significant ($p > 0.05$).

Adrenalectomy did not significantly affect water consumption occurring after sham-clipping. Consumption was 7±3 ml·kg in 6 hr for rats adrenalectomized 24 hr previously and 5±3 for controls.

We showed (in both experiments), therefore, that adrenalectomy did not attenuate water drinking following unilateral renal artery constriction—if anything the effect was one of potentiation. We then went on to investigate (in Experiment 3) whether prior adrenalectomy will decrease the volume of water drunk following another dipsogen—an intravenous injection of hypertonic saline.

EXPERIMENT 3

METHOD

Twenty female rats of 195 to 205 g body weight were divided into two groups. Group 1. Total adrenalectomy was carried out under ether anesthesia. They were then injected with 7 mg prednisolone base·kg^{-1} IP and given 0.15 M NaCl to drink for 24 hr. Group 2. A sham adrenalectomy operation was carried out under ether anesthesia, the animals were given water to drink.

The day following the adrenalectomy or sham adrenalectomy operation, all rats were injected with 6 ml kg^{-1} of 2 M NaCl. The amount of water drunk in one hour following this injection was measured.

RESULTS

Adrenalectomized rats ate and drank the same amounts as sham-adrenalectomized rats during the 24 hr recuperation period. Adrenalectomy, greatly reduced the drinking occurring during the hour following the intravenous administration of hyperosmotic saline. Adrenalectomized rats injected with hyperosmotic saline drank 9±3 ml·kg^{-1} in one hour whereas controls drank 30±3 ml·kg^{-1} (n=5 for both groups, $p<0.001$).

Adrenalectomized rats drank a salty solution during recovery while sham-adrenalectomized rats drank water. This difference may have influenced the drinking of the rats (following a hyper osmotic stimulus) independently of the fact that the rats were adrenalectomized or not. This point was checked in Experiment 4.

EXPERIMENT 4

METHOD

Twenty female Sprague-Dawley rats of 195–205 g body weight were divided into two groups. Group 1. Adrenalectomy was carried out under ether anesthesia. Rats were then injected with 7 mg prednisolone base kg^{-1} IP and given water to drink for the 24 hr recuperation period. Group 2. Sham adrenalectomy was carried out under ether anesthesia. Rats received water following recovery from anesthesia. The day following the adrenalectomy or sham adrenalectomy operation, all rats were injected with 6 ml·kg^{-1} of 2 M NaCl. The amount of water drunk during a 6 hr lapse of time was measured hourly.

RESULTS

Water consumption during the 24 hr recuperation period was the same in adrenalectomized and sham-adrenalectomized rats (102±14 and 89±10 ml·kg^{-1} in 24 hr, respectively, n=10 for both). Food consumption was lowered by adrenalectomy (17±3 and 57±2 g·kg^{-1} in 24 hr respectively, $p<0.001$). Likewise body weight decreased in adrenalectomized rats, body weight loss −3±1 g versus sham-adrenalectomized rats, 5±2 g ($p<0.001$). Water consumption following an intravenous injection of hyperosmotic saline was doubled in previously adrenalectomized rats (see Fig. 2). Six hours water consumption figures were 67±3 and 37±2 ml·kg^{-1} ($p<0.001$) respectively.

As adrenalectomy (with mineralocorticoid substitution) did not decrease the dipsogenic response to renal artery clipping in the fifth, sixth and seventh experiments, we investigated the effect of more widespread catecholamine depletion with reserpine.

EXPERIMENT 5

METHOD

Twenty female Sprague-Dawley rats of 180–200 g body weight were used. In all rats the left kidney was removed under ether anesthesia. Following recovery from anesthesia 10 rats were injected with 2.5 mg reserpine base·kg^{-1} IP (Group 1) and 10 were injected with 0.15 M NaCl (Group 2, controls).

All rats were then given food and tap water ad lib and allowed 24 hr to recover. The following day all rats underwent right renal artery constriction and water consumption was measured for 6 hr.

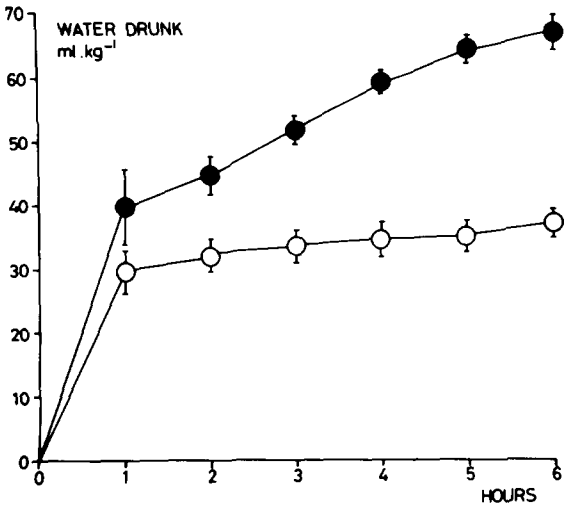

FIG. 2. Water consumption following an intravenous injection of hyperosmotic saline in previously adrenalectomized rats (full circles) or sham adrenalectomized rats (open circles).

Results will be discussed at the end of the Method section of Experiment 7.

EXPERIMENT 6

METHOD

Exactly the same protocol as Experiment 5 was used excepting that a lower dose of 1.25 mg reserpine base·kg^{-1} IP was given.

Results will be discussed at the end of the Method section of Experiment 7.

EXPERIMENT 7

METHOD

Ten female, Sprague-Dawley rats of 185–200 g were injected daily (morning) with 0.1 mg reserpine base·kg^{-1} IP for 7 days. Ten control rats were injected with 0.15 M NaCl.

On the seventh day the left kidney was removed under ether anesthesia before the seventh and final intraperitoneal injection. On the eight day the right renal artery was clipped and water consumption was measured for 6 hr.

RESULTS OF EXPERIMENTS 5, 6 AND 7

The results of these experiments will be described together as all gave negative results. Following either single or multiple dose reserpine pre-treatment, rats had very low water intakes. The results for the 24 hr period prior to right renal artery constriction were 1±0.5, 2±1 and 1±1 ml water·kg^{-1} for rats pre-treated with single doses of 1.25 or 2.5 or the final of seven doses of 0.1 mg reserpine·kg^{-1} respectively. Figures for the corresponding control groups were 57±4, 60±5 and 45±5 ml·kg^{-1}. Rats pre-treated with reserpine did not eat at all during this 24 hr period and lost weight, −6±2, −8±3 and −10±3 g for doses of 1.25, 2.5 and 0.1 mg reserpine·kg^{-1}, respectively. Rats injected with 0.1 mg reserpine·kg^{-1} each day for 7 days started to decrease their food and fluid intakes and their body weights fell by the third day of treatment. All reserpine pre-treated rats failed to

drink at all following right renal artery constriction. Their corresponding controls, pre-treated with intraperitoneal injections of 0.15 M NaCl, drank amounts similar to those reported for the controls of the previous series.

We challenged a few rats treated with each schedule of reserpine with the hyperosmotic saline stimulus. None drank following this challenge. All rats given reserpine were very sedate. We were unable to find a dosage schedule for reserpine pretreatment which had a specific effect on drinking behaviour with no effect on general behaviour (i.e., sedation).

GENERAL DISCUSSION

Our results show that adrenalectomy with mineralocorticoid substitution did not block the drinking occurring after unilateral renal artery constriction in the uninephrectomized rat. It thus appears unlikely that drinking following renal artery constriction is mediated by angiotensin-induced release of catecholamines from the adrenal medulla.

As blockade of beta-adrenoreceptors with l-propranolol did attenuate drinking following renal artery constriction [3], it is possible that the full expression of the drinking response following renal artery constriction depends on angiotensin-induced liberation of catecholamines from tissues other than the adrenal medulla.

We cannot exclude this hypothesis as our attempts to decrease tissue catecholamine content by reserpine pretreatment are not conclusive. We found that single high doses of 2.5 or 1.25 $mg \cdot kg^{-1}$, IP or chronic low doses of 0.1 $mg \cdot kg^{-1}$ IP for 7 days greatly diminished the overall drinking behaviour of the rats. Their spontaneous drinking, as well as that induced by renal artery clipping (or an intravenous injection of hyperosmolar saline) were all greatly decreased. It is, thus, impossible to draw any conclusions as to a specific effect of tissue catecholamine depletion on drinking following renal artery constriction after pre-treatment with reserpine. It is possible that catecholamine depletion with other techniques (such as guanethidine sympathectomy, Johnson [7]) may give more specific answers.

An alternative hypothesis to explain the attenuation of propranolol of drinking following renal artery constriction is that there is a permissive interaction between the renin-angiotensin and beta-adrenergic nervous systems in drinking [3]. We have provided other lines of evidence for this. Thus a non-dipsogenic dose of the beta-adrenoreceptor agonist, isoprenaline, provoked drinking in bilaterally nephrectomized rats when preceded by a non-dipsogenic dose of heterologous renin [1]. Furthermore rats with a diminished kidney renin level drank following isoprenaline administration (but their low circulatory renin levels did not increase, i.e., they did not release renin) [2]. The present results do not invalidate this hypothesis. We would now suggest that the permissive interaction between the renin-angiotensin and beta-adrenergic nervous systems does not involve the adrenal medulla.

The idea that angiotensinergic drinking is independent of the presence of the adrenal glands is not new. Fitzsimons and Simons [5] showed that adrenalectomy did not alter the drinking induced by administration of angiotensinamide to bilaterally nephrectomized rats. Likewise Fitzsimons [4] showed that drinking following caval ligation above the renal veins or administration of a purified extract of rat kidney was not modified by adrenalectomy.

Other forms of drinking, however, may be dependent on the presence of the adrenal glands for their full expression. Thus Gutman and Benzakein [6] showed that adrenalectomy greatly diminished drinking following an extracellular stimulus (subcutaneous injection of a 20% solution of 20 M polyethylene glycol) and our present results show that adrenalectomy (with mineralocorticoid substitution and saline drinking) diminished the dipsogenic effect of an intracellular stimulus (intravenous injection of hyperosmolar saline).

In both the experiments reported by Gutman and Benzakein [6] and our Experiment 3 above, adrenalectomized rats were given a salty solution to drink before the dipsogenic challenge. Following the challenge they were given water to drink. Their prior exposure to a salty drinking solution may modify the animal's willingness to drink water following any sort of dipsogenic challenge. This hypothesis is confirmed by Experiment 4 reported here. Rats were given water to drink during the 24 hr period following adrenalectomy. When challenged with an intravenous injection of hyperosmolar saline these animals in fact drank more than sham-adrenalectomized controls. The results presented here show, therefore, that drinking following two very different stimuli is not impaired by adrenalectomy—the effect is, in fact, one of potentiation.

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