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Hypothalamic Catecholamine Metabolism is Increased by Acute Water Imbalance[1]

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KLEMFUSS, H AND L S SEIDEN *Hypothalamic catecholamine metabolism is increased by acute water imbalance* PHARMACOL BIOCHEM BEHAV **24**(2) 229–235, 1986 —Disruption of water balance alters the metabolism of norepinephrine (NE) and dopamine (DA) in specific regions of the hypothalamus in the rat Rats received one of the following treatments hypertonic saline injection (1 M NaCl, 15 ml/kg), polyethylene glycol (40% polyethylene glycol in normal saline, 15 ml/kg), intragastric water load (10 ml), or ligation of the inferior vena cava Catecholamine metabolism was determined by measuring the concentrations of NE and DA in the hypothalamus after catecholamine synthesis inhibition by alpha-methyl-p-tyrosine methyl-ester hydrochloride (200 mg/kg) No two treatments affected catecholamine metabolism in the same region of the hypothalamus Intracellular dehydration by hypertonic saline increased NE metabolism in the paraventricular nucleus Caval ligation, which stimulates the renal renin-angiotensin system, specifically increased NE metabolism in the preoptic area Water loading increased the metabolism of NE and DA in the dorsomedial/ventromedial region The effectiveness of the various treatments in increasing catecholamine metabolism was independent of the magnitude of their effects on blood pressure or water intake The results suggest that there are multiple noradrenergic systems in the hypothalamus which respond to different types of water balance disruption

Water imbalance Hypothalamus Catecholamine metabolism

CATECHOLAMINERGIC terminals in certain hypothalamic regions may be of particular importance in the control of water homeostasis The preoptic area has been proposed as a site where central or peripheral changes in osmolarity [20,32,] or angiotensin II concentrations, may be sensed Injection of the DA antagonist haloperidol into the preoptic area inhibits drinking in water-deprived rats [9], although intracerebral injections of DA itself are only mildly dipsogenic [6] Cells in the paraventricular nucleus of the hypothalamus synthesize vasopressin which is transported to the pituitary and released in response to dehydration [12] NE administration into the paraventricular nucleus inhibits the firing of neurosecretory cells [25] and promotes antidiuresis in the rat [18] The same treatment also induces preprandial drinking followed by a long-lasting inhibition of drinking [17,18] indicating that the noradrenergic systems in the paraventricular nucleus may be involved in both water intake and the control of excretion Other hypothalamic areas in which changes in catecholamine function have been associated with changes in water balance include the lateral hypothalamus [32,41], anterior hypothalamic nucleus [14] and ventromedial nucleus [10]

Regulation of blood pressure may also be a function of catecholamine neurons in the hypothalamus The hypothalamus is densely innervated by noradrenergic or adrenergic cells from the locus coeruleus, dorsal vagal complex, and A2-C2 area of the medulla [23,33] All three of these catecholaminergic nuclei are involved in the integration of cardiovascular information from peripheral receptors [11,33, 45] Interaction between these brainstem nuclei and the hypothalamus is suggested by the observation that hypertension caused by locus coeruleus lesions can be reversed by posterior hypothalamic lesions [30] Injection of NE to the preoptic or paraventricular areas lowers blood pressure in experimental animals [35,44] Furthermore, there have been several reports that acute alterations in blood pressure will increase the rate of metabolism of hypothalamic catecholamines [27, 28, 38, 47]

If catecholaminergic systems are involved in hypothalamic regulation of water balance or blood pressure, then acute alterations in the osmolarity or volume of plasma should induce changes in the rate of utilization of hypothalamic catecholamines In the present study, the rate of depletion of dopamine and norepinephrine after catecholamine synthesis inhibition was measured in discrete hypothalamic regions following treatments which disturb normal water balance Catecholamine metabolism was altered in different hypothalamic regions depending on the type of water balance disruption, but independent of whether or not the disruption influenced blood pressure or drinking

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TABLE 1
NE IN HYPOTHALAMUS AFTER ACUTE DEHYDRATION

	(pmol/mg protein ± SEM)			
	Polyethylene Glycol	Hypertonic Saline	Isotonic Saline	Saline Control
Preoptic Area	158 ± 11	136 ± 17	159 ± 12	216 ± 12
Paraventricular Nucleus	99 ± 18	57 ± 6‡	122 ± 11	110 ± 6
Lateral Hypothalamus	127 ± 12	128 ± 10	142 ± 10	195 ± 10
Anterior Hypothalamic Nucleus	160 ± 10	139 ± 12	147 ± 12	191 ± 6
Dorsomedial/ Ventromedial Nucleus	116 ± 15	106 ± 13	109 ± 6	140 ± 13

This table presents the effects of polyethylene glycol and hypertonic saline on norepinephrine metabolism in five hypothalamic areas Hypertonic saline treatment significantly increased NE metabolism in the paraventricular nucleus ‡Indicates significant difference from Isotonic Saline Control ($p<0.001$)

The following treatments were used Polyethylene glycol was injected SC in a volume of 15 ml/kg 3 hours before death, Hypertonic saline (1 M NaCl) was injected IP in a volume of 15 ml/kg 105 minutes before death, Isotonic saline (0 15 M) was injected IP in a volume of 15 ml/kg 105 minutes before death, Saline control rats received no treatment other than 1 ml/kg normal saline IP 2 hours before death All other rats received 200 mg/kg AMT 2 hr before death

N=6–12 rats

METHOD

Male Sprague-Dawley rats (Holtzman, Madison, WI) weighing 270–310 g were housed in groups of 6 for at least one week in constant temperature and humidity, with food and water available ad lib and illumination provided from 6 00 a m to 6 00 p m

Two hours before decapitation, rats were injected intraperitoneally with either 200 mg/kg of alpha methyl-p-tyrosine methyl ester HCl (AMT) in 1 0 ml/kg normal saline or an equal volume of saline alone After injection they were housed individually in wire cages with food but without access to water At specified times before decapitation each rat was subjected to one of five treatments which pilot studies, based on previous reports, had shown to increase water intake reliably Before each treatment, rats were lightly anesthetized with ether to prevent struggling and discomfort

Hypertonic saline treatment consisted of a solution of 1 M sodium chloride in distilled deionized water, which was injected intraperitoneally (IP) in a total volume of 15 ml/kg Rats were injected 105 minutes before testing

For the control injection of isotonic saline, rats were injected IP with 15 ml/kg of 0 15 M sodium chloride, and tested 105 minutes after injection

To produce extracellular dehydration, rats were injected subcutaneously (SC) with 15 ml/kg of a 40% (w/v) solution of polyethylene glycol (Baker, average molecular weight 600–7500) dissolved in normal saline Rats were tested 180 min later

For injection of a water load, 10 ml of distilled, deionized water was intubated directly into the rat's stomach over a period of one minute Five ml of normal saline was also injected IP at the same time (105 min before testing)

Caval ligation was performed in fully etherized rats The inferior vena cava was located and the section just above the entrance of the right renal vein was isolated A silk suture was placed around the vena cava and securely tied shut Muscle and skin were fastened with wound clips The entire process required approximately 10 minutes and was completed 2 hours before testing Sham ligation was identical except that the suture was not tied

Brain Dissection

Immediately following decapitation the brain was removed and placed on an ice-cold brain block The dissection was based on Heffner *et al* [13] The brain was positioned such that a razor blade in the first slot lined up with the rostral edge of the optic chiasm Three sections, each one millimeter thick, were taken from the brain immediately caudal to the reference blade The entire medial and lateral preoptic area was taken from the most anterior section (roughly equal to Figs 19 to 24 in the Atlas of Konig and Klippel [15] The optic tract and supraoptic tissue were discarded The paraventricular nucleus was punched from the second section (Figs 25–30 in Konig and Klippel [15]) The remaining hypothalamic tissue in the second and third sections corresponding to Figs 25–36 in Konig and Klippel [15] was divided into medial and lateral segments Medial tissue from the second section consisted primarily of anterior hypothalamic nucleus, while medial tissue from the third section included dorsomedial and ventromedial nuclei Sample protein weights were approximately 1 2 mg in preoptic samples, 0.3 mg in paraventricular nucleus samples, and 0 5–0 6 mg in lateral, anterior, and dorsomedial/ventromedial samples One mg of protein corresponded to about 6–7 mm^3 of tissue

Tissue samples were transferred to Eppendorf tubes con-

TABLE 2

NE IN HYPOTHALAMUS AFTER CAVAL LIGATION

	pmol/mg protein ± SEM		
	Caval Ligation	Sham Ligation	Saline Control
Preoptic Area	88 ± 6‡	160 ± 14	216 ± 12
Paraventricular Nucleus	93 ± 21	116 ± 14	110 ± 6
Lateral Hypothalamus	112 ± 15	139 ± 18	173 ± 14
Medial Hypothalamus	131 ± 10	141 ± 7	159 ± 7

This table presents the effects of caval ligation on norepinephrine metabolism in four hypothalamic areas Medial hypothalamus consists of anterior plus dorsomedial/ventromedial areas There is no statistically significant effect of caval ligation on norepinephrine metabolism in any region except the preoptic area ‡Indicates significant difference from sham ligation rats ($p<0.001$)

Caval ligation was completed 2 hours before death

Caval ligation rats and sham ligation rats received 200 mg/kg AMT 2 hours before death

Saline control rats received no treatment other than 1 ml/kg normal saline IP 2 hours before death

N=6–8 rats

TABLE 3

NE IN HYPOTHALAMUS AFTER WATER LOAD

	pmol/mg protein ± SEM		
	Water Load	AMT Control	Saline Control
Preoptic Area	112 ± 9	130 ± 12	180 ± 16
Paraventricular Nucleus	144 ± 21	137 ± 15	113 ± 13
Anterior Hypothalamic Nucleus	128 ± 16	150 ± 13	168 ± 8
Dorsomedial/ Ventromedial Nucleus	73 ± 4‡	127 ± 8	143 ± 14

This table presents the effect of water loading on hypothalamic metabolism Water load consisted of 10 ml distilled water by gastric tube plus 5 ml of normal saline IP 105 minutes before death Rats receiving water loads and AMT control rats received 200 mg/kg AMT 2 hours before death Saline control rats received no treatment other than 1 ml/kg normal saline IP 2 hours before death

‡Indicates significant difference from AMT control ($p<0.001$)

N=6–8 rats

taining 0 5 ml of ice-cold 0 4 N perchloric acid containing 2 5 mM EDTA They were then frozen on dry ice Within four hours samples were thawed, homogenized and centrifuged Protein was stored at −20°C until assay using the Biorad protein assay (Biorad, Richmond, CA) with bovine serum albumin as standard The supernatant was frozen at −80°C until catecholamine assay using the method of Anton and Sayre [3] as modified by Schellenberger and Gordon [34] Catecholamines were extracted with alumina then eluted in 0 3 ml of 0 1 N perchloric acid, which was injected into a 1 m × 2 0 mm high pressure liquid chromatography column containing Dupont Vydac strong cation exchange resin The mobile phase consisted of an acetate-citrate buffer at pH 5 2 Flow rate was 0 4 ml/min and catecholamines were oxidized by a potential of 0 72 V Recovery averaged 65% for NE and 55% for DA Variability within groups is expressed as standard error of the mean (SEM), and comparisons between groups were made by analysis of variance followed by unpaired two-tailed t-test [39] Animals used in neurochemical determinations were killed at 10 00 a m ±90 min Injections and treatments were scheduled so that one rat receiving a specific treatment was killed at approximately the same time on the same day Generally the intake studies were carried out within one day of neurochemical studies involving the same treatment

Procedure for Water Intake and Blood Pressure Experiments

Animals used in water intake experiments were treated essentially the same as rats used for neurochemical assay, except that at the time when they would have been killed they were transferred into individual cages containing chow and a graduated drinking tube Cumulative water intake for each rat was determined at various intervals up to 24 hours after water was made available Some rats were injected with AMT (200 mg/kg) 2 hours before water access

Femoral arterial blood pressure was measured in conscious rats and in rats anesthetized with 50 mg/kg sodium pentobarbital Systolic and diastolic pressures were measured continuously before, during, and after each treatment in anesthetized rats In a separate experiment, mean arterial blood pressure was measured before, and two hours after, treatments in conscious rats previously catheterized under ether anesthesia

RESULTS

Norepinephrine

Norepinephrine (NE) metabolism was determined in each experiment by comparing the level of NE in each hypothalamic area after AMT treatment with the level after saline treatment The rate of disappearance of NE was consistent between experiments and in most hypothalamic regions AMT injection lowered NE levels in all hypothalamic regions except the paraventricular nucleus to about 75% of NE levels in rats receiving only saline Treatment with AMT did not appreciably decrease NE levels in the PVN

Intracellular dehydration using hypertonic saline administration markedly increased NE metabolism in the paraventricular nucleus This finding was consistent in two separate experiments which are combined in Table 1 Increased NE metabolism after intracellular dehydration was specific to the paraventricular nucleus, since NE metabolism in no other hypothalamic region was affected by hypertonic saline injection

Ligation of the inferior vena cava significantly increased NE metabolism in the preoptic area when compared to either

TABLE 4

DOPAMINE IN HYPOTHALAMUS AFTER ACUTE DEHYDRATION

	(pmol/mg protein ± SEM)			
	Polyethylene Glycol	Hypertonic Saline	Isotonic Saline	Saline Control
Preoptic Area	9 8 ± 1 2	9 2 ± 1 0	8 8 ± 1 1	19 0 ± 1 1
Paraventricular Nucleus	10 5 ± 2 3	5 8 ± 0 8	8 7 ± 2 2	18 3 ± 4 8
Lateral Hypothalamus	11 0 ± 2 3	14 5 ± 5 2	11 8 ± 2 1	30 1 ± 5 1
Anterior Hypothalamic Nucleus	16 4 ± 4 2	11 4 ± 1 2	11 0 ± 2 2	24 8 ± 2 2
Dorsomedial/ Ventromedial Nucleus	14 0 ± 2 6	16 3 ± 1 8	10 3 ± 2 3	24 4 ± 5 2

This table presents the effects of polyethylene glycol and hypertonic saline on hypothalamic dopamine metabolism There is no statistically significant effect of either treatment on dopamine metabolism in any of these regions
See Table 1 for treatment parameters
N=6–12 rats

sham-ligated or control rats receiving no surgical treatment ($p<0$ 001) No other region was affected by caval ligation (Table 2)

Injection of excess water did not affect NE metabolism in any region except the dorsomedial/ventromedial area In this part of the hypothalamus, NE metabolism was significantly increased ($p<0$ 001)

Norepinephrine metabolism was not affected by extracellular dehydration since NE levels after polyethylene glycol were not different from NE levels after isotonic saline in any region studied

Dopamine

The rate of disappearance of DA was similar in every brain region studied (Table 4) Two hours after AMT treatment, hypothalamic levels of DA averaged 47% of saline control DA levels With one exception, no brain region showed a statistically significant change in the rate of DA metabolism after any treatment (Table 4–6)

The one region in which DA metabolism was significantly increased by water balance disruption was the dorsomedial/ventromedial area (Table 6) The increase in DA metabolism which occured in the dorsomedial/ventromedial area after water loading was similar to the increase in NE metabolism in the same region after the same treatment Dehydration by polyethylene glycol or hypertonic saline tended to decrease the loss of DA after AMT (Table 4), but this did not reach statistical significance Although the changes in DA metabolism are not as robust as the NE effects, the dorsomedial or ventromedial hypothalamic nuclei may be sites where dopaminergic mechanisms are involved in ingestive behavior

In summary, these experiments have demonstrated that some procedures that disrupt water balance also alter the rate of NE and DA metabolism in specific regions of the rat hypothalamus Although water load, hypertonic saline treatment, and caval ligation all increase metabolism, different regions are affected by each treatment Polyethylene glycol treatment did not affect catecholamine metabolism in any hypothalamic region examined

TABLE 5

DOPAMINE IN HYPOTHALAMUS AFTER CAVAL LIGATION

	pmol/mg protein ± SEM		
	Caval Ligation	Sham Ligation	Saline Control
Preoptic Area	11 2 ± 1 6	12 3 ± 2 2	22 6 ± 1 8
Paraventricular Nucleus	9 5 ± 1 5	12 6 ± 2 0	23 4 ± 4 2
Lateral Hypothalamus	10 4 ± 1 8	11 8 ± 2 1	30 3 ± 4 8
Medial Hypothalamus	22 1 ± 3 3	23 8 ± 4 4	32 9 ± 4 7

This table presents the effects of caval ligation on dopamine metabolism in the hypothalamus There is no statistically significant effect of caval ligation on dopamine metabolism in any of these regions
Treatments as in Table 2
N=6–8 rats

Effects on Water Balance

All rats used in blood pressure experiments maintained stable baseline blood pressure for at least 10 min The range of values recorded in fifteen anesthetized rats were diastolic pressure 62–80 mm Hg, systolic pressure 93–123 mm Hg, and pulse pressure 26–42 mm Hg Intraperitoneal injection of a volume of either isotonic or hypertonic saline equal to 1 5% of body weight had no effect on diastolic pressure (Table 7) Each of the other treatments, however, caused a decrease in diastolic pressure The pulse pressure (difference between systolic and diastolic pressures) followed the same pattern as

TABLE 6

DOPAMINE IN HYPOTHALAMUS AFTER WATER LOAD

	pmol/mg protein ± SEM		
	Water Load	AMT Control	Saline Control
Preoptic Area	16 6 ± 2 3	17 1 ± 2 7	25 0 ± 2 0
Paraventricular Nucleus	13 7 ± 3 2	12 6 ± 2 0	23 4 ± 4 2
Anterior Hypothalamic Nucleus	26 9 ± 5 4	27 2 ± 4 7	43 0 ± 6 4
Dorsomedial/ Ventromedial Nucleus	10 7 ± 0 7‡	21 6 ± 2 5	41 3 ± 7 1

This table presents the effect of water loading on hypothalamic dopamine metabolism

Treatments as in Table 3

‡Indicates the dopamine levels in the dorsomedial/ventromedial area are different from AMT control ($p<0$ 001)

N=6–8 rats

TABLE 7

BLOOD PRESSURE, WATER INTAKE AND HEMATOCRIT AFTER ACUTE DISRUPTION OF WATER BALANCE

Treatment	Change in Diastolic Blood pressure (mm Hg)	Water Intake (ml)	Hematocrit (%)
Polyethylene Glycol	−22 ± 11	15 ± 2‡	65 3 ± 1 1*
Hypertonic Saline	4 ± 5	9 ± 1‡	60 5 ± 1 3
Isotonic Saline	3 ± 2	3 ± 0 5	54 3 ± 3 4
Saline Control	3 ± 3	2 ± 0 5	57 3 ± 1 7
Caval Ligation	0 ± 4	15 ± 8	53 4 ± 1 6
Water Load	−22 ± 8	0 5 ± 0 5†	53 8 ± 1 5

Change in diastolic blood pressure (mm Hg + SEM) was determined by comparing femoral artery pressure before treatment to pressure at the time when animals used in biochemical experiments would have been killed N=3 rats Statistical analysis was not attempted Immediately after caval ligation, diastolic blood pressure decreased to −40 ± 10 mm Hg, but gradually returned to control levels by 1 hr after ligation

Water was made available to rats at the time when animals used in biochemical experiments would have been killed Food was available at all times Total water ingested over a 2 hr period is presented †Indicates $p<0$ 01 compared to isotonic saline control, ‡Indicates $p<0$ 001 compared to isotonic saline control · N=6 rats

Hematocrit (% ± SEM) was taken immediately after decapitation *Indicates $p<0$ 05 compared to isotonic saline control N=6–12 rats

All treatments were as previously described in the Method section and in Tables 1–3

diastolic pressure, being somewhat decreased in rats given polyethylene glycol, caval ligation, or water load but unchanged after injection of either isotonic or hypertonic saline We subsequently reexamined the effects of some of these treatments in unanesthetized rats The results indicate that anesthesia did not appreciably alter the pressure response to these treatments Two hours after hypertonic saline, the mean arterial blood pressure was 2 1±6 0 mm Hg less than baseline Two hours after water loading the mean arterial pressure was 15 0±8 2 mm Hg below baseline, while three hours after polyethylene glycol treatment mean arterial pressure was 17 2± 10 1 mm Hg less than baseline

Rats treated with hypertonic saline or polyethylene glycol drink more water than untreated animals or rats given isotonic saline injections (Table 7) The rate of ingestion was most rapid immediately after water was presented During the first 30 minutes rats apparently restored most of their water deficit since after one hour the rate of water intake returned to nearly normal The cumulative intake after either polyethylene glycol or hypertonic saline was statistically greater than after isotonic saline injection ($p<0$ 01 for hypertonic saline, $p<0$ 001 for polyethylene glycol) By the time rats had had six hours of access, polyethylene glycol rats had drunk 22 2±2 5 ml (mean±SEM) compared to 9 8±2 1 ml after hypertonic saline and 3 9±0 9 ml after isotonic saline By 24 hours of access total intake was not different for the three groups (polyethylene glycol 49 7±5 7 ml, hypertonic saline 47 2±2 7, isotonic saline, 46 5±1 4)

In agreement with other authors, we find that caval ligation was about as effective as polyethylene glycol treatment in stimulating water intake, while animals given gastric water loads did not drink at all for at least several hours [8,40]

Since animals used for catecholamine metabolism studies were injected with alpha-methyl-p-tyrosine, we determined whether AMT itself would affect drinking When injected according to the same protocol used in the neurochemical studies, AMT had no effect on water intake after polyethylene glycol, hypertonic saline, 24 hour water deprivation, or no treatment, at every time point measured between ten minutes and six hours after water access (n=6, data not presented)

Hematocrit measurements from rats used in neurochemical studies showed that treatment with polyethylene glycol decreased the plasma volume relative to rats given equal volumes of isotonic saline (Table 7) No other treatment produced a significant change in plasma volume at the time of decapitation

DISCUSSION

The present results show (1) caval ligation increases NE metabolism in the preoptic area, (2) hypertonic saline treatment increases NE metabolism in the paraventricular nucleus This treatment had no effect on hematocrit or blood pressure, (3) the hypovolemic stimulus, polyethylene glycol, produced the greatest depletion of plasma volume, a high rate of drinking, and a 30 mm Hg drop in blood pressure None of these changes were associated with a statistically reliable effect on hypothalamic catecholamine metabolism, (4) water loading increased the metabolism of both DA and NE in the dorsomedial/ventromedial region We propose that treatments which interfere with water balance may affect hypothalamic catecholamine metabolism, and that the nature of the metabolism changes depends on the type of stimulus rather than on whether the treatment affects drinking or blood pressure

There have been many studies implicating hypothalamic NE in vasopressin release and water ingestion [8, 25, 32, 33] The present results support these studies up to a point Hypertonic saline treatment and caval ligation, known stimuli for water ingestion, also stimulate NE metabolism However, polyethylene glycol treatment is also dipsogenic, but had no discernible effect on hypothalamic NE metabolism Similarly, all three treatments increase the release of vasopressin from the pituitary [2, 7, 12, 43], but only hypertonic saline has a measurable effect on NE metabolism in the paraventricular nucleus We conclude, therefore, that catecholaminergic neurons in the hypothalamus are not required for either water ingestion or vasopressin stimulation Instead, projections containing NE or DA in particular regions may be activated by specific changes in cardiovascular status or peripheral hydration, initiating other mechanisms which stimulate drinking and vasopressin release We would predict that manipulations of catecholaminergic neurons in the hypothalamus affect afferent information rather than efferent physiological or behavioral responses

Similarly, the present results argue against a direct effect of hypotension on catecholamine metabolism Hypotension produced by different techniques has been reported to increase NE turnover in the paraventricular nucleus [47] or in the posterior half of the hypothalamus [38] These authors have argued that hypotension stimulates catecholaminergic systems in the hypothalamus which act to restore the blood pressure However, while hypotension induced by water load was associated with increased metabolism in the dorsomedial/ventromedial area, a nearly identical hypotension produced by polyethylene glycol had no effect on NE in paraventricular or caudal hypothalamic areas

Antiotensin II in the peripheral circulation may be responsible for the increase in NE metabolism in the preoptic area after ligation of the vena cava Caval ligation is an effective stimulus of the renal renin-angiotensin system [8,16] The ability of caval ligation to raise circulating angiotensin II levels is apparently responsible for the dipsogenic effect of caval ligation, since nephrectomy, but not transection of baroreceptor afferents, prevents caval ligation-induced drinking [8,24] On the other hand, although polyethylene glycol treatment also increases circulating AII levels, polyethylene glycol is a less effective stimulus for AII release than caval ligation [42], and nephrectomy does not affect drinking after polyethylene glycol treatment [42] Neurons in the preoptic area are sensitive to direct application of angiotensin II [22], and intrapreoptic administration of angiotensin II stimulates drinking [31] and hypertension [4,5] Although there is some controversy over whether circulating angiotensin II enters the brain in sufficient quantity to act on preoptic neurons [19,37] it seems likely that caval ligation stimulates preoptic norepinephrine metabolism through actions on the renin-angiotensin system

Assuming that hypertonic saline injection activates osmoreceptors in the brain or periphery, there are several functions that increased NE metabolism in the paraventricular nucleus may serve Paraventricular cells projecting to the neurohypophysis are inhibited by iontophoretic application of small quantities of NE [25] which suggests that one effect of NE released in the paraventricular nucleus might be to inhibit the release of vasopressin into the circulation It is established, however, that hypertonic saline treatment increases the release of vasopressin from the pituitary [7] In addition to the pituitary projections, the PVN also sends processes to various regions of the central nervous system concerned with automatic and limbic function ([29] Swanson and Sawchenko, 1982) These non-pituitary projections come from PVN cells which are excited by the administration of NE into the paraventricular nucleus [25] Therefore, the increased NE metabolism we found in the paraventricular nucleus may influence activity in autonomic and limbic centers of the brain By affecting both the release of vasopressin into the circulation and the activity of central projections to cardiovascular and limbic areas, the increased NE metabolism due to hypertonic saline injection could have many actions on normal water balance Injection of NE directly into the PVN has potent effects on both water ingestion [17] and blood pressure [44] Therefore, it is possible that the increase in paraventricular nucleus metabolism of norepinephrine caused by hypertonic saline may ultimately influence water intake, vasopressin release, and blood pressure

The ventromedial nucleus of the hypothalamus has been implicated in satiety responses, since lesion of the ventromedial nucleus causes hyperdipsia and hyperphagia [36] This would be consistent with the finding that NE metabolism is altered in the dorsmedial/ventromedial region after water loading Alternatively, the ventromedial nucleus may be responding specifically to changes in the osmolarity of the extracellular fluid, as has been reported [26,46]

In summary, we report the existence of multiple noradrenergic systems in the hypothalamus which increase activity in response to changes in water balance Different noradrenergic neurons are stimulated by treatments which increase plasma osmolarity, decrease plasma osmolarity, or stimulate the renin-angiotensin system Activation of volume receptors by polyethylene glycol treatment was without effect on hypothalamic catecholamines The anterior hypothalamic nucleus was shown to be unaffected by any acute treatment This negative result was unexpected since we have previously shown that chronic dehydration specifically increases NE in the anterior hypothalamic nucleus [14] It appears that there are at least four different noradrenergic systems in the hypothalamus which respond to alterations in peripheral water balance

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