Norepinephrine Inhibition of Vasopressin Antidiuresis

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ABSTRACT The effect of norepinephrine on exogenous vasopressin antidiuresis was investigated in water-loaded subjects. After an initial 2 to 3 hr period of water loading (phase 1), 10–100 mU of vasopressin per hr were infused at a constant rate for 1 hr (phase 2) followed by infusion of 10–100 mU of vasopressin per hr *plus* 600 μg of *l*-norepinephrine per hr for 1 hr (phase 3). Endogenous creatinine clearance, osmolal clearance, and free water clearance (in milliliters/minute) and sodium and chloride excretion (in milliequivalents/minute) were measured. In 10 subjects given 10–20 mU of vasopressin per hr during phases 2 and 3, free water clearance decreased significantly from phase 1 to phase 2 (9.3 to 0.15, $P = 0.001$) and increased during phase 3 norepinephrine infusion to 4.7 ml/min ($P = 0.001$). A comparable decrease in phase 2 free water clearance was observed in four subjects given 50 or 100 mU of vasopressin per hr during phases 2 and 3 ($P < 0.01$); however, the phase 3 norepinephrine infusion in these subjects was not associated with an increase in free water clearance. Creatinine clearance, osmolal clearance, and sodium and chloride excretion were unchanged throughout the studies in both groups of subjects.

A two phase study in seven subjects confirmed that 10, 20, or 75 mU of vasopressin per hr sustained antidiuresis during phase 2 for at least 2 hr and that free water clearance values were essentially constant in the individual subject after the first 30 min of infusion. The magnitude of the (phase 3) norepinephrine-induced increase in free water clearance (4.5 ± 0.64 ml/min) during infusion of 10–20 mU of vasopressin per hr, the failure of norepinephrine to increase free water clearance during infusion of 50–100 mU of vasopressin per hr, and the relatively constant endogenous creatinine and osmolal clearance rates would suggest that the norepinephrine inhibition of vasopressin antidiuresis was not the result of alterations in renal blood flow. A post-phase 3 infusion of vasopressin in four subjects resulted in a marked decrease in free water clearance, indicating that the norepinephrine inhibition of vasopressin antidiuresis was not accountable on the basis of decreased medullary hypertonicity.

These data support the hypothesis that catecholamine blocks the cellular mechanism of vasopressin antidiuresis in vivo. The observation that norepinephrine did not inhibit the antidiuresis produced by the infusion of 50 or 100 mU of vasopressin per hr suggests that this inhibition might be competitive. A possible role of catecholamine in the mechanism of cold diuresis is suggested.

INTRODUCTION

The infusion of catecholamines into human subjects has been shown to increase urine volume and free water clearance without altering glomerular filtration rate (1–3) and without altering or only moderately reducing renal plasma flow (3). This effect was most apparent when the control values of free water clearance were negative suggesting that catecholamines exerted this effect by decreasing tubular water reabsorption (3). The report of Strauch and Langdon (4) that epinephrine and norepinephrine inhibit the in vitro action of vasopressin on water transport by the toad bladder suggested that the in vivo effect of catecholamines

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on water excretion might be mediated by a similar mechanism. To test this hypothesis, we investigated the influence of norepinephrine on exogenously administered vasopressin in water-loaded subjects. The results are compatible with the hypothesis that norepinephrine, in nearly physiological concentrations, reduces renal tubular water reabsorption by blocking the renal mechanism of vasopressin antidiuresis.

METHODS

21 healthy young adults aged 21–31 yr and weighing 67–96 kg particpated in the present investigations. Each was admitted to the Clinical Research Center the evening before study, remained fasting, and abstained from tobacco after 10 p.m. The study was conducted in three phases: (*a*) water loading, (*b*) water loading plus vasopressin infusion, and (*c*) water loading plus vasopressin plus epinephrine infusion. *Phase 1.* At 6 a.m. 480 ml of tap water was administered orally and an infusion of 5% dextrose in water begun and maintained at a rate of 250 ml/hr (by an infusion pump) for the subsequent 4–6 hr. Additional tap water was given orally at 30-min intervals to maintain the volume of water intake 400–600 ml in excess of urine volume. Water load data were computed from the zero level at 6 a.m. when the bladder had been emptied and before oral and intravenous input was begun. *Phase 2.* After a stable water diuresis was achieved (2–3 hr) 10–100 mU of vasopressin (Parke, Davis & Co., aqueous Pitressin, lot EJ110) were added to the dextrose and water (250 ml) and infused over a 1 hr period. *Phase 3.* Finally, 10–100 mU of vasopressin and 600 μg of *l*-norepinephrine (Winthrop Laboratories, Levophed, lot 019AA) were added to the dextrose and water (250 ml) during the last 1 hr infusion period. Dead space delay time from the bottle to the vein at the beginning of phases 2 and 3 was minimized by flushing the tubing with an aliquot of the new intravenous mixture.

Subjects were recumbent throughout the studies. Urine was collected, during short-term erect posture, at 30-min intervals for measurement of volume and osmolality and determination of creatinine, sodium, and chloride content. Blood was drawn during each study phase, as atraumatically as possible with disposable needles and syringes, for determination of osmolality and creatinine and sodium concentrations. Creatinine clearance, osmolal clearance, and free water clearance (in milliliters/minute) were calculated.[1] The first 30-min periods of vasopressin (phase 2) and norepinephrine (phase 3) infusion were not included in statistical analyses since circulating concentrations of these hormones had not yet equilibrated to the exogenous infusion. Free water clearances during the final two collection periods of phase 1 and all collection periods of phases 2 and 3 are shown in the figures.

Serum and urine creatinine were measured by the method of Bonsnes and Taussky (5); serum and urine osmolality by freezing point depression with an Advanced Instruments osmometer; serum and urine sodium concentrations by flame photometry and urine chloride concentration with a Cotlove chloridometer. Statistical analyses were performed using Student's *t* test.

RESULTS

Initial studies (2 subjects) were conducted using 100 mU of vasopressin per hr during phases 2 and 3. 50 mU/hr was administered to the second two subjects. Since no inhibition of antidiuresis was observed during norepinephrine infusion at these vasopressin infusion rates, 10–20 mU of vasopressin per hr were administered to the subsequent 10 subjects. Data for the 10 subjects who received 10–20 mU and the 4 subjects administered 50–100 mU of vasopressin per hr are considered separately.

The mean increases in systolic and diastolic blood pressure in these 14 subjects during the norepinephrine infusions were 19 and 14 mm Hg respectively. Pulse rate uniformly decreased; the mean decrease was 12 beats/min. 3 subjects noted no subjective symptoms; the remaining 11 subjects noted a transient feeling of "tightening" of the chest as the major subjective manifestation of the infused norepinephrine.

Creatinine clearance, osmolal clearance, free water clearance, and urine and plasma osmolality are shown for the 14 subjects during the three study phases in Table I. The excess of water intake and infusion over urine output at the time of urine collections is recorded as positive water load (WL, in milliliters).

Four subjects (W. S., R. S., L. R., and J. R.) received separate infusions of vasopressin (15–20 mU/hr) and norepinephrine during phase 3. The data for these subjects and for the six subjects who were given combined infusions were similar and are considered collectively in the upper portion of Table I. Water load in these 10 subjects was relatively constant during the infusions as a result of the supplementary oral tap water. Creatinine and osmolal clearances did not vary significantly during the study. Mean free water clearance, however, decreased significantly (+9.3 to

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[1] Osmolal clearance (C_{osm}) was calculated by $C_{osm} = U_{osm}V/P_{osm}$, where U_{osm} = urinary osmolality (mOsm/liter), V = urine flow (ml/min), and P_{osm} = plasma osmolality (mOsm/liter). Free water clearance (C_{H_2O}) was calculated by $C_{H_2O} = V - C_{osm}$.

TABLE I

Water Load, Creatinine Clearance, Osmolal Clearance, Free Water Clearance, and Urine and Plasma Osmolality Data in 10 Subjects during Water Loading, Water Loading Plus Vasopressin Infusion, and Water Loading Plus Vasopressin Plus l-Norepinephrine Infusion

Subject	Vasopressin infusion rate	Phase 1 Water loading						Phase 2 Water loading + vasopressin						Phase 3 Water loading + vasopressin + norepinephrine					
		WL	C_{Cr}	C_{osm}	C_{H_2O}	U_{osm}	P_{osm}	WL	C_{Cr}	C_{osm}	C_{H_2O}	U_{osm}	P_{osm}	WL	C_{Cr}	C_{osm}	C_{H_2O}	U_{osm}	P_{osm}
	mU/hr	*ml*		*ml/min*			*mOsm/liter*	*ml*		*ml/min*			*mOsm/liter*	*ml*		*ml/min*			*mOsm/liter*
J.F.	10	538	142	2.3	6.5	75	287	595	120	2.4	+0.7	219	287	586	81	1.9	5.6	72	287
J.W.	10	210	175	2.9	11.4	60	292	160	151	2.8	−0.02	288	286	100	145	2.1	8.2	59	287
S.D.	10	530	110	1.8	8.1	51	286	730	89	1.2	−0.7	667	284	735	110	1.7	6.4	61	286
N.A.	10	455	107	1.8	5.4	80	289	525	116	2.1	−1.3	423	287	540	130	2.3	2.7	133	290
W.M.	10	305	142	3.2	9.0	76	286	702	152	3.3	−1.0	404	286	677	130	2.6	1.6	176	282
W.H.	20	120	146	2.4	13.1	44	286	240	116	3.8	+0.2	262	279	140	120	2.7	6.6	81	278
W.S.*	15	400	142	1.8	10.5	42	283	375	119	1.9	+2.2	124	275	460	131	1.9	5.2	82	276
R.W.*	15	1180	132	1.6	8.0	47	280	250	145	1.5	+2.2	100	274	1290	116	1.4	5.5	59	274
L.R.*	20	730	132	2.8	13.7	49	285	810	108	2.8	−0.1	303	278	870	134	3.2	3.3	153	276
J.R.*	20	1040	105	2.1	7.0	66	286	233	110	2.2	−0.7	346	280	363	100	1.9	1.8	157	277
	Mean	551	133	2.3	+9.3	59	286.0	462	123	2.4	+0.15	314	281.6	576	120	2.2	+4.7	103	281.3
	SEM	109	6.8	0.17	0.89	4.6	1.01	76	6.5	0.25	0.39	52	1.59	133	5.9	0.17	0.70	15	0.58
B.R.	50	550	148	2.0	6.0	73	290	670	139	1.2	−0.7	619	285	895	162	1.0	−0.7	960	288
R.R.	50	500	117	1.7	11.9	35	286	585	106	1.3	−0.8	702	286	785	104	2.1	−1.3	805	286
J.McS.	100	900	156	2.0	5.4	76	289	1050	128	1.4	−0.2	651	287	1270	184	1.7	−1.1	832	286
J.L.	100	320	151	3.0	10.1	67	292	370	125	3.2	+0.6	241	290	580	123	1.9	−1.1	681	290
	Mean	567	143	2.2	+8.4	63	289.2	666	125	1.8	−0.25	553	287.0	882	143	1.7	−1.1	820	287.5
	SEM	121	12.7	0.29	1.57	6.0	0.79	142	6.9	0.46	0.20	67	0.68	144	19.3	0.22	0.12	36	0.61

WL, water load; C_{Cr}, C_{osm}, and C_{H_2O}, creatinine, osmolal, and free water clearance; U_{osm} and P_{osm}, urine and plasma osmolality.

* Subjects received separate vasopressin and norepinephrine infusions.

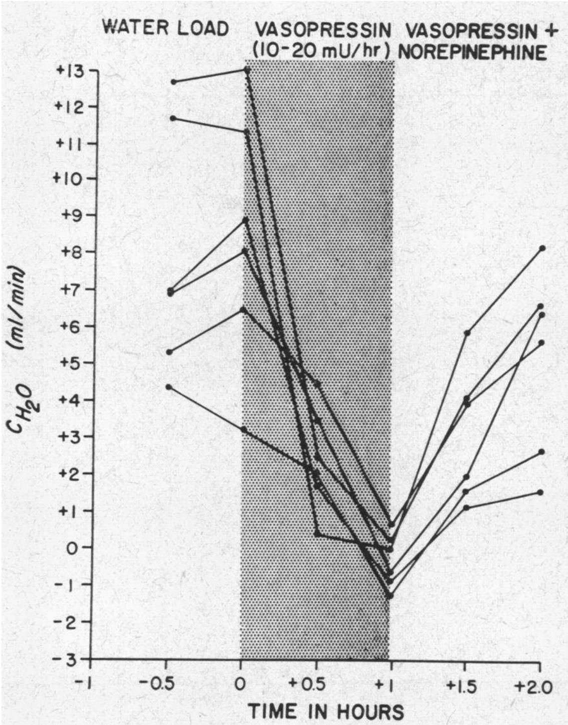

FIGURE 1 The effect of *l*-norepinephrine on free water clearance during infusion of 10–20 mU of vasopressin per hr. The abscissa represents time in hours related to the beginning of vasopressin infusion (0 hr). Urine was collected at 30-min intervals. After water loading, vasopressin was infused for 1 hr and vasopressin plus 600 μg of *l*-norepinephrine infused from the same bottle for an additional hour. The inhibition of vasopressin antidiuresis during norepinephrine infusion is obvious.

+0.15 ml/min, $P = 0.001$) during vasopressin infusion (phase 2) and increased significantly (+0.15 to +4.7 ml/min, $P = 0.001$) during infusion of vasopressin plus norepinephrine (phase 3). The corresponding changes in mean urine osmolality (59 to 314 and 314 to 103 mOsm/liter respectively) also were significant ($P = 0.001$). The free water clearance data are graphically depicted in Fig. 1 for the six subjects who received combined vasopressin and norepinephrine infusions.

The mean water load in these subjects during phase 1 was 551 ml; this value is less than the 1000–1500 ml volumes usually maintained in adult subjects to suppress endogenous vasopressin secretion. However, the free water clearance and urine osmolality values during phase 1 water loading (mean 9.3, range 5.4–13.7 ml/min and mean 59, range 42–80 mOsm/liter respectively) indicate that endogenous vasopressin secretion was effectively suppressed in all subjects. The increase in mean water load during phase 3 (462 to 576 ml) and the mean plasma osmolality values which decreased to low levels of 281.6 and 281.3 mOsm/liter during phases 2 and 3 suggest that water intake was sufficient throughout the study to maintain effective suppression of endogenous vasopressin secretion (6, 7).

Results of the studies employing 50–100 mU of vasopressin per hr are summarized in the lower portion of Table I. Positive water load increased somewhat during the final period (phase 3) in contrast to the water load in the subjects receiving 10–20 mU of vasopressin per hr. This increase was due to the continued antidiuresis during norepinephrine infusion in these subjects. Creatinine and osmolal clearances did not vary

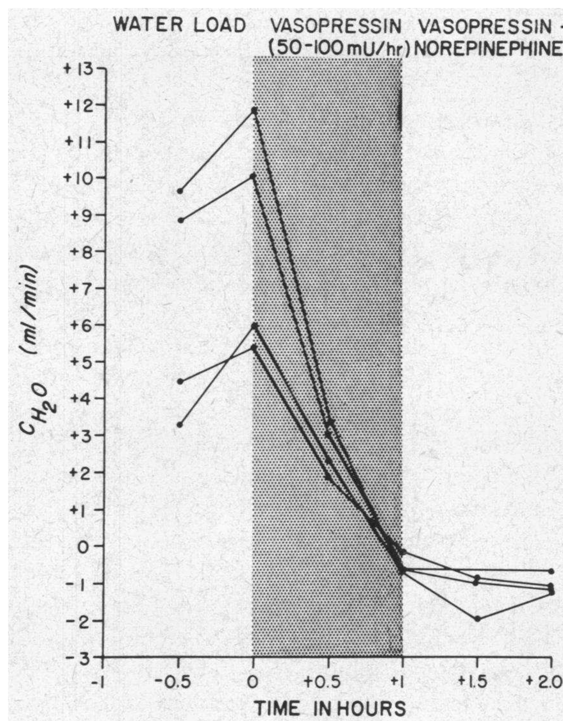

FIGURE 2 The effect of *l*-norepinephrine on free water clearance during infusion of 50–100 mU of vasopressin per hr. The abscissa represents time in hours related to the beginning of vasopressin infusion (0 hr). Urine was collected at 30-min intervals. After water loading, vasopressin was infused for 1 hr and vasopressin plus 600 μg of *l*-norepinephrine for an additional hour. In contrast to the effect of norepinephrine during infusion of 10–20 mU of vasopressin per hr (Fig. 1), norepinephrine did not inhibit the vasopressin antidiuresis.

TABLE II

Sodium and Chloride Excretion during Study Phases 1–3

Subject	Vasopressin infusion rate	Sodium Phase 1	Sodium Phase 2	Sodium Phase 3	Chloride Phase 1	Chloride Phase 2	Chloride Phase 3
	mU/hr	*μEq/min*			*μEq/min*		
J.F.	10	127	170	87	123	137	120
J.W.	10	130	173	93	173	177	93
S.D.	10	40	43	43	40	43	67
N.A.	10	97	103	120	113	143	167
W.M.	10	153	230	120	170	213	127
W.H.	20	140	190	187	123	267	213
Mean		115	152	108	124	163	131
SEM		16.7	27.4	19.5	19.7	31.1	21.4
B.R.	50	30	30	20	10	23	23
R.R.	50	70	83	117	27	43	83
J.McS.	100	57	23	90	67	27	13
J.L.	100	210	250	143	183	200	197
Mean		92	99	93	72	73	79
SEM		40.3	52.9	26.5	39.0	42.5	42.3

significantly during the three study phases. Mean free water clearance decreased significantly during the phase 2 vasopressin infusion (+ 8.4 to − 0.25 ml/min, $P < 0.01$). In contrast to phase 3 results in the subjects receiving 10–20 mU of vasopressin per hr, the phase 3 infusion of norepinephrine plus 50–100 mU of vasopressin per hr did not result in increased free water clearance; mean values were similar during phases 2 and 3 (− 0.25 and − 1.1 ml/min, Table I). Data are depicted graphically in Fig. 2.

Mean and range of plasma sodium concentrations in the 10 subjects receiving combined vasopressin and norepinephrine infusion were 141 (135–146), 139 (133–144), and 138 (134–142) mEq/liter respectively during the three study phases. Sodium and chloride excretion data in microequivalents/minute are shown in Table II. No significant variation in sodium or chloride excretion with phase or vasopressin dose was observed.

In seven subjects a two phase study was conducted as previously described except that the second phase vasopressin infusion was continued for a 2 hr period to insure that the exogenous hormone would sustain antidiuresis over this period and to assure a constant vasopressin effect after the first 30 min of infusion. The free water clearance results in these subjects are shown in Fig. 3. One subject (*A*) received 10 mU, three received 20 mU, and three received 75 mU of vasopressin per hr. A new lot of vasopressin (Pitressin, lot DB-110-1) was used for these infusions. Mean and range of creatinine clearance during phases 1 and 2 were 115 (81–143) and 113 (87–136) ml/min respectively. As can be observed in Fig. 3, the infusion of 10, 20, or 75 mU of vasopressin per hr sustains antidiuresis during water loading for at least 2 hr and free water clearance values plateau after the first 30 min of infusion.

In four subjects a final four phase study was conducted to rule out the possibility that norepinephrine might have inactivated the 10–20 mU of vasopressin when the two drugs were placed in the same bottle, and to attempt to determine whether the norepinephrine infusion might have resulted in increased free water clearance by decreasing renal medullary hypertonicity. The first three study phases were conducted as already described except that norepinephrine, 600 μg/hr (Levophed, lot 019AA), and vasopressin, 15 mU/hr in two subjects and 20 mU/hr in two subjects (Pitressin, lot DB 110-1), were infused separately during phase three. The infusion of vasopressin was continued without norepinephrine during

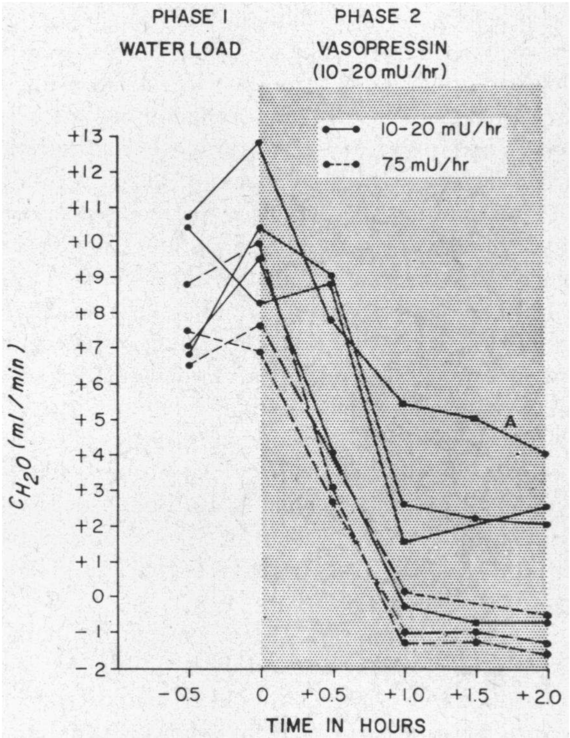

FIGURE 3 Maintenance of antidiuresis during infusion of 10–75 mU of vasopressin per hr. The abscissa represents time in hours related to the time of beginning of vasopressin infusion (0 hr). Urine was collected at 30-min intervals. Subject A received 10 mU/hr, three subjects 20 mU/hr, and three subjects 75 mU of vasopressin per hr during phase 2. Antidiuresis at these vasopressin infusion rates was sustained for at least 2 hr. Free water clearance was nearly constant after the first 30 min of infusion.

phase four. Phase 1–3 data for these four subjects are included in Table I. The free water clearance data during phases 2–4 are shown in Fig. 4. As can be observed, norepinephrine infused separately from vasopressin also inhibited antidiuresis. In addition, the postnorepinephrine infusion of vasopressin (phase 4) produced a marked decrease in free water clearance in each subject.

DISCUSSION

The increase in free water clearance in response to catecholamine infusion has been well documented and seems independent of changes in glomerular filtration rate, renal plasma flow, osmolal clearance, or sodium excretion (1–3). Although Walker, Reutter, Zileli, Friend, and Moore (2) noted the norepinephrine effect on free water clearance during water diuresis, Baldwin, Gombos, and Chasis (3) observed that the increase in free water excretion was most apparent when the control values of free water clearance were negative, an observation which suggests that catecholamines exerted their effect by decreasing tubular water reabsorption. Assuming this effect to be related to vasopressin (ADH), such reduction would most likely have resulted from a decreased rate of ADH secretion or inhibition of the end-organ response to vasopressin. The observation in the present study that norepinephrine inhibited the antidiuresis produced by the infusion of exogenous vasopressin in subjects in whom endogenous vasopressin secretion was suppressed supports the latter explanation and suggests that norepinephrine interferes with a renal mechanism

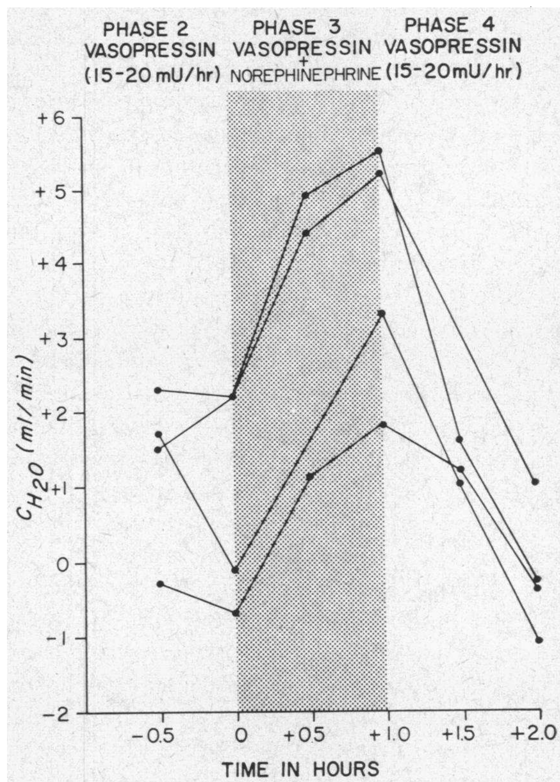

FIGURE 4 The effect of *l*-norepinephrine on free water clearance during infusion of 15–20 mU of vasopressin per hr. After water loading (phase 1, not shown), vasopressin was infused for 1 hr during phase 2. Vasopressin and 600 μg of *l*-norepinephrine were infused separately for 1 hr during phase 3 and vasopressin alone for an additional hour during phase 4. The inhibition of vasopressin antidiuresis during norepinephrine infusion is obvious. The antidiuresis, again manifest during phase 4, indicates that medullary hypertonicity was not dissipated during phase 3 to a degree sufficient to obtund antidiuresis.

for solute-free water reabsorption. Another possibility is that vasopressin clearance from plasma may be accelerated by norepinephrine. This possibility seems very unlikely but cannot be excluded by the present data.

It seems unlikely that renal vascular alterations accounted for the present results. No alteration in creatinine clearance, osmolal clearance, and sodium or chloride excretion was observed (Tables I and II). In addition, the infusion of norepinephrine failed to increase free water clearance, during otherwise similar circumstances, when the rate of vasopressin infusion was increased from 10–20 mU/hr to 50–100 mU/hr (Table I and Fig. 2). A possible effect of norepinephrine on renal medullary blood flow might have occurred and been counteracted by the higher (and not the lower) rates of vasopressin infusion. Thurau and Deetjen (8) have shown that urinary dilution and free water excretion can be produced even in the presence of ADH by increases in renal arterial perfusion pressure. They interpret this effect as being the consequence of dissipation of medullary hypertonicity due to increased vasa recta flow. Since the medullary circulation does not participate in renal autoregulation, increases in systemic pressure (as in the present study) would be paralleled by increasing vasa recta flow, reduction in the medullary osmotic gradient, and decreased urine osmolality. However, the renal medullary vasculature is very sensitive to catecholamines and vasopressin; both drugs produce vasoconstriction of the vasa recta (9). The small increase in systemic blood pressure observed in the present subjects would not be likely to increase vasa recta flow markedly, particularly in the presence of increased medullary vasoconstriction. Moreover, the magnitude of the increase in free water clearance (4.5 ± 0.64 ml/min, Table I) would not seem compatible with such a mechanism; assuming that the distal tubules and collecting ducts remain freely permeable to water, the excretion of free water would not be expected to increase to positive levels even if medullary hypertonicity diminished to an extent approaching that of renal cortex and plasma. Finally, the postnorepinephrine response to vasopressin (phase 4, Fig. 4) indicates that any decrease in medullary hypertonicity which might have occurred was not sufficient to obtund antidiuresis.

A more plausible explanation for reversal of vasopressin antidiuresis by catecholamines would be an effect at the tubular cell level on the ADH-induced water permeability of the distal nephron and collecting duct. The in vitro toad bladder experiments of Strauch and Langdon (4) suggest that norepinephrine might produce its diuretic effect by blocking the cellular mechanism of vasopressin antidiuresis. Although the mode of action of vasopressin is not established, there is evidence suggesting a mechanism that involves cyclic AMP (4, 10, 11) and perhaps tyramine (4) as mediators. In order to explain the inhibitory effect of catecholamines, Strauch and Langdon (4) suggested the possibility of an inhibitor site on adenylcyclase capable of binding these agents. The present observation that norepinephrine inhibits antidiuresis during infusion of 10–20 mU of vasopressin per hr (Fig. 1) but not that produced by 50–100 mU/hr (Fig. 2) suggests that the inhibition is competitive.

The rate of infusion of norepinephrine in the present study (600 μg/hr or about 0.14 μg/kg per min) has been shown by Walker and colleagues (2) to increase mean levels of venous plasma norepinephrine by 21–72%, values which suggest a physiological dose range. The 10–20 mU/hr doses of vasopressin also represent physiological levels. These doses are comparable to the 0.025–0.1 mU/kg per hr doses (about 2–8 mU/hr in adults) which Bader, Eliot, and Bass (12) observed would partially inhibit cold diuresis. The 0.5 mU/kg per hr dose (about 40 mU/hr), which these authors observed would completely inhibit cold diuresis in adult subjects, is very similar to the 50 mU hourly dose which inhibited the diuretic effect of norepinephrine in the present investigations.

The presently observed effect of norepinephrine on free water clearance might explain, at least in part, the water diuresis which has been well documented in adult and newborn human subjects during acute exposure to low environmental temperatures (12–15). This cold diuresis occurs without associated increase in glomerular filtration rate (12, 15), osmolar clearance, or electrolyte excretion (15) and, therefore, probably occurs because of reduction in renal tubular water reabsorption. Catecholamine excretion is known to be increased during cold exposure in animals (16–18), adult humans (19), and infants (20, 21).

Moore and Segar (22) have reported preliminary evidence suggesting that cold exposure in adult human subjects results in decreased blood levels of ADH, presumably secondary to body water redistribution and central inhibition of thoracic volume receptors influencing ADH secretion (22). Such volume redistribution would be a temporary phenomenon, and as such, might explain the usually transient water diuresis during acute cold exposure in adult subjects (12). Cold diuresis in the newborn, in contrast to that in the adult, is prolonged (at least 48 hr, reference 15). Catecholamine response to cold exposure also is prolonged in rats (17) and probably in the human newborn (20). Thus, catecholamine inhibition of vasopressin antidiuresis rather than central inhibition of ADH secretion would seem to offer a more likely explanation for newborn cold diuresis. Both mechanisms, however, may be involved.

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