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Suppression of antidiuretic hormone secretion by clonidine in the anesthetized dog

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Suppression of antidiuretic hormone secretion by clonidine in the anesthetized dog. Studies were performed to determine the mechanism by which the antihypertensive agent clonidine increases urine flow (V). In 11 anesthetized, hydropenic dogs, i.v. administration of clonidine (30 μg/kg) increased arterial pressure from 128 ± 4 to 142 ± 3 mm Hg and slowed heart rate from 138 ± 7 to 95 ± 7 beats/min within 30 min of injection; blood pressure then fell to 121 ± 5 mm Hg 30 to 60 min after injection, and 112 ± 5 mm Hg in the next 30-min period. V increased from 0.36 ± 0.09 to 0.93 ± 0.13 ml/min and urine osmolality (U_{Osm}) decreased from 1378 ± 140 to 488 ± 82 mOsm/kg of H_2O 30 to 60 min following injection ($P < 0.001$). These changes were accompanied by a decrease in $T^c_{H_2O}$. This increased V was not associated with increased glomerular filtration rate (GFR) or solute excretion, and occurred in acutely denervated kidneys and kidneys protected from the initial increase in arterial pressure by constriction of a suprarenal aortic clamp. By contrast, V, $T^c_{H_2O}$ and U_{Osm} were not altered by clonidine administration in seven acutely hypophysectomized dogs receiving a constant infusion of antidiuretic hormone (ADH) (80 μU/kg/min), despite similar hemodynamic changes produced by the drug. The results suggest that clonidine increases V through inhibition of ADH release, possibly via an indirect pathway mediated by the drug's alpha-adrenergic effects on the circulation.

Suppression de la secrétion d'hormone antidiurétique par la clonidine chez le chien anesthésié. Ce travail a été entrepris pour déterminer le mécanisme par lequel la clonidine, agent hypotenseur, augmente le débit urinaire (V). Chez 11 chiens anesthésiés, hydropéniques, la clonidine intraveineuse (30 μg/kg) fait augmenter la pression artérielle de 128 ± 4 à 142 ± 3 mm Hg et ralentit le rythme cardiaque de 138 ± 7 à 95 ± 7 battements/minute dans les 30 min qui suivent l'injection, puis la pression artérielle chute à 121 ± 5 mm Hg 30 à 60 min après l'injection et à 112 ± 5 mm Hg dans les 30 min suivantes. V augmente de $0{,}36 \pm 0{,}09$ à $0{,}93 \pm 0{,}13$ ml/min et l'osmolalité urinaire (V_{osm}) diminue de 1378 ± 140 à 488 ± 82 mOsm/kg H_2O 30 à 60 min après l'injection ($P < 0{,}001$). Ces modifications sont accompagnées par une diminution de $T^c_{H_2O}$. L'augmentation de V n'est pas associée à une augmentation de GFR ou de l'excrétion de substances dissoutes et survient aussi bien quand les reins sont dénervés de façon aiguë ou quand ils sont protégés de l'augmentation initiale de la pression artérielle par une constriction aortique sus-rénale. Au contraire, V, $T^c_{H_2O}$ et V_{osm} ne sont pas modifiés par la clonidine administrée à sept chiens hypophysectomisés qui reçoivent une perfusion constante d'ADH (80 μU/kg/min), malgré des modifications hémodynamiques semblables. Les résultats suggèrent que la clonidine augmente V par l'inhibition de la libération d'ADH, peut-être par une voie indirecte empruntant les affets alpha adrénergiques de la drogue sur la circulation.

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The imidazoline derivative clonidine (2-(2,6-dichlorphenylamino)-2-imidazoline hydrochloride) is a sympathomimetic agent with marked cardiovascular effects. It has proved of value in clinical medicine as an orally administered hypotensive agent [1–3]; it lowers mean arterial pressure through inhibition of central vasomotor and cardiac centers [4–7]. When administered i.v., it produces a transient increase in blood pressure, before its more sustained hypotensive effects are noted [4]. It also causes renal vasoconstriction and may decrease sodium excretion [3], and in addition has been noted to increase urine flow in anesthetized dogs [8, 9] and rats [10]. It is known that norepinephrine increases renal water excretion by inhibiting antidiuretic hormone (ADH) secretion [11, 12] and since clonidine shares many α-adrenergic stimulating properties with norepinephrine, it seemed possible that a similar mechanism could explain the increase in urine flow following clonidine administration. Studies were consequently undertaken to examine this possibility. It was found that clonidine increased urine flow and decreased urinary osmolality and solute-free water reabsorption when given i.v. to intact, hydropenic dogs, but not when given to acutely hypophysectomized animals receiving a constant infusion of ADH. These findings indicate that clonidine suppresses the release of ADH, and thus increases

water excretion by the same mechanism as norepinephrine.

Methods

Studies were performed in 20 male mongrel dogs weighing between 15.2 and 25.6 kg which had been fasted for 24 hr prior to the experiment but allowed free access to water. The animals were anesthetized with sodium pentobarbital (30 mg/kg) i.v. and ventilated by means of a cuffed endotracheal tube attached to a Harvard respirator. Seven animals underwent acute surgical hypophysectomy via a midline approach through the soft palate; these animals then received intramuscular injections of hydrocortisone (10 mg) and desoxycorticosterone acetate (DOCA) (1 mg). In all dogs, polyethylene catheters were placed in each ureter by means of subcostal flank incisions, and in 12 animals catheters were also placed in each renal vein. Selected kidneys were denervated by stripping all visible nerves and coating the renal pedicle with absolute alcohol. In many animals, an adjustable clamp was placed around the aorta above the renal arteries in order to control renal perfusion pressure; catheters placed in the brachial and femoral arteries were used to monitor arterial pressure above and below the clamp, respectively, using transducers (Statham P23AC) attached to a direct-writing recorder (Grass Instruments Co., Quincy, MA). After completion of surgery, a constant infusion of normal saline was started through a catheter in the femoral vein at 0.5 ml/min; this solution contained sufficient inulin and *para*-aminohippuric acid (PAH) to maintain blood concentrations of these substances at approximately 25 and 1 mg/100 ml, respectively. Experiments were conducted under two protocols:

Group I: Effects of i.v. administration of clonidine in intact animals. Urine was collected from 21 kidneys in 11 hydropenic, intact dogs before and after the i.v. injection of clonidine (30 μg/kg of body wt). In four of these animals (eight kidneys) clearances of inulin and PAH were measured, and in six animals renal perfusion pressure (RPP) was controlled by means of the aortic clamp. Observations were continued in all cases for 90 min, and in five experiments for 120 min, following the administration of the drug.

Group II: Effects of i.v. administration of clonidine in acutely hypophysectomized dogs receiving a constant infusion of ADH (vasopressin). In seven animals, a constant infusion of ADH (aqueous Pitressin, 80 μU/kg/min) in normal saline was started following hypophysectomy. Adequacy of hypophysectomy in these animals was demonstrated by the finding of urine hypotonic to plasma from each dog prior to the start of the ADH infusion. Renal clearance measurements were made from 12 kidneys in these seven animals; four kidneys were denervated. RPP was controlled in five of these dogs. Measurements were made before and after the injection of clonidine as described above.

In all experiments, two to five control clearance periods of 5 to 15 min duration were made; arterial and renal venous blood samples were obtained at the midpoints of alternate periods. Following the injection of clonidine, sequential 15-min periods were obtained for the duration of the experiment, with blood samples in alternate periods. For purposes of statistical analysis, values of two successive postdrug periods were averaged and results expressed in 30-min intervals (0–30, 30–60, 60–90, 90–120) following clonidine injection.

Blood samples were collected in chilled, heparinized tubes, and centrifuged in the cold; plasma and urine were analyzed for inulin by the anthrone method [13] adapted for the autoanalyzer [14], and PAH by the method of Harvey and Brothers [15]. Sodium and potassium were measured by flame photometry (Instrumentation Laboratories Model 343, Lexington, MA) and osmolality by freezing point depression (Advanced Instrument Corp., Needham Heights, MA). Arterial hematocrit value was measured in heparinized capillary tubes. Glomerular filtration rate (GFR) was measured as the clearance of inulin, and renal plasma flow (RPF) calculated from the clearance and extraction (E) of PAH according to the formula of Wolf [16]: $RPF = V(U-R)/(A-R)$ where V = urine flow in ml/min, and U, A and R are urine, arterial and renal venous concentration of PAH, respectively. Renal blood flow (RBF) was calculated as $RBF = RPF/1 - Hct$, and renal vascular resistance (RVR) as $RVR = RPP/RBF$. Solute clearance (C_{Osm}) was determined by the product of urine to plasma osmolality ratio and V, and solute-free water reabsorption (T^cH_2O) was calculated as C_{Osm} minus V. Filtration fraction (FF) was determined as GFR/RPF. Student's *t* test for paired data was used to test statistical significance.

Results

Group I. Effects of i.v. administration of clonidine in intact dogs. Following i.v. injection of clonidine in a dose of 30 μg/kg, there was an abrupt and marked increase in blood pressure followed by a progressive decline; on the average, arterial pressure had fallen below the control value 60 to 90 min following administration of the drug (Table 1). A pronounced bradycardia occurred following injection of the drug

and persisted for the duration of the experiment. Associated with these alterations in systemic hemodynamics were consistent rises in hematocrit value and plasma potassium concentration (Table 1); plasma sodium concentration and osmolality were unaffected.

Clonidine also produced marked changes in renal function. GFR fell slightly but significantly 60 to 90 min after administration of the drug, and there was a marked and sustained reduction in RPF which persisted for the duration of the experiments (Table 2). These changes were reflected in the accompanying large increases in RVR and FF. The extraction of PAH increased from 0.86 ± 0.02 (SEM) to 0.91 ± 0.01 30 to 60 min after injection ($P < 0.005$). Sodium excretion ($U_{Na}V$) was decreased, and potassium excretion (U_KV) increased 30 to 60 min after the drug was given (Table 3). This increase in U_KV may have been related to the increased plasma potassium concentration, since fractional potassium excretion (C_K/C_{In}) did not change in the eight kidneys in which it was measured.

The most consistent finding in these studies was an increase in V, which occurred in 19 of the 21 kidneys. This increase was due almost entirely to increased water excretion, urinary osmolality (U_{Osm}) decreasing from 1378 ± 140 mOsm/kg of H_2O to 448 ± 82 (range: 116 to 1442) mOsm/kg of H_2O 30 to 60 min after administration of clonidine ($P < 0.001$, Table 3, Fig. 1).

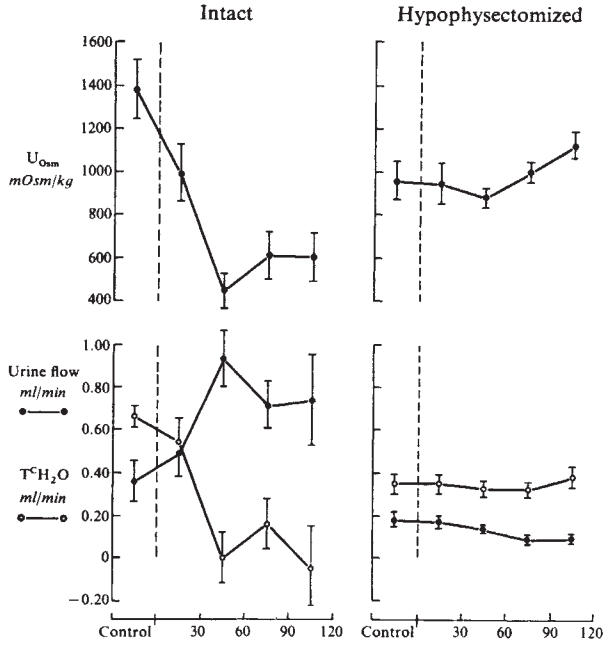

Fig. 1. *Effect of clonidine on urine osmolality (U_{Osm}), urine flow and free water reabsorption (T^cH_2O) in 21 kidneys from 11 intact, hydropenic dogs and in 12 kidneys from 7 acutely hypophysectomized dogs receiving a constant infusion of ADH.* Clonidine injection (30 μg/kg) is indicated by the *broken lines. Points* represent mean ± SEM; results in the intact group at 90 to 120 min are from only nine kidneys.

These reciprocal changes in V and U_{Osm} following clonidine injection were reflected in a decrease in T^cH_2O from 0.66 ± 0.05 to 0 ± 0.12 ml/min at 30 to 60 min. This effect of the drug to promote renal water excretion was transient; by 60 to 90 min after administration, V had fallen, and U_{Osm} had increased, although both values remained significantly different from the control observation (Table 3). In nine kidneys of this group (five animals), collections were continued up to 120 min following drug injection. At 60 to 90 min, U_{Osm} for these nine kidneys averaged 473 ± 143 mOsm/kg of H_2O, and increased to 603 ± 113 (range: 123 to 1517) mOsm/kg of H_2O in the next 30-min period ($P < 0.05$), further indicating that the effects of the drug on water excretion were transient. Overall, this tendency for U_{Osm} to increase late in the experiments coincided with the peak hypotensive effect of clonidine. However, in two experiments, blood pressure remained at or above control levels for the two hours following clonidine injection. U_{Osm} from the kidneys of these animals remained depressed and did not show the tendency to increase at the end of the experiment that was exhibited by the group as a whole.

In six denervated kidneys clonidine produced a decrease in U_{Osm} from 946 ± 253 during control to 334 ± 129 mOsm/kg of H_2O at 30 to 60 min ($P < 0.01$). In six of the 11 animals, RPP was controlled by means of the aortic clamp so that the acute hypertension produced by i.v. administration of clonidine was not transmitted to the kidneys. U_{Osm} in these 11 kidneys fell from 1295 ± 214 to 407 ± 113 mOsm/kg of H_2O ($P < 0.005$) by 30 to 60 min following injection of the drug. Solute clearance was not increased at any time after the administration of clonidine. Thus, the enhanced water excretion caused by clonidine occurred despite renal vasoconstriction and decreased $U_{Na}V$ was present in denervated as well as innervated kidneys, and was observed in the absence of increases in RPP, GFR or solute excretion.

Group II: Effects of i.v. administration of clonidine in acutely hypophysectomized dogs. The group of hypophysectomized animals had lower blood pressure, GFR and rates of electrolyte excretion and solute clearance during control measurements than the group of intact animals (Tables 1 and 2). Infusion of ADH produced a mean control U_{Osm} of 952 (range: 532 to 1641) mOsm/kg of H_2O in the 12 kidneys. Intravenous injection of clonidine caused hemodynamic changes similar to those observed in the intact group (Table 1); by 30 to 60 min following the injection, mean arterial pressure had fallen to control levels, and by 90 to 120 min it had fallen to 84 ± 5 mm Hg, a value significantly below the control value of 106 ± 6 mm Hg

Table 1. Effects of i.v. administration of clonidine on arterial pressure, heart rate,

	Brachial artery pressure *mm Hg*					Heart rate *beats/min*					
	C[a]	0–30	30–60	60–90	90–120	C[a]	0–30	30–60	60–90	90–120	C[a]
Group I[b]											Intact hydropenia ($N=11$)
Mean	128	142	121	112	113	138	95	97	95	—	44.1
SEM	±4	±3	±5	±5	±7	±7	±7	±6	±9	—	±2.0
P		<0.025	NS	<0.05	NS		<0.001	<0.001	<0.001		
Group II[b]											Acute hypophysectomy with constant
Mean	106	136	103	89	84	142	88	93	96	97	43.4
SEM	±6	±8	±9	±8	±5	±7	±10	±7	±8	±9	±2.0
P		<0.005	NS	NS	<0.02		<0.001	<0.001	<0.001	<0.001	

[a] C = control period; subsequent columns refer to time (in minutes) after injection of clonidine.
[b] SEM = standard error of the mean. *P* = level of statistical significance (paired *t* test) compared with control value. NS = not significant ($P>0.05$).

Table 2. Effects of i.v. administration of clonidine on renal

	GFR *ml/min*					RPF *ml/min*				
	C[b]	0–30	30–60	60–90	90–120	C[b]	0–30	30–60	60–90	90–120
Group I										Intact hydropenia ($N=8$)
Mean	54.6	62.2	52.7	46.0	54.3	178	100	118	102	116
SEM	±5.3	±17.0	±6.1	±3.7	±2.5	±22	±17	±18	±7	±9
P		NS	NS	<0.005	NS		<0.005	<0.005	<0.005	<0.001
Group II										Acute hypophysectomy with constant infusion of
Mean	21.1	22.0	20.9	19.3	22.5	119	85	73	64	71
SEM	±2.2	±2.1	±2.2	±2.1	±3.2	±17	±9	±10	±9	±9
P		NS	NS	NS	NS		<0.02	<0.001	<0.001	<0.01

[a] GFR = glomerular filtration rate, RPF = renal plasma flow, FF = filtration fraction, RVR = renal vascular resistance. Other abbreviations as in Table 1.
[b] C = control period; subsequent columns refer to time (in minutes) after injection of clonidine.

Table 3. Effects of clonidine injection on

	V *ml/min*					U_{Osm} *mOsm/kg of H_2O*					C_{Osm} *ml/min*			
	C[b]	0–30	30–60	60–90	90–120	C[b]	0–30	30–60	60–90	90–120	C[b]	0–30	30–60	60–90
Group I											I.V. administered clonidine in intact			
Mean	0.36	0.49	0.93	0.71	0.74	1378	991	448	608	603	1.02	1.02	0.93	0.87
SEM	±0.09	±0.11	±0.13	±0.11	±0.21	±140	±138	±82	±110	±113	±0.12	±0.08	±0.07	±0.06
P		<0.01	<0.001	<0.005	NS		<0.001	<0.001	<0.001	<0.005		NS	NS	NS
Group II											I.V. administered clonidine in hypophysectomized dogs receiving			
Mean	0.19	0.18	0.16	0.14	0.14	952	938	871	987	1111	0.54	0.52	0.47	0.47
SEM	±0.03	±0.02	±0.01	±0.01	±0.02	±88	±94	±46	±51	±62	±0.07	±0.05	±0.05	±0.05
P		NS	NS	NS	NS		NS	NS	NS	NS		NS	NS	NS

[a] V = urine flow, U_{Osm} = urine osmolality, C_{Osm} = solute clearance, T^cH_2O = free water reabsorption, $U_{Na}V$ = sodium excretion, U_KV = potassium excretion. Other abbreviations as in Table 1.
[b] C = control period; subsequent columns refer to time (in minutes) after injection of clonidine.

hematocrit value and plasma potassium concentration

Hematocrit *vol %*				Plasma potassium *mEq/liter*					Plasma osmolality *mOsm/kg of H_2O*				
0–30	30–60	60–90	90–120	C[a]	0–30	30–60	60–90	90–120	C[a]	0–30	30–60	60–90	90–120
50.8	51.6	51.1	49.0	3.6	4.1	4.0	4.1	3.8	293	292	293	294	293
±3.0	±1.1	±2.5	±3.1	±0.1	±0.1	±0.1	±0.2	±0.3	±4	±3	±3	±3	±4
<0.005	<0.005	<0.02	<0.05		<0.02	<0.01	<0.05	NS		NS	NS	NS	NS
infusion of vasopressin ($n=7$)													
46.2	44.3	43.4	43.1	3.7	4.1	4.0	4.1	4.3	299	300	298	297	295
±2.1	±1.8	±1.8	±1.9	±0.1	±0.2	±0.1	±0.2	±0.2	±6	±6	±4	±6	±7
<0.025	NS	NS	NS		<0.02	<0.01	<0.02	<0.05		NS	NS	NS	NS

hemodynamics in intact and hypophysectomized dogs[a]

FF					RVR *mm Hg/ml/min*				
C[b]	0–30	30–60	60–90	90–120	C[b]	0–30	30–60	60–90	90–120
0.33	0.53	0.46	0.45	0.48	0.455	0.710	0.579	0.585	0.492
±0.04	±0.07	±0.03	±0.02	±0.03	±0.085	±0.180	±0.102	±0.064	±0.031
	<0.05	<0.001	<0.005	<0.001		NS	<0.02	<0.02	<0.01
vasopressin ($N=12$)									
0.20	0.27	0.30	0.34	0.34	0.590	0.848	0.861	0.936	0.804
±0.02	±0.03	±0.03	±0.04	±0.05	±0.054	±0.097	±0.084	±0.096	±0.107
	<0.001	<0.001	<0.005	<0.005		<0.01	<0.001	<0.005	<0.05

renal water and electrolyte excretion[a]

T^cH_2O *ml/min*						$U_{Na}V$ *μEq/min*					U_KV *μEq/min*				
90–120	C[b]	0–30	30–60	60–90	90–120	C[b]	0–30	30–60	60–90	90–120	C[b]	0–30	30–60	60–90	90–120
hydropenic dogs (21 kidneys, 11 dogs)															
0.68	0.66	0.54	0.01	0.16	−0.05	64.4	39.0	31.2	37.2	17.3	33.0	40.5	45.2	38.7	34.1
±0.05	±0.05	±0.11	±0.12	±0.12	±0.20	±15.2	±7.0	±6.7	±9.2	±5.3	±2.9	±4.0	±5.0	±3.0	±5.3
NS		NS	<0.001	<0.001	<0.05		NS	<0.05	NS	NS		<0.05	<0.05	NS	NS
a constant infusion of vasopressin (12 kidneys, 7 dogs)															
0.53	0.34	0.35	0.32	0.32	0.38	19.8	11.3	9.7	8.6	10.2	21.8	21.0	23.7	24.1	28.5
±0.07	±0.05	±0.04	±0.04	±0.04	±0.05	±7.8	±4.0	±2.7	±2.6	±2.9	±2.0	±2.0	±2.9	±3.2	±4.2
NS		NS	NS	NS	NS		NS	NS	NS	NS		NS	NS	NS	NS

(Table 1). Plasma potassium concentration and hematocrit value were likewise increased by clonidine (Table 1). No changes in plasma sodium concentration or plasma osmolality were observed.

In addition to these systemic changes, clonidine produced alterations in renal function which were similar to those observed in the studies in intact animals (Table 2). Changes in GFR were small but a large fall in RPF was observed, in association with rises in RVR and FF, and an increase in the renal extraction of PAH (E_{PAH}) from 0.83 ± 0.03 to 0.87 ± 0.02 ($P < 0.001$). $U_{Na}V$ fell slightly, although the mean difference at 30 to 60 min was not statistically significant. In contrast to the findings in intact animals, there was no increase in U_KV following clonidine.

Clonidine failed to alter renal water excretion or U_{Osm} in the hypophysectomized dogs. V remained at the control level after administration of the drug (Fig. 1, Table 3). U_{Osm} was 871 ± 46 mOsm/kg of H_2O at 30 to 60 min after injection, the time period when U_{Osm} was maximally depressed in the group I studies; this value was not significantly different from the control value of 952 ± 88 mOsm/kg of H_2O. There were no changes in C_{Osm} or T^cH_2O. This lack of effect of clonidine on renal water excretion was not influenced by renal denervation and was the same in kidneys in which RPP was maintained constant during the transient hypertensive phase following drug injection.

Discussion

The present studies confirm that i.v. administration of clonidine increases V in anesthetized, hydropenic dogs, and in addition show that this increased V is associated with a decrease in U_{Osm} and T^cH_2O. Other investigators reported increased V after clonidine injection, but did not determine the mechanism responsible for this effect [8–10]. In the present studies, the increase in renal water excretion did not occur as a result of increased RPP, since arterial pressure, after an initial rise, was equal to or below control values 30 to 60 min following injection of the drug, the time period when V was highest and U_{Osm} lowest. In addition, control of RPP by an aortic clamp so that the kidneys were not exposed to the initial hypertensive effects of the drug did not alter this response. GFR and solute excretion rates were either unchanged or decreased following clonidine administration so that these factors could not account for the enhanced water excretion. These observations suggested, therefore, that the increased water excretion induced by clonidine was not hemodynamically mediated, but rather occurred as a result of central inhibition of ADH release or through inhibition of the action of ADH on the renal tubule.

To discriminate between those two possibilities, studies were performed in acutely hypophysectomized dogs with absent or markedly reduced sources of endogenous ADH. These animals received a constant infusion of ADH at a dose (80 μU/kg/min) shown in other studies [11] to produce urine osmolalities comparable to those observed in intact hydropenic animals, although less than that required to produce a maximally concentrated urine [7]. Renal function in these animals was less than that observed in the intact group, consistent with previous observations on the effect of acute hypophysectomy on renal function [18, 19]. The mechanisms responsible for this decrease in renal function after hypophysectomy are not entirely clear, although it has been demonstrated that administration of growth hormone [20], adrenocorticotropic hormone (ACTH) [21] or oxytocin [22] to the hypophysectomized animal will improve renal function. The hypophysectomized dogs in the present study received intramuscular injections of hydrocortisone and DOCA which should have been large enough to prevent any circulatory abnormality associated with deficiency of either of these hormones. The two groups of animals were otherwise treated identically.

In this group of hypophysectomized dogs receiving a constant infusion of ADH, clonidine failed to influence the rate of water excretion. U_{Osm} in this group was comparable to, although slightly lower than, that seen in the intact dogs, and failed to change after clonidine injection even though the drug produced similar effects on blood pressure and heart rate in the two groups of animals. It is possible that the greater increase in RVR noted in these hypophysectomized dogs after clonidine administration could have masked any tendency for the drug to alter V directly. This does not seem likely, however, in view of the qualitatively similar changes in RVR seen in the intact group, where effects on U_{Osm} were pronounced. It thus seems probable that the action of clonidine to increase renal water excretion was due to inhibition of ADH release rather than to antagonism of the action of ADH on the renal tubule.

It is now well-established that a number of nonosmotic stimuli influence the release of ADH [23]. Factors leading to decreased ADH secretion include left atrial distention and increased activity of carotid and aortic baroreceptors [24, 25], while cervical vagotomy [25], carotid artery occlusion [25], hemorrhagic hypotension [26] and diminished blood volume [27] all increase ADH release. The studies of Schrier and his associates have extended and clarified some of these phenomena [11, 12, 28–30]. They have

shown that α-adrenergic stimulation with norepinephrine infusions suppresses ADH release through an indirect neural reflex pathway dependent on intact carotid baroreceptors [11, 12]. Beta-adrenergic stimulation with isoproterenol produces antidiuresis through enhanced ADH release, via a mechanism related to the systemic hypotension (and consequent altered baroreceptor activity) resulting from isoproterenol administration [28, 29]. Although other pathways could conceivably be involved, the data most strongly suggest that adrenergic stimulation modulates ADH secretion through circulatory alterations which cause changes in baroreceptor neural activity [12, 29]. In accord with this hypothesis are the studies of Berl and Schrier demonstrating that infusion of prostaglandin E_1, a compound without known adrenergic stimulating properties, produced antidiuresis in conjunction with systemic hypotension [30]. Thus, changes in carotid arterial pressure caused by these pharmacological agents lead to alterations in ADH secretion by altering baroreceptor neural tone [12, 29].

The results of the present studies may best be interpreted against this background. Clonidine is a potent α-adrenergic agonist, producing cardiovascular effects which mimic in part those of norepinephrine, and which are prevented by the α-blocking agent phentolamine [5, 31]. Thus, it is possible that the acute hypertensive effects of clonidine altered baroreceptor activity, and led to suppression of ADH release, resulting in an increase in renal water excretion. Consistent with this suggestion is the finding that U_{Osm}, having reached a nadir 30 to 60 min after drug administration, then commenced to rise, and this increase in U_{Osm} was correlated with the peak hypotensive action of clonidine. Thus, as hypotension occurred, baroreceptor activity changed in an opposite fashion to lead to enhanced secretion of ADH and consequent antidiuresis (Table 3).

Support for this proposal is provided by observations in two experiments in which the hypotensive action of clonidine was not manifested in the two-hour study period. In these two experiments, U_{Osm} remained at a low level for the duration of the study, showing no tendency to increase as was seen in other experiments where hypotension did occur. Thus, overall, the effects of clonidine to suppress ADH release can most readily be related to alterations produced in carotid perfusion pressure, leading to changes in baroreceptor activity.

These studies do not, however, rule out other possible pathways. Clonidine is known to decrease cardiac output primarily by a reduction in heart rate [3, 4]; under these circumstances, left atrial pressure could increase and, if it rose sufficiently, could lead to decreased ADH release [24]. Alternatively, changes in baroreceptor activity in the region of the aortic arch [23, 25], or altered parasympathetic afferent tone carried by the vagus nerve [25], could influence ADH release. Finally, some other, as yet unmeasured, effect of α-adrenergic stimulation by clonidine could lead to suppression of ADH release. Regardless of which of these possible mechanisms is operating, the present findings are most consistent with the hypothesis that clonidine suppresses the release of ADH indirectly as a consequence of its potent effects on the circulation.

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