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Modification of the Antidiuretic Effect of Vasopressin by Acid and Alkaline Loads *

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Impaired urinary concentrating ability has been described in various clinical and experimental conditions. In many of these conditions the urine is alkaline, and other abnormalities in its ionic composition have been described or may be expected from the circumstances (1–8). It appeared possible, therefore, that the antidiuretic effect of endogenous vasopressin might be influenced by the pH and by the ionic composition of the body fluids and of the tubular urine.

This paper deals with the effect of vasopressin in dogs infused with hypotonic solutions of sodium chloride, ammonium chloride, and sodium bicarbonate and shows that the antidiuretic action of small doses of vasopressin is modified by the administration of acid and alkaline solutions.

Methods

The experiments were carried out on untrained fasting female dogs weighing 11.8 to 27 kg. The dogs were kept on a diet of Purina and powdered milk. They were anesthetized by intraperitoneal injection of 30 mg per kg sodium thiopentone (intraval sodium), the effect of which lasted for about 30 minutes. During this time polyethylene tubes were inserted into veins and artery, a catheter was inserted into the bladder, and an infusion of ethanol was started at a rate of 0.1 to 0.15 ml per minute. This infusion, which was maintained throughout the experiments, kept the animals under light anesthesia and served also to abolish the release of endogenous antidiuretic material (9, 10).

Hypotonic solutions of sodium chloride, ammonium chloride, and sodium bicarbonate were infused at a rate of 7.4 ml per minute, with a Bowman constant infusing pump. The solutions were made up to contain 100 mOsm per L of the electrolyte solution and 100 mOsm per L of glucose. Thus, the amount of electrolytes infused was 740 μOsm per minute. Inulin was added to the infusion for the determination of glomerular filtration rate.

During each experiment only one type of electrolyte solution was used. The infusion was given until a constant urinary flow with low osmolality was obtained, which usually took 3 to 4 hours. The solution was then changed for an identical one, containing vasopressin [1] in varying amounts. In the experiments with sodium bicarbonate the vasopressin was given in a glucose solution into a separate vein, in order to avoid prolonged contact of the vasopressin with the alkaline solution. Urine samples were collected every 10 to 20 minutes for determination of pH and total osmolality. Blood samples were taken every 20 minutes for the determination of total osmolality. In part of the experiments the blood pH was determined at various times during the infusion. The vasopressin infusions were continued to allow antidiuretic effect to become evident and constant, and after an interval, during which the corresponding solution without vasopressin was infused, a higher concentration of vasopressin was given. In a few instances, this was done without a vasopressin-free interval. The range of vasopressin dosage in these experiments was 0.48 to 12.6, 0.27 to 6.5, and 0.28 to 10.0 μU per kg per minute for the experiments with sodium chloride, ammonium chloride, and sodium bicarbonate, respectively.

As it was observed that the dogs possessed individual degrees of sensitivity towards vasopressin, additional experiments were carried out on six dogs, in which the three types of salt solutions were given to the same dog in separate experiments. There was an interval of at least 2 weeks between subsequent experiments. In this set of experiments only two doses of vasopressin were used (0.48 and 0.72 μU per kg per minute).

Osmolality was determined cryoscopically with a thermistor-type apparatus (Fiske); the pH in blood and urine was determined with a Beckman pH meter. Inulin was

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[1] Pitressin, lot no. L749B, Parke, Davis & Co., Detroit, Mich.

measured by the method of Roe, Epstein, and Goldstein (11).

Results

Representative experiments with each type of solution and with increasing doses of vasopressin are illustrated in Figures 1 to 4.

Figure 1 shows the results of administering 2.5, 7.6, and 12.6 μU per kg per minute of Pitressin to dog J during the infusion of hypotonic sodium chloride solution. A definite antidiuretic effect, i.e., a fall in urinary flow, a rise in urinary osmolality, and a corresponding fall in free water clearance became manifest during the administration of the smallest amount of vasopressin used. The effect became more pronounced during the infusion of the intermediate dose, whereas the largest dose had a similar, but somewhat lesser effect.

In the experiments with ammonium chloride (Figure 2, dog K) the vasopressin dosage was gradually raised from 0.37 to 0.75, 1.5, and finally 3.0 μU per kg per minute. In these experiments the small initial amount of vasopressin had an antidiuretic effect, which equaled that obtained in the sodium chloride experiments with a much larger initial dosage. The administration of 1.5 and 3.0 μU per kg per minute had a more pronounced antidiuretic effect than doses 4 to 5 times as large given in the sodium chloride experiments.

Figure 3 (dog L) illustrates one of the experiments with sodium bicarbonate solution, with a vasopressin range of 0.28, 0.55, 5.5, and 10.0 μU per kg per minute. Only during the administration of the two larger amounts of vasopressin could a definite antidiuretic effect be observed, which was still less, however, than that seen with similar or even smaller amounts in the sodium chloride and ammonium chloride experiments. The two initial doses of vasopressin resulted in a rise of urinary flow, whereas the urinary osmolality remained unchanged.

In Figure 4, the period to period changes in three different experiments on the same dog (dog S), and with the same amount of vasopressin (0.48 μU per kg per minute), are compared.

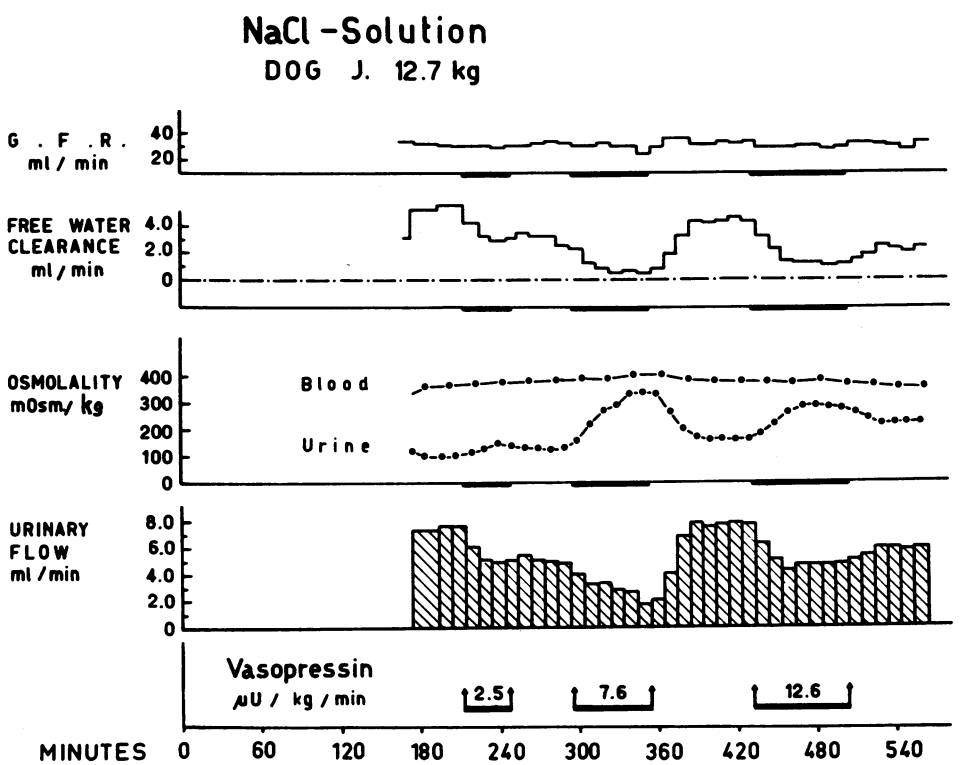

FIG. 1. CHANGES IN URINARY VOLUME, OSMOLALITY, AND FREE WATER CLEARANCE CAUSED IN DOG J BY THE ADMINISTRATION OF VASOPRESSIN DURING THE INFUSION OF HYPOTONIC SODIUM CHLORIDE SOLUTION. GFR = glomerular filtration rate.

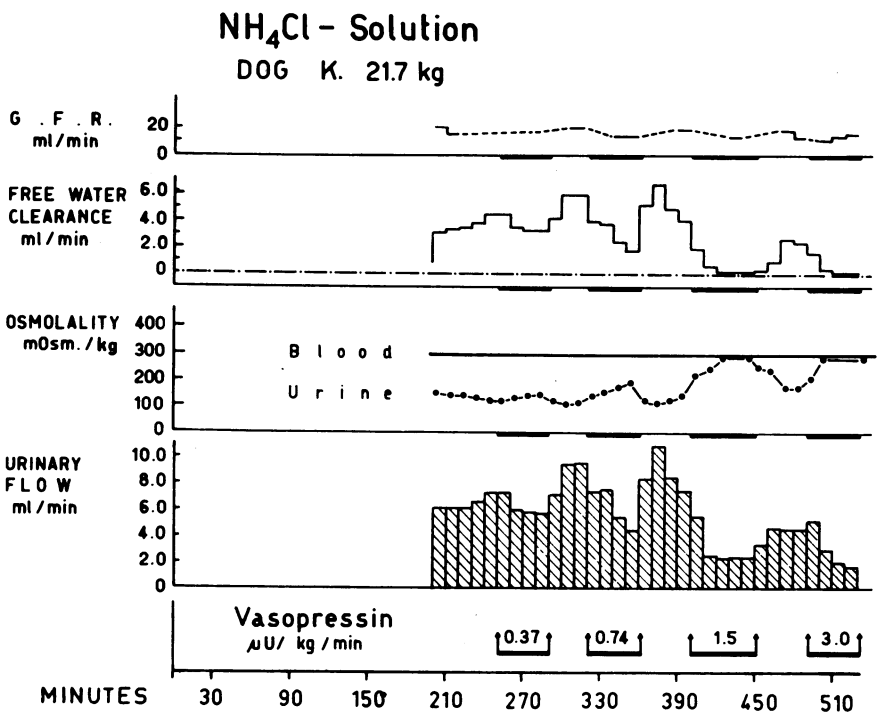

FIG. 2. CHANGES IN URINARY VOLUME, OSMOLALITY, AND FREE WATER CLEARANCE CAUSED IN DOG K BY THE ADMINISTRATION OF VASOPRESSIN DURING THE INFUSION OF HYPOTONIC AMMONIUM CHLORIDE SOLUTION.

With NH_4Cl and NaCl pronounced antidiuresis was observed; with $NaHCO_3$ only minor changes were noted.

Table I compares the effect of vasopressin on urinary flow, urinary osmolality, and free water clearance during the infusion of the three salt solutions in identical dogs. In most of the animals the effect of vasopressin on urine volume and osmolality was largest with ammonium chloride and smallest or absent with sodium bicarbonate, whereas with sodium chloride intermediate effects were observed. In dog U, an antidiuretic effect could only be seen during the infusion of NH_4Cl.

In Tables II to IV the results of all experiments are summarized, with data concerning glomerular filtration rate, osmolar excretion, and changes in urinary pH included.

A. *Antidiuretic effect.* In all NH_4Cl experiments and in 15 of 16 experiments with NaCl an antidiuretic effect occurred, whereas with $NaHCO_3$ a definite antidiuresis could be observed only in 9 of 15 experiments.

B. *Glomerular filtration rate.* In most instances, the GFR remained constant or showed only minor alterations throughout the experiments. Such changes as occurred did not show any definite pattern, and rises as well as falls in GFR were observed, which did not accompany changes in the same direction of the urinary flow. In some of the experiments on identical animals, GFR seemed to be somewhat lower during the infusion of NH_4Cl than during the infusion of the other solutions.

C. *Solute excretion.* Although the salt solutions were infused at a constant rate (740 µOsm per minute) throughout the whole duration of the experiments, the solute output showed considerable fluctuations, especially after the infusion of vasopressin. Rises were somewhat more frequently observed than falls, but no correlation became manifest between these changes and either the type of salt solution or the vasopressin dosage employed. During the control periods, the urines were markedly hypotonic even with the highest solute excretion rates.

D. *Changes in pH.* The urinary pH was 6.0 to 7.0, 5.6 to 7.1, and 7.3 to 8.4, respectively, during

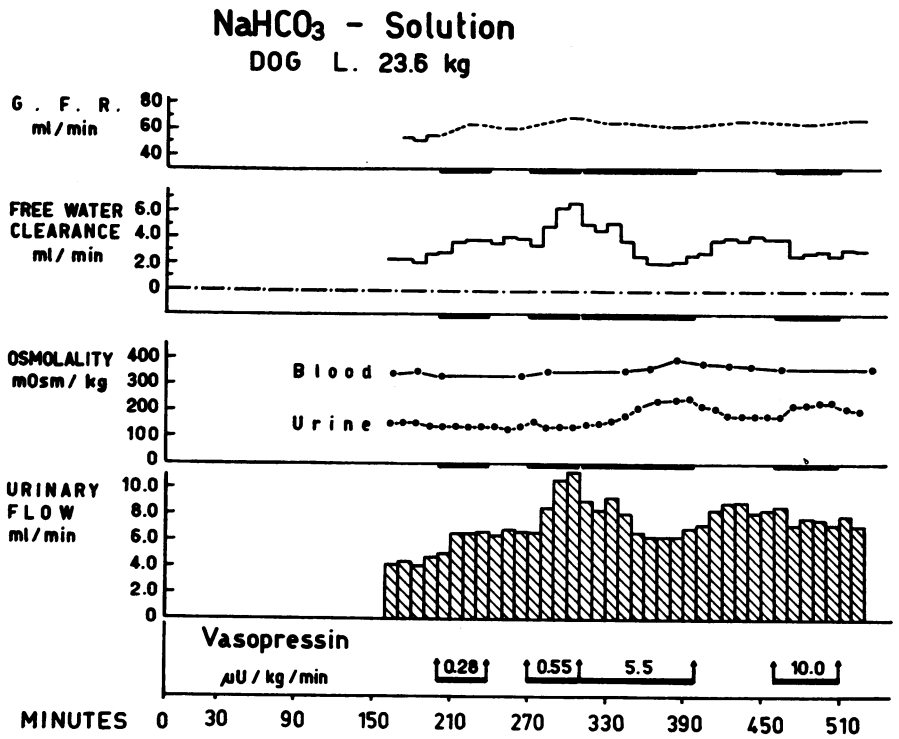

FIG. 3. CHANGES IN URINARY VOLUME, OSMOLALITY, AND FREE WATER CLEARANCE CAUSED IN DOG L BY THE ADMINISTRATION OF VASOPRESSIN DURING THE INFUSION OF HYPOTONIC SODIUM BICARBONATE SOLUTION.

the control periods of the NaCl, NH_4Cl, and $NaHCO_3$ experiments; the corresponding values for blood pH ranged between 7.24 to 7.30, 7.0 to 7.18, and 7.32 to 7.38. During the vasopressin infusion rises in urinary pH were observed in some of the NaCl and $NaHCO_3$ experiments, whereas in some of the NH_4Cl experiments the pH became somewhat lower. No changes in blood pH were recorded during the vasopressin administration.

Table V contains data for statistical comparison of the antidiuretic effect of vasopressin during the infusion of the three salt solutions. Although the three groups were compared without subdivision according to vasopressin dosage levels, significant differences became apparent. Urinary flow and free water clearance were significantly more depressed in the NaCl experiments as compared with $NaHCO_3$, with p values below 0.01. Still larger differences became apparent between the NH_4Cl and the $NaHCO_3$ experiments, with $p < 0.001$. The differences between the NaCl and the NH_4Cl experiments approached statistical significance, with $p \backsim 0.06$ for urinary flow and $p < 0.05$ for free water clearance. This comparison between the NaCl and the NH_4Cl data is somewhat biased by the fact that the NaCl series comprises more experiments with larger vasopressin dosages (above 1.5 μU per kg per minute) than the NH_4Cl series (six in the former as against two in the latter; see Tables II and III). If only the experiments with vasopressin dosage levels up to 1.5 μU per kg per minute were compared, the p values would be below 0.01 also for these two sets of experiments.

Discussion

The antidiuretic effect of vasopressin differed in magnitude with the three types of salt solutions employed in these experiments. Compared with the sodium chloride experiments, vasopressin had a more pronounced effect in the ammonium chloride experiments and a much less effect in the sodium bicarbonate experiments.

Among the factors affecting urinary flow and

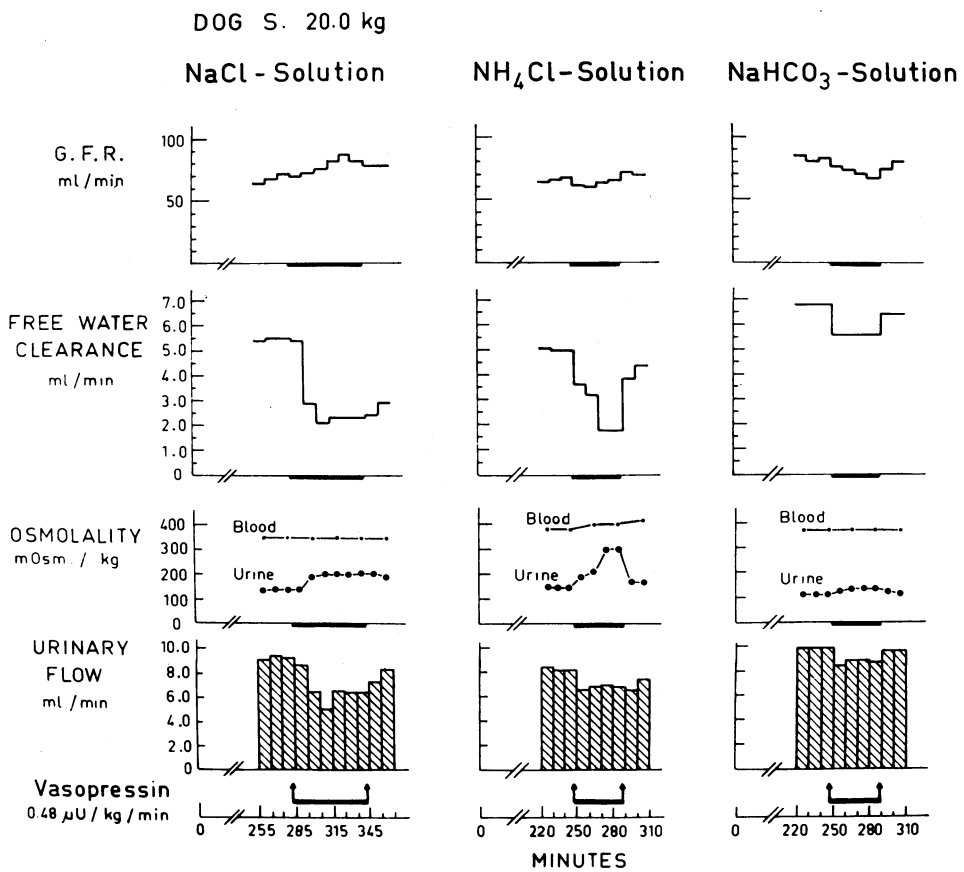

FIG. 4. CHANGES IN URINARY VOLUME, OSMOLALITY, AND FREE WATER CLEARANCE IN THREE SEPARATE EXPERIMENTS ON DOG S WITH THREE DIFFERENT INFUSIONS.

free water clearance, apart from the endogenous and exogenous antidiuretic hormone, changes in the glomerular filtration rate and in total solute excretion need to be considered.

In the majority of instances, changes in urinary flow were accompanied by a steady glomerular filtration rate, whereas in part of the remainder the filtration rate changed in a direction opposite to that of the urinary flow. Moreover, changes in filtration rate in both directions occurred with about equal frequency in the experiments with all three types of salt solutions. The differences in the vasopressin effect observed in these experiments cannot be connected, therefore, with any changes in the glomerular filtration rate.

The effect of solute excretion on the urinary concentration and on the response to vasopressin is of major importance, especially with high rates of solute excretion (12). However, it is safe to assume that at persistently low levels of urinary osmolality during the control periods, an antagonistic effect of the solute excretion on the urinary concentration mechanism can be excluded. Actually, a pronounced antidiuretic response to vasopressin was seen even with high solution excretion rates in all three groups of experiments, whereas, on the other hand, vasopressin failed to reduce urinary flow in some of the sodium bicarbonate experiments even at low rates of solute output. Thus, the differences in the response to vasopressin among the three groups of experiments cannot be related to the magnitude of the solute excretion.

We may conclude, therefore, that the observed differences in the response to vasopressin were caused by the changes in the composition of the body fluids and of the urine, brought about by the different salt solutions. During the infusion

of an alkaline solution and the secretion of urine with a high pH, a relative vasopressin insensitivity obtained, whereas the infusion of an acid solution, by which the urinary pH was lowered, enhanced the antidiuretic effect of vasopressin.

It cannot be stated, however, from these experiments, whether the changes in the urine, i.e., the urinary pH and the excess or relative lack of certain ions, were the deciding factors, or whether the varying response to vasopressin was due to more subtle ionic changes in the plasma or the tubular cells. For the sake of brevity, in the following discussion mainly the changes in pH will be considered, although other changes on both sides of vasopressin-sensitive membranes may be equally important.

Studies on the transfer of water through the skin of the intact frog and toad and through the isolated toad bladder have shown that in these preparations, too, the effect of vasopressin depends on the ionic composition of the fluid on both sides of the membrane (13–18). The importance of the pH in particular has been demonstrated by Bentley (14), who found that the permeability of the toad bladder to water, which was increased by Pituitrin, returned to control values when the pH of the bathing solution on the serosal side was reduced from 7.6 to 6.8 or below. Schwartz and co-workers confirmed this observation (17) and reported also that with constant pH the vasopressin-induced permeability decreased when the P_{CO_2} on the serosal side was raised (18). Orloff and Handler have made analogous observations on the pH effect with theophylline, which acts on the toad bladder in a similar way to vasopressin (19).

Although our *in vivo* experiments can be compared only with caution to these *in vitro* studies, the following remarks seem appropriate. In the membrane experiments it is the lowering of the pH at the serosal surface of the bladder or skin that caused a decrease in vasopressin sensitivity, whereas in the experiments described here the rise in pH at the mucosal surface of the tubular lumen caused a similar response. Thus, the common feature of both types of experiments would be the difference in pH obtaining across the membranes, a rise in pH at the outer (epithelial) side causing the same effect as lowering the pH on the inner (serosal) surface.

TABLE I

Effect of vasopressin in six dogs during the infusions of three different salt solutions; changes in urinary flow, urinary osmolality, and free water clearance

	Urinary flow	Urinary osmolality	Free water clearance
	ml/min	*mOsm/kg*	*ml/min*
1. Dog S, 0.48 μU/kg/min			
NaCl	9.1 → 5.3	140 → 200	5.4 → 2.3
NH_4Cl	7.3 → 6.8	150 → 300	4.5 → 1.8
$NaHCO_3$	9.8 → 8.5	113 → 126	6.7 → 5.5
2. Dog U, 0.48 μU/kg/min			
NaCl	4.0 → 4.3	161 → 168	2.2 → 2.2
NH_4Cl	4.5 → 2.6	161 → 390	2.7 → 0.1
Dog U, 0.72 μU/kg/min			
NaCl	3.8 → 3.4	163 → 176	2.5 → 2.0
$NaHCO_3$	3.9 → 3.9	161 → 161	2.4 → 2.4
3. Dog W, 0.48 μU/kg/min			
NaCl	4.4 → 3.1	123 → 187	3.0 → 1.6
NH_4Cl	4.4 → 1.4	133 → 304	2.7 → 0.2
$NaHCO_3$	5.1 → 4.9	113 → 163	3.6 → 2.8
4. Dog X, 0.48 μU/kg/min			
NaCl	6.7 → 5.6	133 → 164	3.9 → 2.8
NH_4Cl	7.3 → 1.8	133 → 426	4.3 → 0.6
$NaHCO_3$	5.8 → 5.7	183 → 186	2.4 → 2.4
5. Dog Y, 0.72 μU/kg/min			
NaCl	6.0 → 5.2	118 → 168	3.9 → 2.6
NH_4Cl	4.1 → 2.3	109 → 455	2.9 → 3.8
$NaHCO_3$	5.5 → 5.0	133 → 150	3.1 → 2.5
6. Dog Z, 0.72 μU/kg/min			
NaCl	5.0 → 4.3	130 → 155	2.9 → 2.1
NH_4Cl	7.7 → 1.5	109 → 436	5.0 → 0.5
$NaHCO_3$	5.4 → 6.7	100 → 100	3.6 → 4.5

In human and experimental diabetes insipidus Alexander, Filbin, and Fruchtman (20) were unable to raise the urinary concentration to normal by the administration of vasopressin, and they made the observation that in these experiments the urinary hydrogen concentration was always decreased. In severe human diabetes insipidus we have found that a single injection of 0.02 to 0.03 U of Pitressin during the infusion of sodium bicarbonate solution failed to produce antidiuresis, whereas the same amounts were effective during the infusion of sodium chloride solution (21). Curtis and de Wardener (22) repeated these experiments in two patients with less severe diabetes insipidus. Although these authors obtained antidiuresis during sodium bicarbonate infusions, their figures also show a diminished response to vasopressin during the secretion of alka-

TABLE II

Changes in urinary flow (V), glomerular filtration rate (GFR), urinary osmolality (U_{osm}), free water clearance (FWC), osmolar excretion ($U_{osm} \times V$), and urinary pH during vasopression infusion in dogs receiving hypotonic sodium chloride solution

Dog	Vaso-pressin	V		Difference % of control	GFR		U_{osm}		FWC		Difference % of control	$U_{osm} \times V$		Urinary pH
		Control	Vasopressin*		Control	Vasopressin*	Control	Vasopressin*	Control	Vasopressin*		Control	Vasopressin*	
	μU/kg/min	*ml/min*			*ml/min*		*mOsm/kg*		*ml/min*			*μOsm/min*		
R	0.48	8.0	6.2	−22.5	81	80	126	206	5.2	2.8	−46.8	1,010 (1,550)	1,275	7.0–7.0
S	0.48	9.1	5.3	−41.8	69	83	140	200	5.4	2.3	−57.4	1,272	1,060	7.0–7.0
U	0.48	4.0	4.3	+ 7.5	45	45	161	168	2.2	2.2	0.0	644	722	7.0–7.0
W	0.48	4.4	3.1	−29.5	56	56	123	187	3.0	1.6	−46.4	542	580	7.0–7.0
X	0.48	6.7	5.6	−16.4	73	68	133	164	3.9	2.8	−28.2	890	915	6.6–6.8
U	0.72	3.8	3.4	−10.5	38	36	163	176	2.5	2.0	−20.0	620	598	7.0–7.0
Y	0.72	6.0	5.2	−13.3	88	85	118	168	3.9	2.6	−33.3	710	865	7.0–7.1
Z	0.72	5.0	4.3	−14.0	83	86	130	155	2.9	2.1	−27.6	655	675	7.0–6.8
O	0.86	7.7	7.0	−10.0	108	91	145	140	4.4	4.0	− 8.0	1,116	980	6.0–6.5
R	1.5	8.7	6.4	−26.4	80	63	140	240	5.5	2.4	−56.2	1,218 (1,635)	1,535	7.0–7.0
J	2.5	7.5	4.9	−34.7	31	28	103	140	5.3	2.9	−45.7	772 (645)	686	6.0–6.0
R	3.0	10.0	5.2	−48.0	71	72	133	340	6.6	0.7	−89.4	1,330	1,770	7.0–7.0
O	5.15	5.0	2.3	−54.0	82	71	173	308	2.4	0.2	−91.7	865	708	6.0–7.0
O	6.4	7.0	2.7 (→ 8.5)†	−61.4	91	93 (→ 109)†	140	280 (→ 150)†	4.0	0.4 (→ 4.7)†	−89.3	980	756 (→ 1,275)†	6.5–7.0 (6.5)
J	7.6	4.8	2.1	−56.3	33	26	133	327	3.2	0.5	−83.1	638 (880)	686	6.0–7.0
J	12.6	7.7	4.6	−40.2	34	29	165	285	4.3	1.1	−74.8	1,270 (1,150)	1,310	6.2–7.0
Mean				−29.5							−49.9			
SD				20.7							29.5			

* The values given in these columns were obtained during 2 to 3 periods of vasopressin infusion when the effect was maximal. For the osmolar excretion also transitional values are recorded (in parentheses) when these were in a different direction from the final values.

† In this experiment an unexplained return towards control values occurred while the vasopressin infusion continued.

TABLE III

Changes in urinary flow, glomerular filtration rate, urinary osmolality, free water clearance, osmolar excretion, and urinary pH during vasopressin infusion in dogs receiving hypotonic ammonium chloride solution

Dog	Vaso-pressin	V		Difference % of control	GFR		U_{osm}		FWC		Difference % of control	$U_{osm} \times V$		Urinary pH
		Con-trol	Vaso-pressin*		Con-trol	Vaso-pressin*	Con-trol	Vaso-pressin*	Con-trol	Vaso-pressin*		Control	Vaso-pressin*	
	μU/kg/min	*ml/min*			*ml/min*		*mOsm/kg*		*ml/min*			*μOsm/min*		
S	0.27	8.2	7.7	−6.1	64	62	150	162	5.0	4.5	−10.0	1,230	1,250	6.0–6.0
K	0.37	6.9	5.7	−17.4	15.5†	12	125	136	3.8	3.1	−18.4	860	775	6.0–6.0
S	0.48	7.3	6.8	−6.8	60	55	150	300	4.5	1.8	−60.0	1,100	2,040	6.0–6.0
U	0.48	4.5	2.6	−42.0	37	34	161	390	2.7	0.1	−96.3	725	1,015	6.0–7.0
W	0.48	4.4	1.4	−68.2	40.5	46.5	133	304	2.7	0.2	−92.6	585	426	7.0–6.7
X	0.48	7.3	1.8	−75.3	67	69	131	426	4.3	−0.6	−114.0	950	770	7.1–7.1
S	0.72	7.3	6.6	−9.6	55	57	170	266	4.3	1.9	−55.8	1,240	1,755	6.0–6.0
Y	0.72	4.1	2.3	−44.4	67	66	109	455	2.9	−3.8	−231.0	440	1,035	7.0–7.1
Z	0.72	7.7	1.5	−80.5	70	67	109	436	5.0	−0.5	−110.0	835	653	6.7 6.8
K	0.74	9.3	4.8	−59.1	20	15	112	180	5.9	1.7	−71.2	1,040 (1,130)	864	6.0–6.0
K	1.5	7.8	2.2	−71.8	19	14	136	307	4.4	0.02	−99.5	1,060 (570)	676	6.0–6.0
K	3.0	4.5	1.9	−57.8	16	16	132	310	2.5	0.02	−99.2	593	590	6.0–6.0
P	6.5	8.8	1.0	−88.6	63	68	111	326	5.8	0.0	−100.0	975 (1,100)	326	6.0–6.0
Mean				−48.3							−89.1			
SD				29.6							52.0			

* See footnote, Table II.

† Dog K had a very low GFR, possibly due to renal disease. Water and solute excretion and concentrating ability were comparable to those in the other dogs.

TABLE IV

Changes in urinary flow, glomerular filtration rate, urinary osmolality, free water clearance, osmolar excretion, and urinary pH during vasopressin infusion in dogs receiving hypotonic sodium bicarbonate solution

Dog	Vaso-pressin	V		Difference % of control	GFR		U_{osm}		FWC		Difference % of control	$U_{osm} \times V$		Urinary pH
		Con-trol	Vaso-pressin*		Con-trol	Vaso-pressin*	Con-trol	Vaso-pressin*	Con-trol	Vaso-pressin*		Control	Vaso-pressin*	
	μU/kg/min	*ml/min*			*ml/min*		*mOsm/kg*		*ml/min*			*μOsm/min*		
L	0.28	4.4	6.5	+49.4	54	65	145	142	2.4	3.8	+55	632	925	7.0–7.0
S	0.48	9.8	8.5	−13.3	83	72	113	126	6.7	5.5	−17.9	1,100	1,075	7.0–7.6
W	0.48	5.1	4.9	−3.9	50	60	113	163	3.6	2.8	−22.2	575	800	7.2–7.4
X	0.48	5.8	5.7	−1.7	81	80	183	186	2.4	2.4	0.0	1,060	1,060	8.3–8.4
L	0.55	6.7	10.8	+61.2	62	70	138	140	4.1	6.6	+61.7	925	1,510	7.0–7.0
M	0.6	5.7	11.1	+94.7	65	68	82	84	4.2	8.1	+90	468	933	7.4–7.4
U	0.72	3.9	3.9	0.0	38	39	161	161	2.4	2.4	0.0	630	630	7.8–8.0
Y	0.72	5.5	5.0	−9.1	71	72	133	150	3.1	2.5	−19.0	730	760	7.7–8.1
Z	0.72	5.4	6.7	+24.0	69	66	100	100	3.6	4.5	+25.0	565	670	7.3–7.5
M	1.15	10.7	11.4	+6.5	68	69	83	120	7.9	7.2	−8.9	890	1,370	7.4–7.4
M	1.5	12.2	11.0	−9.8	65	85	100	127	8.2	6.4	−22.6	1,220 (1,550)	1,400	7.4–7.6
M	3.0	11.1	9.5	−14.4			127	166	6.8	4.2	−37.3	1,410	1,580	7.6–7.6
L	5.5	10.8	6.5	−39.8	70	64	140	243	6.6	2.3	−64.9	1,510 (1,300)	1,580	7.0–7.5
M	6.0	7.5	3.4	−54.7	74	57	120	240	4.6	1.0	−78.0	900	815	7.6–7.6
L	10.0	8.3	7.3	−12.0	67	65	194	226	4.0	2.8	−29.3	1,610 (1,700)	1,650	8.0–8.0
Mean				+5.1							−1.4			
SD				35.2							46			

* See footnote, Table II.

TABLE V

Statistical evaluation of the differences in the effect of vasopressin on urinary flow and free water clearance during the infusion of NaCl, NH_4Cl, and $NaHCO_3$ solutions

	D*	SD†	t	p
A. Urinary flow				
$NaCl/NaHCO_3$	34.6	10.4	3.32	<0.01
$NH_4Cl/NaHCO_3$	53.4	12.2	4.37	<0.001
$NaCl/NH_4Cl$	18.8	9.71	1.93	~0.06
B. Free water clearance				
$NaCl/NaHCO_3$	46	14.0	3.2	<0.01
$NH_4Cl/NaHCO_3$	85.7	18.6	4.6	<0.001
$NaCl/NH_4Cl$	39.2	16.1	2.43	<0.05

* D = difference between the means of per cent changes obtained from Tables II to IV.

† SD = standard deviation of the differences of the means.

line urine. In this connection it should be pointed out that the differences in responsiveness to vasopressin, as described in the present experiments and as observed in diabetes insipidus, were only found with small quantities of vasopressin and in the complete or nearly complete absence of endogenous antidiuretic hormone; with larger, albeit still submaximal, doses of vasopressin, the differences tended to disappear. This finding may explain why a dependence of the vasopressin effect on the ionic composition of body fluids and urine has so far escaped attention.

As to the clinical observation of polyuria with alkaline urine, our observations may furnish an explanation for the diminished renal concentration power in some of these conditions. However, the role played in these conditions by the pH of the urine and by other peculiarities of its ionic structure, or by the composition of the plasma, needs further study.

Summary

Dogs anesthetized with sodium thiopentone and ethanol were given intravenous infusions of hypotonic solutions of sodium chloride, ammonium chloride, and sodium bicarbonate, at a rate of 7.4 ml per minute, until a constant flow of hypotonic urine was obtained. Vasopressin was then infused at a constant rate in amounts from 0.27 to 12.6 μU per kg per minute. Urinary flow, pH, and osmolality and free water clearance and glomerular filtration rate were determined. It was found that during the infusion of sodium chloride, at urinary pH between 6 and 7, vasopressin caused a reduction in urinary flow and a rise in urinary osmolality, with a fall in free water clearance, even in the smallest amounts given. A still larger antidiuretic effect was obtained with ammonium chloride, at urinary pH of 5.6 to 7.1. In contrast, during the infusion of sodium bicarbonate, at a urinary pH of 7.3 to 8.4, the antidiuretic effect of vasopressin was much less apparent. The differences between either the NaCl or the NH_4Cl experiments and those carried out with $NaHCO_3$ were highly significant; those between the NaCl and the NH_4Cl experiments approached statistical significance.

The changes in urinary flow and free water clearance were not correlated with changes in glomerular filtration rate and in total solute excretion.

It is concluded from these experiments and from analogous observations in human diabetes insipidus that the antidiuretic effect of vasopressin is modified by the administration of acid and of alkaline salt solutions. During the infusion of alkaline solutions the renal tubules show a decreased responsiveness to exogenous vasopressin, whereas the tubular sensitivity to vasopressin is enhanced during the administration of an acid solution.

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