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Influence of Histamine on Electrolyte and Water Handling of the Canine Kidney (39860)

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Several chemically distinct vasodilators, among them acetylcholine, bradykinin, and PGE, have been shown to increase water and electrolyte excretion when infused into the renal artery (1-9). This has been thought to be due to their common ability to alter renal hemodynamics. The ubiquitous substance histamine, a potent vasodilator, appears to be another to add to the group, but its effect on urine volume differs markedly depending on whether it is infused into a systemic vein, which results in oliguria, or into the renal artery, when polyuria ensues. In the present investigation, the polyuria resulting from intra-arterial infusion has been examined further, particularly with reference to the free-water and electrolyte clearance. A remarkable constancy of glomerular filtration rate, in the face of increases in renal blood flow, has made this an interesting agent to investigate because the sodium load to the nephrons remains essentially constant as a consequence. Thus, the possible role of physical factors in the nephrons' reabsorptive mechanisms for water and salt reabsorption could be further explored.

Methods. This study was performed on 13 mongrel dogs ranging 17-24 kg in weight (average 19). The animals were anesthetized with sodium pentobarbital, 30 mg/kg, in 0.9% saline. Constancy of anesthesia was maintained with periodic administration of small adjunct doses of the anesthetic agent. The preoperative procedure included removal of food for 18-24 hr, but the animals were allowed free access to water during this period.

The right and left femoral arteries and right femoral vein were isolated and catheterized. Mean arterial blood pressure (MABP) was measured through the right femoral arterial catheter with a Statham P23Db pressure transducer and a Brush recorder. Saline solution (0.9%) containing creatinine and *p*-aminohippurate (PAH) was infused through the venous catheter at a minimal rate (0.2 ml/min) so as not to disturb the fluid balance. An initial 25-ml priming solution of PAH and creatinine in 0.9% saline was injected intravenously to establish plasma levels of PAH averaging about 3 mg/100 ml, and of creatinine, 20 mg/100 ml. A catheter was placed in the left femoral artery for withdrawal of blood samples for clearance analysis. The washed cells were returned to the animal in a volume of dextran equal to that of the plasma used for analyses.

The left renal vessels were isolated, retroperitoneally, through a flank incision. A catheter was placed in the ureter. The spermatic vein was catheterized, with the catheter tip placed at the junction of the renal vein. Left renal blood flow was measured with an electromagnetic flow meter probe (Carolina Medical Electronics) placed on the left renal artery.

Plasma and urine samples were taken for the measurement of concentrations of Na^+, Ca^{2+}, K^+, creatinine, PAH, and total osmolality. Total urinary and plasma electrolytes were measured by atomic-absorption spectrophotometry. Plasma ionized Ca^{2+} was taken as 50% of total calcium (10). Creatinine was measured in urine and trichloroacetic acid-plasma filtrate by the method of Kennedy *et al* (11). The concentration of PAH was measured by the method of Smith et al (12), and total osmolality was measured by freezing-point depression on an Advanced Instruments osmometer.

The general protocol of the experiment was to allow 1 hr following completion of surgery, at which time the priming injection was given and infusion of maintenance solution was started, before collection of urine and blood samples was begun. Paired collection periods of 15-min duration each were alternated with paired 15-min control pe-

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riods, with a 15-min discard period preceding the paired collections. For the experiments in which histamine was infused, the infusion was begun 7.5 min prior to the paired experimental urine period collections and continued for the two 15-min periods. A total of 14 collection periods was made in each experiment.

In eight animals, all males, histamine dihydrochloride in saline was infused directly into the left renal artery at the following rates: 7.5, 15, and 30 μg/min. These dosages were given in a randomized manner, alternating with control periods. The average rates per 100 g kidney weight were 14.5, 29, and 58 μg/min, respectively.

Control experiments were done in five animals (four males, one female) for the time period utilized in the histamine infusion periods (total of 6 hr).

Student's *t* test for equal and unequal sample sizes was applied to the data to determine the significance of the changes within a group of animals [Handbook of Chemistry and Physics," 45th ed., p. A-109. The Chemical Rubber Co., Cleveland, Ohio (1964-1965)].

Results. Control observations. There were no statistically significant hemodynamic changes, although there was a slight tendency for renal blood flow (RBF) and glomerular filtration rate (C_{CR}) to increase. Hence, filtration fraction (FF) (C_{CR}/DPF) remained constant. Likewise, electrolyte clearances, urine volume, and urine/plasma osmolality U/P_{Osm} showed no significant trends.

Effect of histamine on renal hemodynamics. The results appear in Fig. 1. Because the histamine dosage was given in a randomized manner (high to low, low to high, and random alteration of low to high), the data are presented as averages from low to high dosage relative to the paired control periods preceding and following. RBF showed a progressive increment as dosage of hista-

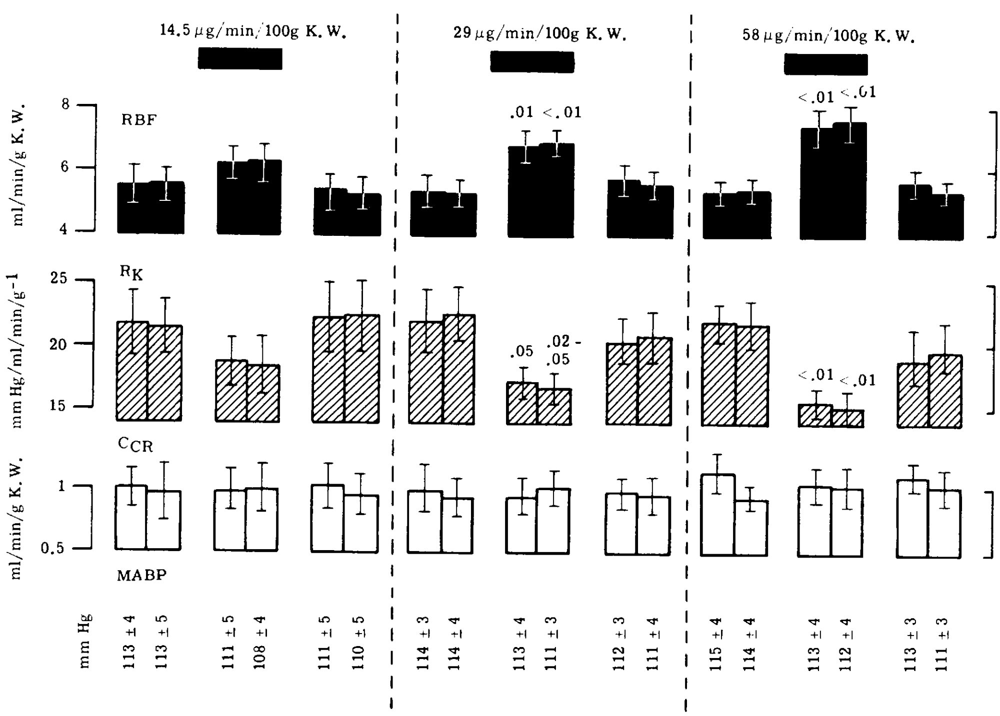

FIG. 1. Influence of intra-arterial histamine infusion on renal blood flow (RBF), renal vascular resistance (R_K), and glomerular filtration rate (C_{CR}). Values are means ± 1 SE. Paired periods of infusion are bracketed by paired control and recovery periods immediately preceding and following the infusion periods. The drug dosage was randomly infused. Note progressive increase in RBF in dose-related manner. R_K varies reciprocally. Observe constancy of C_{CR}. K.W.: kidney weight.

mine was increased, and R_K decreased inversely. However, GFR, as estimated by C_{CR}, remained constant. Minimal systemic effects were manifested, as judged by the minor decreases in MABP: The greatest average decrement was 5 mm Hg (4.4%) (group A), and the overall average decrease was only 2.3 mm Hg.

The constancy of GFR in the face of increased RPF (Fig. 2) resulted in decreases in FF. (See lower panel in Fig. 3.) The extraction of PAH was also reduced during the increased RPF caused by the histamine.

Influence of histamine in renal electrolyte clearance. The basic pattern observed was an increase in fractional clearance of Na^+, K^+, and Ca^{2+} as histamine infusion rates were increased. However, a better relationship appeared to be with the increment in RBF. Hence, the effects on electrolyte handling are presented as percentage changes in relation to the increase in RBF, experimental/control, in Fig. 3 and the succeeding Fig. 4. Control averages for these functions are shown in Table I. The graphs are arbitrarily divided into three sections, containing 16 clearance observations in each range. It will be observed that fC_{Na}, fC_{Ca}, and fC_K increased with RBF.

Histamine effect on urine volume and free water clearance. $\dot{V}_u$ (urine flow, ml/min) increased in direct proportion to RBF (Fig. 4). Concomitantly, there were significant decrements in $fT^c_{H_2O}$ and U/P_{Osm}. fC_{Osm} increased, but with statistical significance only in phase 3 of highest RBF.

Discussion. The present observations confirm earlier investigations showing a dose-related response of renal blood flow to histamine infusion, whether given intra-arterially (13) or systemically (14, 15). The agent acts by decreasing arteriolar resistance (6, 13), and the adjustments occur in both the afferent and efferent arteriolar segments in such a manner that glomerular filtration rate remains constant, as shown in the present investigation and by others (6, 13, 14, 15). Consequently, filtration fraction (FF) decreases. The action thus resembles that of other known dilator agents [acetylcholine (4, 7, 16), bradykinin (7, 8), and prostaglandin E (1–5, 9, 17)].

C_{PAH} does not increase as much as does total plasma flow, and this is reflected in the

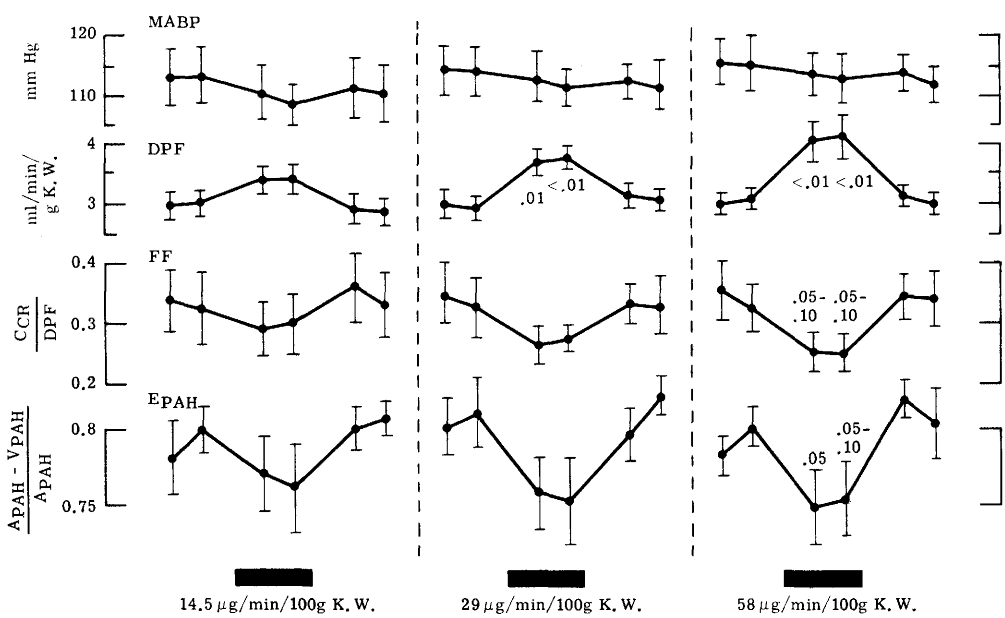

FIG. 2. Influence of histamine infusion on MABP (mean arterial blood pressure), DPF (direct plasma flow), FF (filtration fraction), and the extraction ratio of PAH (E_{PAH}) [$E_{PAH} = (A_{PAH}) - RV_{PAH})/A_{PAH}$. Values are means ± 1 SE for the same experiments depicted in Fig. 3. Random infusion of histamine was employed. Increments in DPF increase in dose-related manner; this results in decreases in FF, with observed constancy of GFR (C_{CR}).

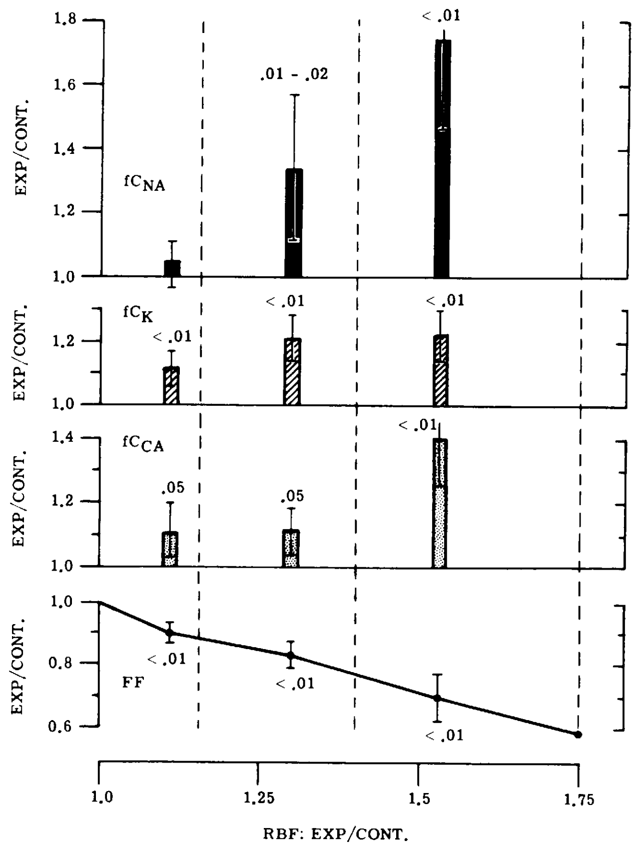

FIG. 3. Changes in ratio, experimental/control of fractional electrolyte clearance (fC_{Na}, fC_K, fC_{Ca}). Fractional clearance (f) = ratio of $C_x/C_{CR} \times 100$. The three vertical panels represent arbitrary averages (± 1 SE) of 16 clearance periods each. Note decrement of FF (bottom curve) in relation to increases in RBF (and DPF). See Table I for control averages.

decrease in E_{PAH}, which showed an inverse correlation with directly measured RPF (Fig. 2). This is an effect similar to that noted with intra-arterial infusion of acetylcholine (18). The view is favored here that it is likely that both cortical and medullary blood flow increase as a consequence of the vasodilatory action of histamine. It is probable that intrarenal pressure rises, as reflected in the increase in small vein pressure, and in turn presumably the peritubular capillary pressure rises; consequently, lymph flow is enhanced by histamine (6).

The influence of histamine on urine volume is quite different when comparing systemic intravenous infusion to intra-arterial. With systemic infusion an antidiuretic effect is observed (14, 15) which seems to be related to an increased release of ADH. Studies by Bhargava *et al.* (19) in dogs led them to conclude that histamine administered by intracerebroventricular route activated a central adrenergic mechanism which in turn caused the release of ADH. Bennett and Pert (20) produced an antidiuresis in cats by injection of histamine into the supraoptic nucleus.

However, intra-arterial infusion which at a given dosage maximizes the effect in the kidney, while minimizing systemic and central effects, resulted in polyuria (6, 13), and this was directly related to the increase in RBF. The increase was seen with constancy of GFR, and with progressive decrements in FF. Related changes of importance were the decrease in $fT^C_{H_2O}$ (negative free-water clearance) and U/P_{Osm}, implicating a diminution of urinary concentrating capacity. These alterations could result from washout of the gradient of osmolality due to increased med-

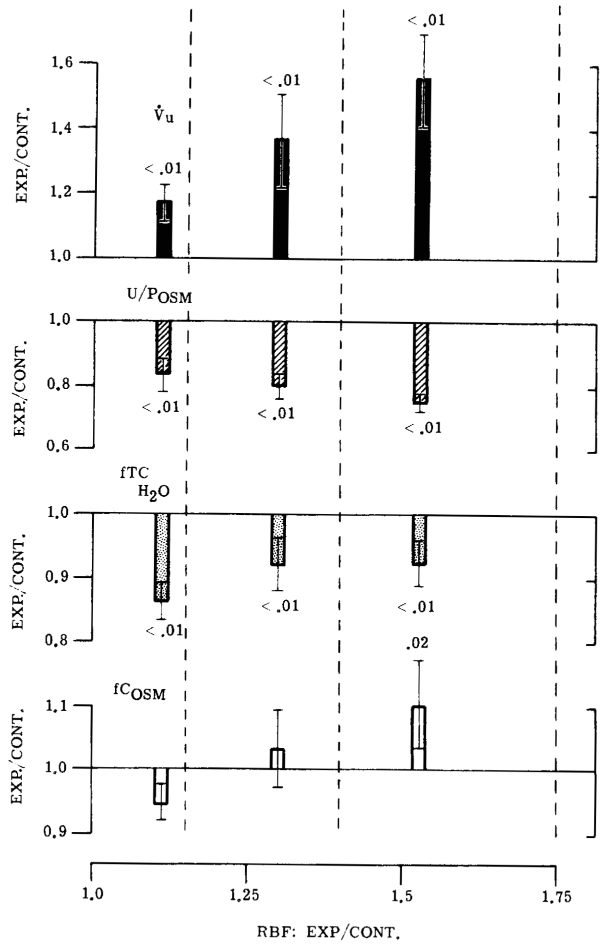

FIG. 4. Changes in ratio of urine volume in milliliters per minute ($\dot{V}_u$), urine-to-plasma ratio of osmolality (V/P_{Osm}), fractional negative free-water clearance ($fT^C_{H_2O}$), and fractional osmolar clearance (fC_{Osm}) to three stages of increase in RBF resulting from histamine infusion (mean ± 1 SE). The data are from the same experiments depicted in Fig. 3. See Table I for control averages.

TABLE I. CONTROL AVERAGES OF ELECTROLYTE AND FREE-WATER CLEARANCE DATA USED FOR COMPUTING RATIO, EXPERIMENTAL/CONTROL, IN FIGS. 3 AND 4 (n = 46).

Function	Mean	SE
fC_{Na}[a]	0.534	0.076
fC_K	18.70	1.10
fC_{Ca}	0.40	0.03
$\dot{V}_u$ (ml/min)	0.293	0.026
U/P_{Osm}	3.91	0.089
$fT^C_{H_2O}$	1.88	0.174
fC_{Osm}	5.45	0.174

[a] fC = Fractional clearance (C_X/C_{CR} × 100).

ullary blood flow, as demonstrated for histamine by Itskovitz *et al.* (23). Possibly, impairment of the collecting tubule responsiveness to ADH is involved.

It should be noted at this juncture that the fractional clearance of electrolytes and osmolar constituents likewise increased in relation to increments in RBF. In the light of this, a possible interpretation lies with the "physical factors" concept (16, 21, 22, 24). Transmittance of increased hydrostatic pressure to the peritubular capillaries, resulting from decreased arteriolar vascular resistance, and decreased plasma colloid osmotic pressure in this vascular segment, a consequence of the decrease in FF, could favor enhanced loss of water, Na^+, and other electrolytes by the proximal nephron, as viewed in the light of this theory. The altered forces would oppose the nephron-to-blood flux of water and contained electrolytes. This interpretation of the action of histamine has received support from O'Brien and Williamson (13). Increased delivery of H_2O and Na^+ to the diluting segment could result in an increase in free-water clearance (or reduction in $T^C_{H_2O}$) if sodium chloride delivered is reabsorbed here more completely than H_2O, according to current theory.

Summary. Intra-arterial infusion of histamine results in dose-related increases in RBF, while GFR remains constant, resulting in progressive decrease in FF. Renal extraction of PAH (E_{PAH}) decreased reciprocally with RBF, possibly a result of enhanced plasma flow rates. MABP remained quite stable. Increase in minute urine volume ($\dot{V}_u$), and fractional clearance (fC) of Na^+, K^+, Ca^{2+}, and osmality appeared to be related to the increments in blood flow, while simultaneous decrements in $fT^C_{H_2O}$ and U/P_{0sm} occurred. The physical factors hypothesis could account for the observed changes in urine volume and electrolyte clearance, but other factors must also be considered, such as loss of nephron-concentrating ability because of washout of the gradient of osmolality, a possible direct effect of histamine on the collecting duct H_2O permeability, or inhibition of ADH action.

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