EFFECT OF DIAPHYLLIN ON THE OSMOREGULATORY FUNCTION OF THE DOG'S KIDNEY

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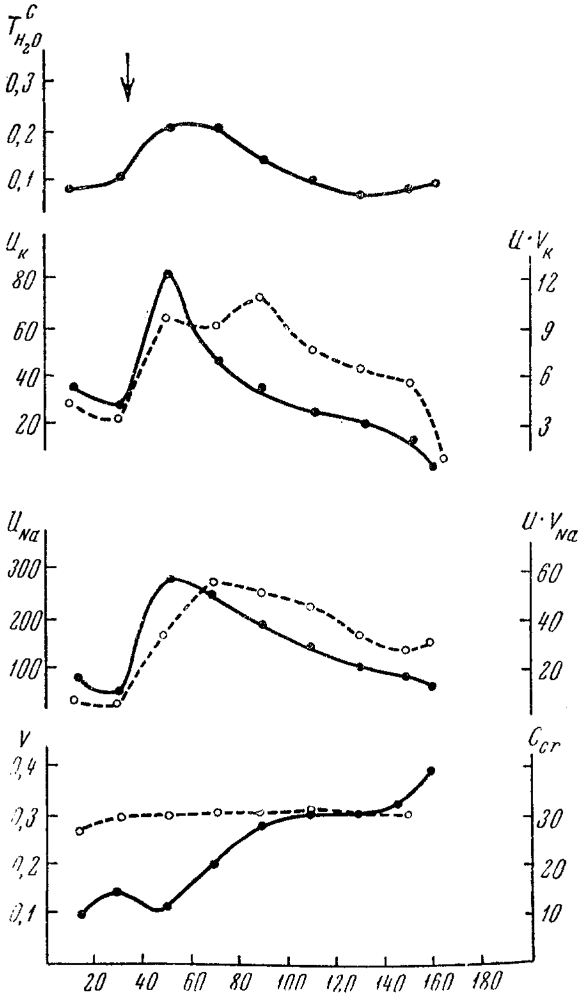
The increase in diuresis after administration of theophylline and its preparations is usually explained by an increase in the glomerular filtration and a decrease in the tubular reabsorption of water and salts [1, 3, 6, 8, etc.]. According to some investigators, the tubular effect is also attributable to the fact that xanthine derivatives depress

Dynamics of Changes in Kidney Function Following Administration of Diaphyllin

	Intravenous injection of 10 ml of 2.4% solution of diaphyllin		Intramuscular injection of 1 ml of 24% solution of diaphyllin	
	before injection	at maximum of effect	before injection	at maximum of effect
Diuresis (in ml/min)	0.15 ±0.035	0.30 ±0.023	0.13 ±0.019	0.22 ±0.035
	P = 0.009		P = 0.05	
Concentration of sodium (in meq/liter)	50 ±18	140 ±20	42 ±7.8	121 ±29.6
	P = 0.016		P = 0.04	
Excretion of sodium (in μeq/min)	6.45 ±2.1	36.7 ±3.2	4.4 ±1.2	25 ±4.5
	P < 0.001		P = 0.004	
Concentration of potassium (meq/liter)	57.3 ±19	80 ±8.5	39.4 ±7.2	60.5 ±7
	P > 0.1		P = 0.07	
Excretion of potassium (in μeq/min)	7.35 ±1.8	23.6 ±2.9	5.15 ±0.9	12.5 ±2.02
	P = 0.002		P = 0.01	
Osmolar concentration (in mosm/liter)	715 ±123	715 ±106	726 ±88	755 ±91
Ratio between osmolar concentrations of urine/plasma	2.38 ±0.44	2.36 ±0.16	2.3 ±0.28	2.44 ±0.33
Osmolar clearance (in ml/min)	0.27 ±0.052	0.73 ±0.085	0.27 ±0.026	0.45 ±0.059
	P = 0.003		P = 0.03	
Hyperosmotic reabsorbtion of water (in ml/min)	0.15 ±0.01	0.42 ±0.066	0.14 ±0.018	0.24 ±0.049
	P = 0.007		P = 0.09	
Glomerular filtration (creatinine clearance, in ml/min)	29 ±1.8	42 ±9.9	33 ±2.0	30 ±2.6
	P > 0.1			



Effect of diaphyllin on the diuresis, filtration, elimination of sodium and potassium, and reabsorption of osmotically free water in a dog. Arrow—moment of injection of diaphyllin (intramuscularly). Along the axis of ordinates, from top to bottom, on the left: diuresis in ml/min (V), sodium concentration in meq/liter (U_{Na}), potassium concentration in meq/liter (U_K), hyperosmotic reabsorption of water (in ml/min)($T^C_{H_2O}$); on the right: filtration as creatinine(in ml/min)(C_{Cr}), excretion of sodium (in μeq/min)(UV_{Na}), excretion of potassium (in μ/meq/min)(UV_K); along the axis of abscissas—time (in min); the continuous lines and the dark circles correspond to the indices on the ordinate on the left; the broken lines and the unshaded circles to the ordinate on the right.

the action of antidiuretic factors on the kidney [5]. However, the suggestion that the reabsorption of water by the kidney is reduced under the influence of the xanthines was made, not as a result of direct determination of the concentration of osmotically active substances in the urine, but purely as a logical assumption based on an increase in the volume of urine excreted. The diuresis is known to be increased not only as a result of a decrease in the tubular reabsorption of water, as in water diuresis, but also as a result of an increase in the excretion of osmotically active substances when the excretion of osmotically free water, on the other hand, is decreased.

To elucidate the mechanism of the diuretic action of the xanthines, it is important to determine their effect on the elimination of water by the kidney. If the increase in diuresis under the influence of theophylline and its preparations were attributable, even partly, to a decrease in the permeability of the tubule wall to water and to depression of the action of antidiuretic substances, the mechanism of xanthine diuresis would differ in principle from the mechanism of action of the other diuretics. The existing diuretics are natriuretics and not hydruretics; the diuresis is increased as a result of depression of the reabsorption of salts and an osmotic, and not a water, diuresis develops.

The object of the present investigation was to analyze the mechanism of the xanthine diuresis.

EXPERIMENTAL METHOD

The investigation was carried out on four dogs with ureters exteriorized separately by Orbeli's method. Altogether 23 experiments were performed. The dogs were given an ordinary intake of water and salt. On the day of the experiment the animals received neither water nor food. Diaphyllin (Gedeon Richter) was injected intravenously in a dose of ~0.5 ml/kg body weight (8-10 ml of a 2.4% solution) or intramuscularly in a dose of 1 ml of a 24% solution.

The content of sodium and potassium in the urine and blood serum was determined by means of a Zeiss flame photometer, and the osmolar concentration of these fluids was measured by a cryoscopic method [2]. The glomerular filtration was calculated from the clearance of endogenous creatinine. The chemical estimation of the creatinine was carried out by the method of Bonsnes and Tosca. For the analysis of the various aspects of kidney function, formulas based on the principle of clearance were used.

EXPERIMENTAL RESULTS AND DISCUSSION

The intravenous or intramuscular injection of diaphyllin in all the experiments caused an increase in diuresis and an increase in the concentration of sodium and potassium in the urine (see table). The natriuresis developing under the influence of diaphyllin was due, in all probability, to depression of the reabsorption of sodium in the tubules and not to an increase in filtration. This hypothesis is supported by the results of experiments in which the preparation was injected by different methods. After intramuscular injection no significant change in filtration took place, whereas the sodium concentration in the urine and its excretion in the urine increased almost to the same extent as after intravenous injection of diaphyllin.

The importance of the action of the preparation directly on the cells of the tubules became clear after analysis of the potassium excretion. Under the influence of the preparation not only the concentration of potassium in the urine, but also its excretion, increased. The increase in the excretion of potassium in the urine following intramuscular injection was about 250%, whereas the glomerular filtration was unchanged, but after intravenous injection, when the increase in filtration was 50% the potassium excretion increased to 329% of the level observed in the control period. It may be concluded from these results that diaphyllin has a direct tubular action—it depresses the reabsorption of potassium from the filtrate or stimulates the secretion of potassium into the urine. Hence, under the influence of diaphyllin the excretion of the main cations—sodium and potassium—by the kidney is increased.

The total concentration of osmotically active substances in the urine was changed in xanthine diuresis and remained higher than in the blood serum, although the volume of urine excreted was almost doubled. Consequently, the dominant factor in the mechanism of the diuresis developing after injection of diaphyllin was an increase in the excretion of salts by the kidneys and not a decrease in the permeability of the tubule wall to water. Under the influence of diaphyllin, the diuresis was of the osmotic and not of the water type.

Analysis of the osmoregulatory function of the kidney after injection of the preparation showed that the amount of reabsorbed osmotically free water not only was not reduced, as might be expected if diaphyllin had neutralized the action of the antidiuretic factors, but was considerably increased (see table). The mean data from eight experiments are given in the table. The dynamics of the effect of diaphyllin in a typical experiment is shown in the figure. The hyperosmotic reabsorption was determined from the amount of osmotically free water absorbed in the terminal portions of the tubules from the primary urine, isoosmotic with the blood plasma. Evidently this amount was the greater the more permeable the tubule wall to water and the higher the osmotic gradient in the interstitial tissue of the renal medulla. The results obtained demonstrate an increase in the hyperosmotic reabsorption of water in diaphyllin diuresis.

The results obtained in dogs do not agree with those reported by Buchborn and co-workers [7], who described a decrease in the hyperosmotic reabsorption of water after intravenous injection of euphyllin (aminophylline) in man. They explained this effect by a decrease in the gradient in the interstitial tissue of the renal medulla as a result of an increase in the blood flow through this part of the kidney. The reason for the disagreement between the results may lie either in the difference in the effect of diaphyllin on the blood flow of the renal medulla in man and the dog, or in some unexplained technical variation in the conduct of the experiments in the two cases. It is also very probable that the diuretic effect of diaphyllin depends on the relative degree of its effect on the hemodynamics and on the renal tubules. This comes to light clearly when the experiments with intravenous and intramuscular injection of the drug are compared. The intravenous injection of diaphyllin led to a sharp change in the hemodynamics, which was accompanied by an increase in the glomerular filtration, an increase in the volume of tubular fluid, and a sharper increase in the diuresis and the excretion of osmotically active substances.

The results described suggest that diaphyllin increases the permeability of the tubule wall to water, for the hyperosmotic reabsorption of water increases. Indirect confirmation of this hypothesis is given by the observations of Schmitz [11] and of Mudge and Weiner [9]. Schmitz found that in dogs, when the diuresis was at a certain level, administration of theophylline led to a decrease in its value, despite an increase in glomerular filtration; he explained this effect by an increase in the reabsorption of water in the tubules. Mudge and Weiner also concluded from indirect evidence that the xanthines can increase the permeability of the renal tubules to water. The available data show that theophylline potentiates the action of the hormones of the neurohypophysis, by influencing one of the enzymes of the system responsible for the effect of these hormones [4,10]. Very probably the increase in the hyperosmotic reabsorption of water after injection of diaphyllin was due in part to potentiation of the action of the peptides of the pituitary on the kidney.

The results of the present investigation thus show that the increase in the diuresis in dogs after injection of diaphyllin is due not only to an increase in filtration but also to the action of the drug on the tubules, increasing the excretion of osmotically active substances (mainly salts of sodium and potassium) and of water, bound osmotically with them, from the kidney. In the conditions of diaphyllin diuresis the hyperosmotic reabsorption of water is increased, indicating the high permeability of the wall of the tubule to water. Consequently, the hypothesis suggested by certain investigators that the permeability of the tubules to water is diminished and the action of antidiuretic factors on the kidney is depressed by diaphyllin did not find experimental confirmation.

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