THE MECHANISM OF CHANGES IN WATER AND SALT METABOLISM IN LIVER PATHOLOGY

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In previous studies we have shown that experimental liver injury (in dogs) is accompanied by changes in urination [1]. In some animals diuresis progressively diminished even on maintenance of a carbohydrate diet, while in others inhibition of urination was observed only on a meat diet. The fall in diuresis could not be explained by changes in the rates of glomerular filtration and renal plasma flow. The increase in reabsorption of water in the kidney tubules plays the decisive role in the suppression of urination in all cases.

It is known that the rate of water reabsorption in the kidneys depends on the concentration of hypophysial antidiuretic hormone (ADH) in the blood. This concentration does not affect the glomerular filtration rate [9, 11, 19]. The blood ADH concentration is determined by the rate of its elaboration and, according to several workers, by the degree of inactivation in the liver [4, 10, 16, 21]. Therefore, a number of investigators explain the change in water metabolism in liver disease by the lack of ADH inactivation caused by injury to liver tissue. They note the increase in hormone content of the urine and blood serum in patients with liver pathology [8, 22]. However, other authors believe that abnormally and normally functioning livers neutralize ADH to the same extent and therefore its concentration in the blood and urine in such patients is within normal limits [5, 6, 17, 20].

In this paper we have studied the content of pituitary ADH in the blood of dogs with disturbed liver function. These studies were undertaken to elucidate the mechanism of antidiuresis during liver injury.

EXPERIMENTAL

The experiments were performed on ten dogs with gastric and urinary bladder fistulas. Five of the dogs were controls; in the other five liver function was disrupted by obstructing total bile flow or suturing the Eck-Pavlov fistulas. In all animals the state of diuresis, the basic processes of urine formation and the serum and urinary electrolytes were systematically studied by flame photometry (Zeiss model III photometer). In all, 286 experiments were performed. The blood ADH concentration in the dogs was determined by the biological method of Heller [12] in 29 experiments; assessment was made of the degree of diuresis inhibition in rats with constant water balance after intravenous injection of dog serum. The antidiuretic activity was expressed in microunits of pituitrin.

RESULTS

In control animals before administration of water, the antidiuretic activity of one ml of blood serum varied (within limits) up to five microunits of pituitrin, and at one hour after administration of water into the stomach (moment of maximum diuresis) the activity fell so that it could not be determined by the Heller method (Table 1).

In experimental dogs the antidiuretic activity was studied both when antidiuresis and tubular reabsorption of water were high, and when the animal was in a relatively good state and urine secretion rose and the level of tubular water reabsorption fell.

It appears that after impeding total bile outflow, in the period of intoxication and low diuresis, the blood serum antidiuretic activity in dogs rises sharply both before administration of water and at one hour after (see Table 1

TABLE 1. Antidiuretic Activity of 1 ml of Blood Serum (in microunits of Pituitrin) in Control Dogs and in Dogs with Experimental Liver Pathology

Name of dog	No. of expt.	Time after operation (in days)	Quantity of urine (in ml excreted at two hours after water loading	Antidiuretic activity	
				prior to admin. of water	one hour after admin. of water
Control dogs					
Blackie	1	–	–	1.5	0.0
"	2	–	–	0.0	0.0
Laddie	3	–	–	1.0	0.0
Brovka	4	–	–	5.0	0.0
Bezushka	5	–	–	2.0	0.0
Gray	6	–	–	1.0	0.0
Dogs with Obstruction to Total Bile Outflow					
Venerka	10	264	330.0	0.0	0.0
"	11	274	80.0	17.3	58.0
"	12	315	50.0	22.0	63.0
"	13	446	281.3	5.5	0.0
Laddie II	14	21	41.7	18.0	6.2
"	15	26	51.9	14.0	5.1
"	17	80	28.0	143.0	Not deter.
Kashtanka	19	14	42.3	262.0	200.0
Dogs with Eck-Pavlov fistula					
Whitey	20	164	94.0	66.0	11.0
"	21	215	–	14.0	10.8
"	22	288	624.8	4.0	0.0
"	24	329	58.0	118.0	60.0
Myshka	26	77	233.2	4.5	3.3
"	27	82	185.7	6.0	3.0
"	29	93	38.0	24.0	38.0

TABLE 2. Amount of Water Diuresis and Content of Uninary Electrolyte in Dog Kashtanka Before and After Obstruction of Bile Outflow

No. of expt.	Time after operation (in days)	Amount of urine excreted within two hours after admin. of water (in % of value of water admin.	Electrolyte content of urine excreted within two hours after admin. of water (in milliequivalents)		Na/K
			Na	K	
132	Before operation	114.0	18.23	2.83	6.44
134	11	30.1	13.86	7.68	1.80
135	13	11.8	1.07	4.68	0.23
138	20	12.4	1.20	5.03	0.24

TABLE 3. Effect of Cortisone on Diuresis and Antidiuretic Activity of Blood Serum in Dogs with Liver Pathology

Name of dog	No. of expt.	Period after operation (in days)	Diuresis at two hours (in ml)		Antidiuretic activity of one ml of serum	
			before cortisone	after cortisone	before coritsone	after cortisone
Laddie II	235	81	28.0	306.0	143.0	0
"	256	87	38.0	198.0	39.0	0
Whitey	264	338	56.0	182.0	21.0	0

experiments Nos. 11, 12, 14, 15, 17, 19). At a relatively high diuresis the antidiuretic activity of the serum remains within control limits (see Table 1) experiments Nos. 10 and 13). This phenomenon is observed in all animals with obstruction of bile outflow and with Eck-Pavlov fistula (see Table 1). In the dog Kashtanka obstruction to bile outflow led particularly quickly to antidiuresis. In this dog we also observed the highest level of serum antidiuretic activity—up to 262 microunits of pituitrin (see Table 1, experiment No. 19).

Thus, experimental injury to the liver leads to an increase in the level of ADH in the blood of the dog. This is explained either by a decrease in the inactivation of ADH in the liver or by an increase in hormone secretion by the pituitary gland. ADH increases water reabsorption in the renal tubules and inhibits diuresis.

In dogs with liver pathology we found a disruption in the secretion of electrolytes as well as changes in diuresis. In the first period of the pathologic process the secretion of both sodium and potassium decreased. The Na/K index of the urine was not significantly altered (38 experiments).

With symptomatic intoxication the excretion of sodium in the urine fell significantly with the sharp drop in urination. The data obtained in experiments on the dog Kashtanka are presented as an example (Table 2).

Changes in electrolyte excretion are related, evidently, to the increase in aldosterone content of the blood, which, according to the majority of authors [13, 23, and others] occurs with liver pathology.

Thus, it may be hypothesized that change in the blood concentration of ADH and aldosterone play a decisive role in the mechanism of disturbed water and salt metabolism in liver pathology.

The questions arises whether by lowering one of the stated hormones in the blood we may (and to what degree) restore the disruption in water and salt metabolism caused by disturbed liver function. According to the data in the literature, cortisone has an inhibitory effect on the secretion of ADH [7, 22]. Some authors consider that cortisone promotes inactivation of ADH by hepatic cells and thus lowers the hormone concentration in the blood [2, 3]. Many investigators, however, deny such antagonism between ADH and cortisone [14, 15, 18].

We decided to study the effect of cortisone on diuresis and electrolyte excretion in the dog. It appeared that cortisone, injected intravenously in a dose of 2.5 mg/kg, removes the inhibition to urination in dogs with disturbed liver function (60 experiments). An increase in diuresis occurs because of the decrease in blood ADH concentration (Table 3).

It is interesting that cortisone in dogs which are in a state of acute intoxication removes the inhibition to diuresis not by altering the electrolyte excretion. In healthy animals the same dose of hormone is statistically certain to raise the sodium excretion and to depress potassium excretion. Evidently cortisone, by lowering the ADH concentration in the blood of the dog with liver injury, may not show a significant effect on salt metabolism, while the aldosterone concentration in the organism is elevated.

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