MECHANISM OF ACTIVE TRANSPORT OF Ca^{++} FROM BLOOD INTO BILE

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Experiments on dogs and rabbits have shown that the increase in calcium excretion with the bile after introduction of its salts into the gastro-intestinal tract or portal vein is accompanied by increased ATPase and alkaline phosphatase activity of the liver tissue. Elimination of calcium from the blood into the bile in dogs takes place against the concentration gradient, demonstrating the active character of transport of these ions by the liver cells.

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Existing hypotheses concerning the mechanism of passage of electrolytes into the bile by trans- and intercellular filtration through capillary membranes [3] and by active secretion [1] are based on data for the bile–plasma ratio of monovalent ions, and do not take into consideration the special features of calcium transport. The membrane barrier between the blood and bile is known to be permeable only for substances of low molecular weight [2]. Consequently, because calcium has the ability to form complexes with proteins and other organic compounds, it cannot diffuse freely into the bile and a certain expenditure of energy is required to provide for its transport.

The object of the present investigation was to study the relationship between Ca^{++} transport from the blood into the bile, metabolism of phosphorous compounds, and the intensity of phosphorylation in the liver.

EXPERIMENTAL METHOD

Increased elimination of calcium from the bile was brought about in dogs and rabbits in long-term experiments by introduction of a 2.5% solution of calcium lactate (30 mg/kg body weight) into the duodenum, and in acute experiments by injection of 1% $CaCl_2$ solution directly into the portal vein. Electrolytes were determined by flame photometry, total and inorganic phosphorus by the Fiske–Subbarow method, alkaline phosphatase activity of the liver tissue by the use of Na-β-glycerophosphate, and ATPase activity by the use of adenosine-5-triphosphoric acid (incubation for 1 h and 20 min, respectively, at 37°). The results obtained were subjected to statistical analysis.

EXPERIMENTAL RESULTS

Long-term experiments on dogs in which calcium lactate was injected into the duodenum showed that during the first 15-30 min after administration of the salt its concentration in the bile increased from 8.1 ± 0.28 to 12.5 ± 42 meq/liter. During the next hour the calcium concentration was 32-48% over the control level, falling toward the end of the second hour to 11% over the control. There was a stimultaneous increase in the concentration of inorganic phosphorus from 15.6 ± 0.55 to 21 ± 1.26 mg%. The increase in concentration of inorganic phosphates was accompanied by a slight decrease in the fraction of organic phosphates.

The study of these processes in dogs and rabbits under acute experimental conditions showed that with an increase in the elimination of calcium by the liver, produced by infusion of $CaCl_2$ solution into the portal blood flow, the phosphatase activity of the liver was sharply increased.

The ATPase activity in dogs rose by a statistically significant degree (by 33.2%) after injection of $CaCl_2$ solution, and the alkaline phosphatase activity rose by 37.6%. In rabbits the alkaline phosphatase

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TABLE 1. Changes in Phosphatase Activity of Liver Tissue during Increase Ca^{++} Elimination with the Bile (M ± t)

Index	Dogs		Rabbits	
	control	2 h after infusion of $CaCl_2$	control	2 h after infusion of $CaCl_2$
ATPase activity of liver tissue (in mg inorganic P/g tissue)	7.23± 0.38(13)	9.63± 0.38(13) P < 0.001	14.55± 0.41(15)	15.36± 0.55(15) P < 0.1
Alkaline phosphatase activity of liver tissue (in mg inorganic P/g tissue)	3.90± 0.39(13)	5.37± 0.42(13) P < 0.02	2.17± 0.21(15)	3.21± 0.32(15) P < 0.01
Ca^{++} concentration in bile (in meq/liter	6.9± 0.5(13)	10.9± 1.0(13) P < 0.01	2.6± 0.08(15)	4.4± 0.45(15) P < 0.001
Elimination of total Ca with bile (in μeq/kg/h)	1.7± 0.21(13)	3.6± 0.42(13) P < 0.02	10.8± 0.88(15)	14.4± 1.48(15) P < 0.05

Note. Number of observations given in parentheses.

activity rose by more than 42%, but the increase in ATPase activity did not exceed 5.5% of the control value. Meanwhile, a marked increase was observed both in the concentration of Ca in the bile and also in the total Ca eliminated with the bile (Table 1). Its concentration in dogs rose by 57.9%, and the bile–plasma ratio reached 1.64 : 1. Whereas in carnivores, the calcium concentration in the bile is higher than in the blood plasma, in rabbits the bile–plasma ratio does not exceed 0.7 : 1.

After administration of $CaCl_2$ the calcium concentration in the bile increased during the next 2 h by more than 69%, reaching 4.4 ± 0.45 meq/liter compared with 5.9 ± 0.41 meq/liter in the blood plasma.

Differences between the calcium composition of the bile in carnivorous and herbivorous animals are evidently explained by the higher concentration of bile acids, lipoprotein complexes, and other osmotically active substances, which play an important role in the mechanism of Ca transport from the blood into the bile against the concentration gradient, in the bile of dogs. The high concentration of organic anions in the bile of dogs is also reflected in the concentration of monovalent ions. Whereas the sodium level in the bile of the carnivores was 8-15% higher than its concentration in the blood plasma, and the potassium concentration was 30-31% higher, in rabbits their concentrations in the bile were higher than in the plasma by 6-8 and 10-13%.

Analysis of these results indicates differences in the ability of the liver of dogs and rabbits to concentrate electrolytes in the bile. Since the bile of carnivores has a higher concentration than the blood, this indicates that the elimination of calcium is not a simple filtration process but one of active transport, involving the participation of ATPase and alkaline phosphatase enzyme systems and also the phosphate metabolism in the liver which is connected with their activity.

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