RATE OF SYNTHESIS OF BILE PHOSPHOLIPIDS IN THE LIVER IN VARIOUS FUNCTIONAL STATES

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The results of the author's previous investigations of the role of the bile-forming function of the liver in phosphorus metabolism are described elsewhere [1,2,4]. In chronic experiments on dogs with a fistula of the gall bladder, it was found that radioactive phosphate (P^{32}), when introduced into the alimentary tract or the blood stream, is quickly incorporated into the phospholipids of the bile.

The principal phospholipid in the bile in dogs is lecithin. Twenty four hours after administration of P^{32}, 99% of the total P^{32} contained in the bile is in the lecithin.

Special experiments have been performed to determine whether the phospholipids of the bile are reabsorbed and reutilized. The phospholipids obtained by the method of biosynthesis were administered to a dog by mouth. It was found that the lecithin of the bile is reabsorbed to a considerable degree in the intestine in an unsplit form. The use of the isotope dilution method has shown that the lecithin of the bile, when absorbed into the blood stream from the alimentary tract, does not pass directly into the composition of the newly secreted bile.

The present paper describes the results of further investigations undertaken to study the dynamics of the changes in the rate of synthesis of the phospholipids of the bile and blood in the liver in the period of development of hepatitis without jaundice, and to examine the influence of the circulation of bile in the body on the rate of synthesis of the biliary lecithin in the liver.

EXPERIMENTAL METHOD

Experiments were conducted on 20 dogs with a fistula of the gall bladder, formed by means of Schiff's (without ligation of the common bile duct) or Schwann's (with ligation of the duct) operation. As reported previously [3], despite great care of the animals, some time after the operation the dogs of this group developed hepatitis, and in these circumstances they were a convenient model for studying the pathological process in the liver.

On the day of the experiment, the dogs, in a fasting state, were given radioactive phosphate ($Na_2HP^{32}O_4$) in a mixture of milk (50-100 ml) and water (100 ml) in a dose of 100-200 pulses/min/g body weight.

Samples of bile and blood were taken 30, 60, 90, 120, 180, 240, 300, and 360 min, and 24 h after administration of the isotope. The total phosphorus content in the bile and its radioactivity were determined. From these results, the specific activity was calculated by the method described previously [3]. The fraction of the radioactive phosphorus of the bile incorporated into lecithin was found by chromatography of the bile on paper [1,2]. The experiments on the same dog were repeated at different times (up to 2 years) after the operation of forming the fistula of the gall bladder.

In some dogs with a Schiff's gall-bladder fistula the development of the pathological process in the liver was hastened by administration of carbon tetrachloride. At the end of the experiments, the liver of some animals was investigated histologically.

EXPERIMENTAL RESULTS

As reported previously, the course of the specific activity curves of the bile against time after administration of P^{32} was regular, despite the fact that the concentration of total phosphorus in the bile fluctuated. The maximal increase in the specific activity of the bile occurred 18-20 h after administration of the P^{32}. In the experiments to be described, the course of the curves remained regular, although a difference was clearly detected in the specific

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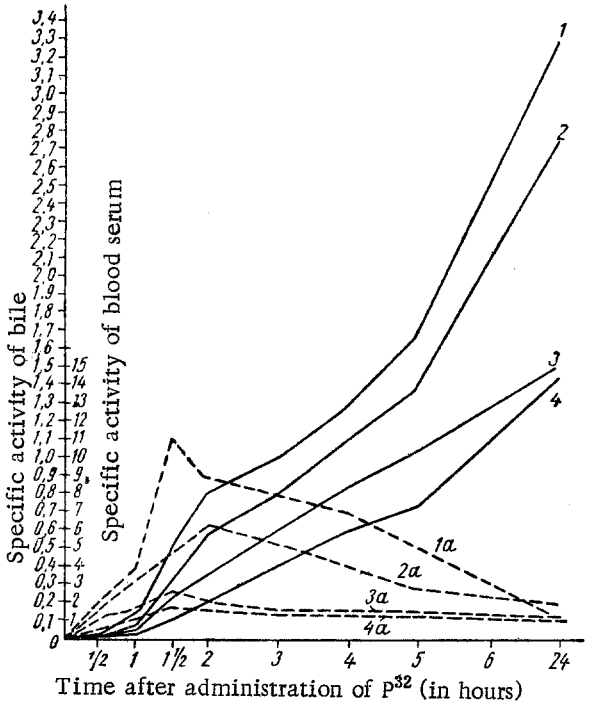

Fig. 1. Specific activity of bile (1-4) and of blood serum (1a-4a) at various intervals after the operation. The dog Seryi. Operation by Schiff's method: 1,1a) 1 month 16 days later; 2,2a) 4 months 5 days later; 3,3a) 5 months later; 4,4a) 12 months later.

activity of the bile in the same dog as the time interval after the operation increased. The specific activity of the bile fell steadily, both on the day of administration of the P^{32} and on the next day, and the curves approximated more and more to the axis of abscissas.

The results of the experiments on the dog Seryi, with a gall-bladder fistula but without ligation of the common bile duct, are given in Fig. 1. Similar results were obtained in experiments on the dogs Ryzhik, Laska, and Lira. In the animals with a gall-bladder fistula and with ligation of the bile duct, the changes described took place sooner after the operation than in the dogs in which the duct was not ligated. This is clear from Fig. 2 which shows the curves of the specific activity of the bile of the dog Karo. The same results were obtained with the dogs Mumu, Dzhek, Tobik, etc.

Chromatography of the bile on paper showed that, with an increase in the time after the operation, during the first few hours after administration of the P^{32}, the fraction of the isotope incorporated into the biliary phospholipids diminished (Fig. 3). Twenty four hours after administration of the P^{32}, the fraction was equal to 99% of the total radioactivity of the bile. On this basis, the specific activity of the total biliary phosphorus, determined 24 h after administration of P^{32}, could be taken as the specific activity of the phospholipids of the bile. The specific activity of the bile 24 h after administration of P^{32} is also shown in Figs. 1 and 2. In the same dog, this clearly diminished as the time after the operation increased. Changes developed faster still in the dogs in which the common bile duct had been ligated. In these animals 1 month after the operation, the specific activity on the day after administration of P^{32} was lower than in the dogs in which the common bile duct had not been ligated.

It was previously reported that, in dogs with hepatitis, the absorption of P^{32} and its utilization in the body are reduced. The curves of the specific activity of the blood serum also become low and sloping [3].

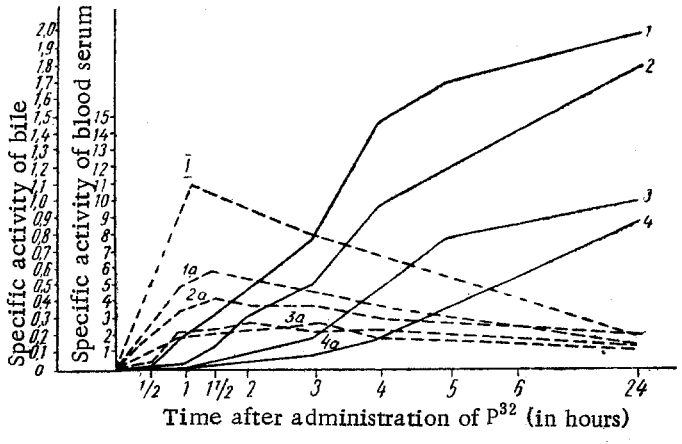

Fig. 2. Specific activity of bile (1-4) and of blood serum (1a-4a) at various intervals after the operation. The dog Karo. Operation by Schwann's method: I) specific activity of blood serum before operation; 1,1a) 1 month later; 2,2a) 2 months 12 days later; 3,3a) 13 months later; 4,4a) 19 months later.

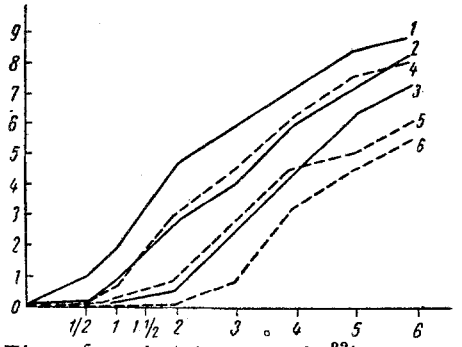

Fig. 3. Percentage of organically bound P^{32} in relation to total radioactivity of the stain obtained by chromatography of the bile secreted at various times after formation of the fistula. The dog Seryi: 1) 1 month 16 days later; 2) 3 months 5 days later; 3) 9 months later. The dog Milka: 4) 21 days later; 5) 4 months 19 days later; 6) 8 months later.

The present investigation showed that the curves of the specific activity of the total phosphorus of the blood serum in dogs with a gall-bladder fistula in the period immediately after the operation (for 1-2 months) were indistinguishable from the control curves obtained with the same or other dogs before the operation. With an increase in the time after formation of the gall-bladder fistula, the specific activity of the blood serum fell. The low level of the specific activity of the blood serum then persisted until the animal's death. Meanwhile, the level of the specific activity of the bile, as mentioned above, continued to fall from one experiment to the next. It thus follows that the decrease in the specific activity of the biliary phospholipids cannot be attributed entirely to a disturbance of the absorption of P^{32}; it was also due to a disturbance of the synthetic processes in the liver cells. These changes were more marked in the dogs which were losing bile, for in these animals, the disturbance of the synthetic activity of the liver cells was aggravated by a disturbance of the circulation of bile. Similar results were obtained in the dogs with a Schiff's fistula of the gall bladder, which developed hepatitis both as a result of the entry of infection from the biliary tract and as a result of the toxicosis caused by carbon tetrachloride.

Histological investigation of the liver of the dogs confirmed that hepatitis was present. The changes observed were similar to those described by the author elsewhere [3].

Hence, at the time of the origin and development of the pathological process in the liver, the rate of synthesis of the biliary phospholipids in the liver falls. When the normal circulation of bile in the body is disturbed, these changes are more marked.

These results are important in explaining the pathogenesis of the hyperphospholipemia in mechanical jaundice. This question will be discussed in a subsequent communication.

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