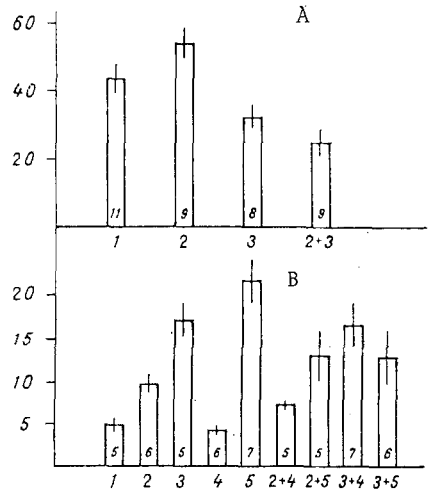

Fig. 1. Role of muscarinic acetylcholine receptors in proliferation of corneal epithelial cells in rats. Abscissa, groups of rats; 1) control; 2) trauma to SMSG; 3) botulinus toxin; 4) pilocarpine; 5) atropine. Ordinate, mitotic index (in %). A) Experiment 1; B) experiment 2. Numbers inside columns show number of corneas.

It can thus be concluded that the parasympathetic nervous system has a restraining effect on cell proliferation. This is manifested both in the intact organ (corneal epithelium) and when regeneration is stimulated as a result of trauma to SMSG.

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LIPOPROTEIN METABOLISM IN THE LIVER AND INTESTINAL WALL OF RABBITS AFTER A SINGLE LOADING WITH SUNFLOWER OIL AND CHOLESTEROL

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KEY WORDS: lipoprotein metabolism; intestinal wall; liver; sunflower oil; cholesterol.

Besides many other factors, an increase in the degree of risk of the onset of cardiovascular diseases is associated also with elevation of the blood cholesterol (CS) concentration. CS enters the blood mainly from the liver and intestine in the composition of lipoproteins (LP), which are its principal transport form. Accordingly, when mechanisms of pathogenesis of hypercholesteremia are studied, the necessity arises for investigation of pathophysiological changes in LP formation and metabolism in the liver and cell wall. Existing data in the

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literature on this subject are inadequate. Little is known of the mechanisms of disturbances of LP metabolism in the initial stages of hypercholesteremia. The character of disturbances of LP metabolism in the intestinal wall leading to elevation of the blood CS level is not clear. Most investigations of the role of the liver in regulation of the blood LP level have been carried out on the isolated organ or *in vitro*.

The investigation described below accordingly was carried out in order to study initial changes in LP metabolism in the liver and intestinal wall during changes in the blood CS level in rabbits induced by alimentary loading.

EXPERIMENTAL METHOD

Experiments were carried out on 27 male rabbits weighing 3.5 ± 0.2 kg. The rabbits were deprived of food for 18 h before the experiments. The control diet (group 1) consisted of 30 g carrot/kg body weight. Rabbits of the experimental groups were given in addition to carrot a single dose of 5 g/kg sunflower oil (group 2) or 0.5 g/kg CS in 5 g/kg sunflower oil (group 3). Samples of lymph and blood were taken after laparotomy under pentobarbital anesthesia by puncture of the intestinal lymphatic trunk (ILT), the abdominal aorta (AA), portal vein (PV), and hepatic vein (HV). Samples were analyzed 3 h after feeding (four rabbits each in groups 1 and 2, six in group 3) and again 15 h after feeding (three rabbits in group 1, five rabbits each in groups 2 and 3). Concentrations of chylomicrons (CM) and very-low-density lipoproteins (VLDLP) plus low-density lipoproteins (LDLP) were investigated in samples of lymph, and CM, VLDLP + LDLP, and high-density lipoproteins HDLP) in the blood serum [2, 3].

EXPERIMENTAL RESULTS

The results (Table 1) showed that 3 h after feeding on the experimental diets the CM level in all blood vessels studied in rabbits of groups 2 and 3 was 61-83% lower than in the control. Addition of CS to the diet reduced the VLDLP + LDLP concentration in the blood from PV and HV by 63.4 and 49.3%, respectively, compared with the animals of group 2. In the animals of group 2 a general tendency was observed for the HDLP concentration in the blood from the regions studied to rise, but this increase was statistically significant only in blood from PV. The addition of CS to the diet prevented this effect.

Comparison of the content of individual LP fractions in blood flowing into and out of the intestine (AA and PV) showed that a characteristic feature of the rabbits fed on a diet containing CS, by contrast with the control and in rabbits receiving a diet without CS, was retention of the VLDLP + LDLP fraction in the intestine and also an increase in the HDLP concentration in blood from PV compared with that in blood from AA.

The role of the liver in LP metabolism was revealed by comparing the concentrations of individual LP fractions in blood flowing to the liver (20% in AA and 80% in PV) and flowing from it (HV). No significant changes were found in the concentrations of the LP fractions as a result of their passage through the liver 3 h after feeding in the rabbits of groups 1 and 2, whereas in the rabbits of group 3 significant retention of the HDLP fraction (by 58.2%; $P < 0.02$) in the liver was established.

The CM level in the blood from all vessels studied 15 h after feeding in the control group was 72-90% lower than that determined 3 h after feeding ($P < 0.05$; Table 2). Loading with sunflower oil led to an increase of 4.5 times in the CM concentration in blood from PV. Addition of CS to the diet caused a 2.6-fold increase in the blood CM level from AA compared with that in rabbits receiving added sunflower oil only, whereas the CM concentration in blood from PV in the animals of group 3 was lowered by 2.4 times compared with the values in rabbits of group 2.

The blood level of the atherogenic VLDLP + LDLP fraction was lower 15 h after loading with sunflower oil than in the control. The fall in the level of this fraction in blood from PV and HV was particularly marked, amounting to 74.6 and 50.0%, respectively. The VLDLP + LDLP concentration in blood from the animals of group 3 showed a tendency to fall, just as it did 3 h after feeding. Meanwhile addition of CS to the diet increased the concentration of this fraction in the blood by comparison with that in the animals of group 2. The increase was particularly marked in blood from PV (by 139.2%).

The concentration of the antiatherogenic HDLP fraction in blood from the rabbits of group 2 reached even higher values, 7.6, 5.2, and 4.3 times higher than the control values in blood from AA, PV, and HV, respectively. A similar pattern also was observed in the ani-

TABLE 1. LP Concentration in Intestinal Lymph and in Blood Serum (in g/liter) 3 h after Feeding (M ± m)

Diet	Vessels	Lipoprotein fractions		
		CM	VLDLP + LDLP	HDLP
Oil	ILT	16,29±2,11 (3)	4,36±0,68 (3)	—
Oil + CS		11,31±0,80 (3)	4,16±0,64 (3)	—
Control		0,87±0,11 (3)	0,80±0,16 (3)	0,56±0,06 (4)
Oil	AA	0,34±0,07 (4) a	0,54±0,10 (3)	1,05±0,42 (3)
Oil + CS		0,18±0,03 (4) a	0,43±0,04 (6)	0,50±0,04 (4)
Control	PV	0,69±0,16 (3)	0,65±0,22 (3)	0,75±0,05 (3)
Oil		0,22±0,04 (3) a	0,71±0,06 (3)	1,27±0,50 (3)
Oil + CS		0,17±0,04 (4) a	0,26±0,02 (6) b	1,04±0,09 (4)
Control	HV	0,69±0,12 (4)	0,81±0,29 (3)	0,78±0,05 (3)
Oil		0,20±0,06 (3) a	0,69±0,06 (3)	1,27±0,09 (4) a
Oil + CS		0,12±0,03 (4) a	0,35±0,04 (6) b	0,62±0,12 (3) b

Legend. Here and in Table 2: a) $P < 0.05$ compared with control, b) The same compared with group 2; number of animals given in parentheses.

TABLE 2. LP Concentration in Intestinal Lymph and Blood Serum (in g/liter) 15 h after Feeding (M ± m)

Diet	Vessels	Lipoprotein fractions		
		CM	VLDLP + LDLP	HDLP
Oil	ILT	18,50±2,29 (5)	4,64±0,16 (4)	—
Oil + CS		27,35±0,90 (5)	4,22±0,67 (4)	—
Control		0,12±0,05 (3)	0,37±0,07 (3)	0,42±0.09 (3)
Oil	AA	0,10±0,02 (4)	0,26±0,02 (4)	3,22±0,20 (3) b
Oil + CS		0,26±0,03 (3) b	0,37±0,04 (3)	1,10±0,35 (3)
Control	PV	0,07±0,01 (3)	0,47±0,05 (3) a	0,48±0,14 (3) a
Oil		0,33±0,04 (4) a	0,12±0,01 (3)	2,51±0,15 (4)
Oil + CS		0,14±0,03 (4) b	0,29±0,02 (3) a,b	1,84±0,13 (3) b
Control	HV	0,19±0,03 (3)	0,40±0,04 (3)	0,84±0,27 (3)
Oil		0,32±0,05 (4)	0,20±0,04 (4) a	3,65±0,54 (3) a
Oil + CS		0,23±0,05 (3)	0,32±0,03 (4)	3,36±0,18 (3) a

mals of group 3. However, the HDLP level in blood from AA and PV of the rabbits receiving CS was 65.7 and 26.7% lower, respectively, than that in the animals of group 2.

In the animals of group 2 retention of the VLDLP + LDLP fraction and the HDLP fraction in the intestinal wall was intensified: Their concentrations in blood from AA were 53.9 and 22.8%, respectively, higher than the corresponding levels in blood from PV ($P < 0.05$). The fact that the HDLP concentration in blood from PV was significantly higher than the control values in rabbits receiving sunflower oil with CS points to intensified synthesis of this fraction in the liver.

Analysis of the results of a study of the LP concentration in the intestinal lymph reveals that addition of CS to the diet stimulated CM synthesis by enterocytes, and in the present experiments this was found 15 h after feeding. The VLDLP + LDLP level in the intestinal lymph was relatively constant.

Feeding rabbits with sunflower oil and CS thus causes the CM concentration to fall after 3 h in blood flowing to and from the intestine and liver, which indicates the possibility that the breakdown of particles during circulation of the blood may be intensified as a result of an increase in size during their formation [5, 6]. A tendency for the CM level in the blood to rise compared with the control was observed 15 h after feeding the rabbits with the experimental diets. The presence of a high CM level in blood from PV in rabbits fed with sunflower oil is evidence that in the initial stages of development of chylomicronemia the number of particles entering the blood stream directly from the enterocytes is increased. the low CM concentration in blood from PV after addition of CS to the rabbits' diet could be attributed to congestion in the capillaries and venules, as was found in rabbits after a single loading with CS [1]. A single loading with sunflower oil lowers the blood concentration of VLDLP + LDLP and stimulates HDLP synthesis by the liver. Under these circumstances these fractions are deposited in the intestinal wall. When CS was added to the rabbits' diet retention of VLDLP + LDLP in the intestine was accompanied by increased liberation of HLDLP into the blood from PV, evidently as a result of the increased supply of CS to the enterocytes,

for a role of HDLP in the transport of excess CS from the tissues into the liver has been postulated [7]. A diet with CS increases the outflow of CM into lymph of ILT, and this undoubtedly promotes lipoidosis of the blood vessel walls and, in particular, the walls of the vessels of the heart [4].

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INVESTIGATION OF THE ROLE OF CYCLIC AMP AND PROSTAGLANDIN E_2 IN THE MECHANISM OF THE INHIBITORY ACTION OF NICOTINIC ACID ON PLATELET AGGREGATION

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Nicotinic acid inhibits platelet aggregation in man and animals *in vivo* [1].

The object of this investigation was to study the mechanism of the antiaggregating action of nicotinic acid on platelets and, in particular, to determine the character of its immediate effect on platelet function *in vitro* and also on the concentration of cyclic adenosine-3,5-monophosphate (cAMP) and of prostaglandin E_2 (PGE_2), which are endogenous regulators of platelet aggregation [2-4, 6, 8], in the platelets.

EXPERIMENTAL METHOD

Nicotinic acid was added in a concentration of 16.2 mM to whole donors' blood, kept in TsOLIPK 7b preservative. The aggregating power of the platelets was studied and their content of cAMP and PGE_2 determined 1.5-2 h after the blood was taken and also after keeping for 1, 3, 5, and 7 days at 4°C.

Platelet aggregation induced by ADP (1 μM), adrenalin (5 μM), and thrombin (0.5 i.u./ml), was studied by Born's method [5]. The degree of aggregation was determined by the method of Wu and Hoak [11]. The intracellular platelet concentration of cAMP was determined radioimmunologically with the aid of a diagnostic kit from the Radiochemical Centre, Amersham, England. The PGE_2 concentration in the platelets was investigated radioimmunologically by means of the diagnostic kit from Clinical Assays, USA. In control experiments donors' blood not containing nicotinic acid was used. Each index was studied in 15-30 series of experiments. The experimental results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

During storage of preserved blood there was a constant rise in the cAMP level (Table 1), which became statistically significant on the first day ($P < 0.05$). The PGE_2 level also was statistically significantly increased on the 3rd day of keeping ($P < 0.05$), but later it fell,

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