cells of Ec type in these foci. On the basis of the results it can be postulated that Ec, by binding to the apical plasmalemma of Ec cells, potentiate their functional activity. Their secretory products (serotonin, substance P, and motilin), secreted into the intercellular space, act on neighboring epitheliocytes and nearby vessels (the paracrine effect). These substances can play the role of diarrhea-inducing factors in choleragenic toxicosis, as is confirmed by data in the literature [9-11]. Hormones secreted by S cells (secretin) and by G cells (gastrin) may also participate in intensifying secretion of fluid into the intestine [5, 8].

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COMPENSATORY AND ADAPTIVE CHANGES IN THE SMALL INTESTINE AND LIVER OF RABBITS ON SHORT-TERM CHOLESTEROL FEEDING

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Since cholesterol (Ch) is a risk factor of ischemic heart disease, much attention has been paid in the literature to regulation of the blood Ch level under normal conditions and in various disturbances (excess Ch in the diet, emotional stress, hereditary hypercholesterolemia – HCh, progressive atherolsclerosis, and so on). The discovery of low-density lipprotein (LDL) receptors explained the mechanism controlling the concentration of Ch-carrying lipoproteins (LP). It was shown that the blood LDL level is determined by the balance between activity of 3-hydroxy-3-methylglutaryl-CoA reductase, which participates in intracellular Ch synthesis, and the number of LDL receptors [6]. Competitive relationships have been found between chylomicrons (ChM) and very low density lipoproteins (VLDL) during binding with liver receptors [7, 9]. It has been shown that Ch is accepted from liver cell membranes by high density lipoproteins (HDL) [5]. Regulation of Ch transport at the level of the small intestine is less clear. Yet it can be postulated that regulation at that level is particularly important in the the case of insufficiency of liver function. Experiments

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TABLE 1. Time Course of Serum TCh and LP Concentrations (in mg%) in Blood from Auricular Vein During 4 Days of Cholesterol Feeding (M ± m)

Time of determination		TCh	Lipoprotein fractions	
Day	Time of day		ChM + VLDL + LDL	HDL
1-st	10 a.m.	25,3±0,7 ($n = 17$)	92,8±6,7 ($n = 24$)	70,0±9,5 ($n = 24$)
	1 p.m.	60,1±4,1 ($n = 12$)*	104,6±16,6 ($n = 13$)	75,8±10,9 ($n = 13$)
	4 p.m.	77,1±6,2 ($n = 9$)*	92,9±13,9 ($n = 11$)	105,0±15,5 ($n = 11$)
2nd	10 a.m.	75,3±13,8 ($n = 12$)	185,5±17,6 ($n = 15$)*	6,9±13,7 ($n = 16$)
	1 p.m.	98,9±6,6 ($n = 10$)	152,6±19,5 ($n = 10$)	88,2±17,7 ($n = 10$)
	4 p.m.	65,0±6,3 ($n = 5$)	172,9±30,6 ($n = 7$)	123,1±23,9 ($n = 7$)
3-rd	10 a.m.	158,5±8,7 ($n = 13$)*	263,9±32,5 ($n = 18$)*	121,0±15,1 ($n = 18$)*
	1 p.m.	172,1±10,4 ($n = 9$)	258,0±24,9 ($n = 9$)	76,5±20,6 ($n = 8$)
	4 p.m.	191,7±32,6 ($n = 9$)	253,1±18,3 ($n = 9$)	62,0±13,5 ($n = 6$)*
4-th	10 a.m.	139,4±10,8 ($n = 9$)	351,9±25,1 ($n = 11$)*	156,8±29,3 ($n = 10$)
	1 p.m.	203,0±1,7 ($n = 3$)*	242,3±41,2 ($n = 6$)	179,6±52,3 ($n = 6$)
	4 p.m.	237,3±96,6 ($n = 3$)	228±40,9 ($n = 6$)	126,7±52,3 ($n = 6$)
5-th	10 a.m.	208,3±68,6 ($n = 3$)	303,5±91,8 ($n = 4$)	89,0±20,4 ($n = 4$)

Legend. *P < 0.05 compared with control before Ch loading. Here and in Table 2: n) number of animals.

TABLE 2. Time Course of Serum TCh and LP (in mg%) in Blood from Central Vessels During 4 Days of Cholesterol Feeding (M ± m)

Blood vessel	Time of determination, days	TCh	Lipoprotein fractions		
			ChM	VLDL + LDL	HDL
AA	VLDL + LDL	28,3±2,2 ($n = 3$)	28,0±7,9 ($n = 9$)	56,7±9,1 ($n = 9$)	45,7±11,2 ($n = 9$)
	1-st	162,3±14,4 ($n = 3$)	62,4±20,7 ($n = 5$)	81,6±30,3 ($n = 5$)	35,0±5,0 ($n = 6$)
	2-nd	400,0±17,0 ($n = 6$)	160,0±40,0 ($n = 6$)	371,3±76,8 ($n = 6$)	111,0±35,0 ($n = 6$)
	3-rd	172,8±29,4 ($n = 4$)	121,3±38,3 ($n = 6$)	306,7±45,6 ($n = 6$)	144,0±27,8 ($n = 6$)
	4-th	269,7±24,8 ($n = 3$)	79,6±16,5 ($n = 5$)	274,0±85,0 ($n = 5$)	30,0±9,0 ($n = 5$)
PV	VLDL + LDL	29,0±3,5 ($n = 3$)	21,5±2,0 ($n = 9$)	44,2±11,6 ($n = 9$)	48,3±9,2 ($n = 7$)
	1-st	153,0±6,4 ($n = 3$)	51,6±10,6 ($n = 5$)	90,4±31,1 ($n = 5$)	86,3±17,2 ($n = 6$)
	2-nd	363,7±6,2 ($n = 3$)	185,5±28,2 ($n = 6$)	278,3±60,2 ($n = 6$)	98,3±27,0 ($n = 6$)
	3-rd	254,7±51,0 ($n = 3$)	199,3±59,8 ($n = 6$)	322,0±35,1 ($n = 6$)	74,3±10,0 ($n = 6$)
	4-th	164,0±30,6 ($n = 3$)	90,0±25,2 ($n = 4$)	290,5±59,6 ($n = 4$)	74,0±15,6 ($n = 5$)
HV	VLDL + LDL	27,3±5,0 ($n = 3$)	26,7±3,3 ($n = 9$)	45,6±12,9 ($n = 9$)	57,2±9,4 ($n = 9$)
	1-st	160,7±3,0 ($n = 3$)	46,8±4,9 ($n = 5$)	94,8±48,2 ($n = 5$)	55,0±7,6 ($n = 6$)
	2 nd	174,3±6,1 ($n = 3$)	94,2±21,6 ($n = 6$)	332,0±81,6 ($n = 6$)	91,3±26,8 ($n = 6$)
	3 rd	202,0±54,2 ($n = 4$)	165,2±29,9 ($n = 5$)	343,6±46,8 ($n = 5$)	118,7±16,2 ($n = 6$)
	4 th	226,3±28,8 ($n = 3$)	84,4±27,9 ($n = 5$)	222,8±72,2 ($n = 5$)	57,6±9,5 ($n = 5$)

on rabbits have shown that decisive role of the intestinal wall in regulation of the blood Ch level as early as during the first hours after a single exposure to Ch [2, 3].

The aim of this investigation was to study compensatory and adaptive mechanisms of regulation of Ch and LP metabolism in the intestinal wall and liver of rabbits in the early stages of HCh.

EXPERIMENTAL METHOD

Experiments were carried out on 24 male rabbits weighing 3.0 ± 0.2 kg, kept on the ordinary animal house diet. Control animals had 100 g of grated carrot added to their diet daily for 4 days. Experimental rabbits received carrot with Ch in a dose of 0.5 g/kg body weight. Blood was taken from the auricular vein before and 3 and 6 h after exogenous Ch loading. Blood was taken from the abdominal aorta (AA) and the portal and heptaic veins (PV and HV respectively) on the 2nd, 3rd, 4th, and 5th days on which the animals received a high cholesterol diet, before the next dose of Ch and after laparotomy under pentobarbital anesthesia. Concentrations of total cholesterol (TCh), by the method of Girard and Assous, and of ChM, VLDL, LDL, and HDL were determined in the blood serum [1, 2]. TCh and LP in the intestinal wall and liver was estimated on the basis of their concentrations in outflowing and inflowing blood. Structural changes in the mucosa of the jejunum and liver were investigated by light and electron microscopy.

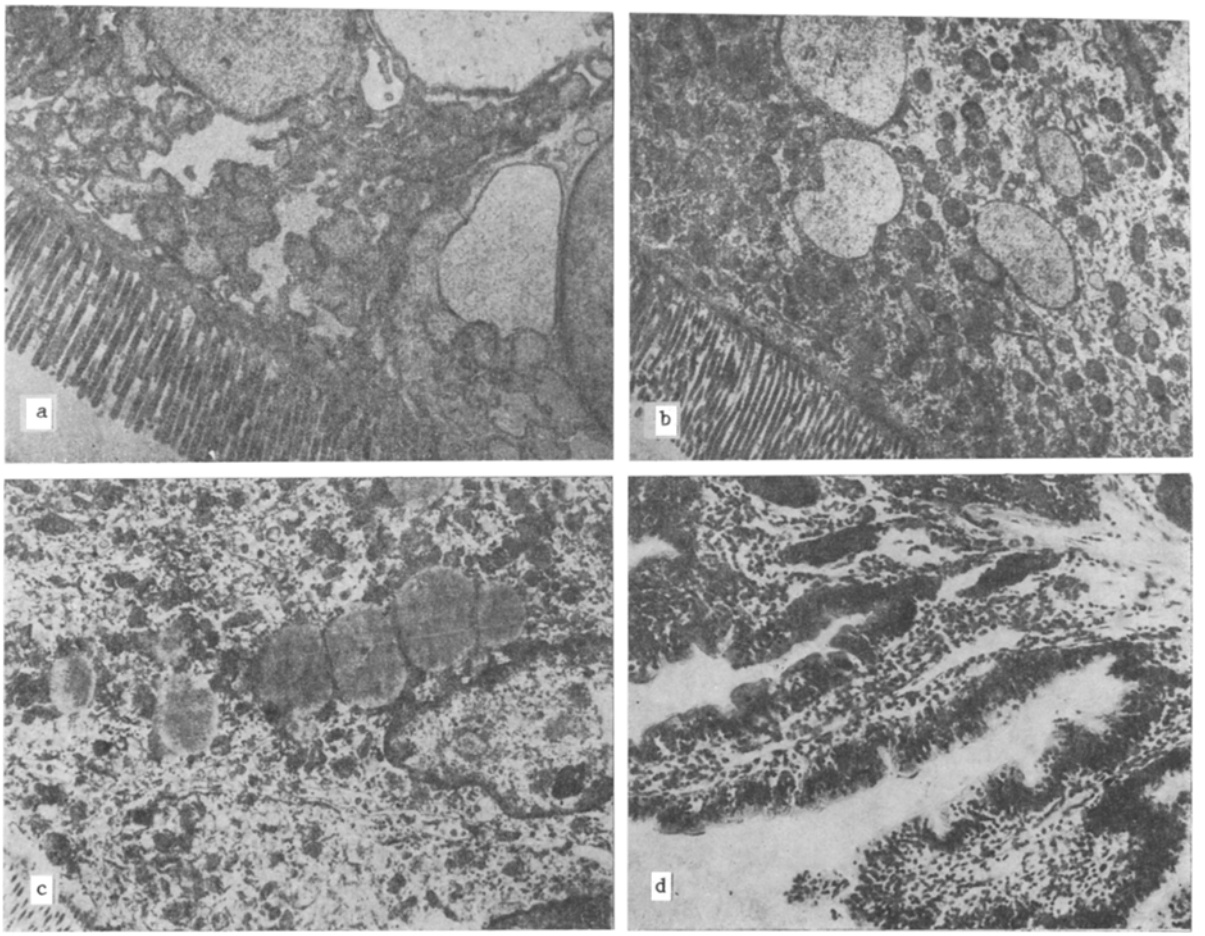

Fig. 1. Structural changes in jejunal epitheliocytes in early stages of experimental HCh. a) Marked dilatation of cisterns of RER, translucency of mitochondrial matrix after 6 h (7500 ×); b) increase in number of vacuolar tubules with finely granular material, increased electron density of membranes of RER and terminal network, and many secondary lysosomes after 6 h (6000 ×); c) besides ChM, lipid drops of different sizes can be seen in epitheliocytes on 4th day (7500 ×); d) hypertrophy of jejunal mucosa, infiltration of villi by lymphocytes and plasma cells, and increased number of IEL on 4th day of diet (112 ×). Goldman's stain.

EXPERIMENTAL RESULTS

The TCh concentration in the peripheral blood was increased after 3 h on the 1st day by 138%, but later (6 and 24 h) it was unchanged (Table 1). The total level of ChM, VLDL, and LDL was increased (twofold) only after 24 h. Changes caused by repeated administration of Ch (2nd day) were observed after 24 h: the TCh concentration was increased by another 108%, concentrations of ChM, VLDL, and LDL by 42%, and HDL by 57%. During the 3rd day on a high cholesterol diet the TCh level changed. Concentration of ChM, VLDL, and LDL continued to rise, and by the 4th day they were four times higher than in the control. The HDL concentration fell to the control level after 6 h, but by the 4th day it again exceeded it by 130% ($P < 0.01$). During the 4 days of the high cholesterol diet the TCh concentration rose rapidly (by 64% after 3 h), and this high level remained throughout the period of observation (21 h). Meanwhile, no significant changes were observed in concentrations of both atherogenic and anti-atherogenic LP. The TCh concentration in blood of the central vessels after 24 h on a high cholesterol diet was on average five times higher than in the control ($P < 0.001$, Table 2). HDL formation in the intestinal wall was intensified: the HDL concentration in blood flowing from the intestine was 2.5 times higher than in the inflowing blood ($P < 0.02$). After 2 days the TCh concentration in blood circulating in the intestinal wall reached a maximum: it was then on average 13 times higher than in the control ($P < 0.001$). Meanwhile the liver retained 52% of the TCh and 48% of the ChM ($P < 0.05$) entering

it with the inflowing blood. On subsequent days on the diet the TCh level fell in blood flowing through the intestine. On the 3rd day increased elimination of HDL from the circulation by the intestinal wall was observed; the arteriovenous difference (AVD) of the concentrations was 48% ($P < 0.05$). However, by the 5th day on the diet HDL formation in the intestinal wall was again increased: the negative AVD was 147% ($P < 0.05$).

The light-optical investigation revealed hypertrophy of lymphoid follicles, infiltration of the stoma with lymphocytes and plasma cells, and an abundance of interepithelial lymphocytes (IEL) in the mucosa of the jejunum 6 and 24 h after Ch feeding. Individual epitheliocytes of the villi showed dystrophic changes. After 2 days on the diet signs of focal hypertrophy appeared in the mucosa (Fig. 1d). On the 3rd and 4th days microvessels of the lymphatic and blood systems in the mucosa were greatly dilated and filled with lipemic plasma, with signs of perivascular plasmarrhagia. The electron microscopic study showed edema and destruction of mitochondria in the first few hours of the experiment in the epitheliocytes of the villi, the cisterns of the rough endoplasmic reticulum (RER) were dilated (Fig. 1a), the number of lysosomes was increased, and concentrations of ChM could be seen. Meanwhile cells with an increased number of vacuolated tubules containing finely granular material were observed. Membranes of RER and the terminal network had increased electron density, and numerous polysomes could be seen (Fig. 1b), evidence of intensification of protein and enzyme synthesis. Lipophages, lymphocytes, plasma cells, IEL, and pericytes all participated in the process of resorption and digestion of lipids in the small intestine. Structures similar to ChM, lipid drops of different sizes, phagolysosomes, and myelinlike structures could be seen in the cytoplasm of these cells. The dystrophic changes became more severe in the jejunum on the 3rd and 4th day of the diet, and deposition of lipids was observed in the epitheliocytes (Fig. 1c). After the first few hours of the experiment focal circulatory and combined degenerative and inflammatory changes took place in the liver. After a longer period on the high cholesterol diet (2nd, 3rd, and 4th days) evidence of disturbance of the complex structure and organization of the hepatic trabeculae was obtained, hepatocytes were greatly swollen and showed signs of marked fatty, vacuolar, and cloudy-swelling degeneration, and the intensity of round-cell infiltration increased in the vicinity of the microvessels and bile ducts.

Disturbances of Ch and LP metabolism in the small intestine and liver of the rabbits associated with short-term cholesterol feeding were thus combined with considerable structural changes in these organs. At the same time several compensatory and adaptive reactions were discovered. In particular, against the background of the rapid rise in TCh concentration in the general blood stream, increased HDL formation in the intestine was observed. During the first day on the diet this effect was evidently connected mainly with the excessive concentration of alimentary Ch in the intestinal wall: the supposed protective role of HDL consists of transfer of excess Ch from the tissues into the liver [8]. Later this comepnsatory and adaptive function is taken over by the liver itself: it eliminated from the circulation many ChM, thus freeing the blood stream from the excessive Ch concentration, which undoubtedly promoted stabilization of its blood level. Meanwhile we know that mechanisms of excretion of alimentary Ch by the liver in rabbits are not sufficiently effective. Because of this, the function of regulating the circulating Ch level was taken over again by the intestine. While HDL were stored in the intestinal wall, consumption of Ch did not change its concentration in the general blood stream. Considering the fact that during this time the AVD of the Ch concentration in the intestine was zero, it can be tentatively suggested that the increased entry of alimentary Ch into the circulation was balanced by deposition in the form of HDL. The second rapid rise of the blood Ch concentration in connection with feeding is evidence of depression of the powers of adaptation of the rabbits. At the same time, it was combined with a second increase in the intensity of HDL formation in the intestinal wall. Hence, pathological changes appear in the wall of the small intestine and liver or rabbits during short-term cholesterol feeding. Meanwhile a series of protective mechanisms exists, which brings about qualitative changes in Ch transport, mainly at the small intestinal level.

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