

EFFECT OF OXYGEN ON BIOSYNTHESIS OF CHOLESTEROL
IN EXPERIMENTAL ATHEROSCLEROSIS

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Oxygen is known to inhibit or depress the course of experimental atherosclerosis of the aorta and coronary vessels in rabbits [3, 7]. According to N. N. Kipshidze's findings [1], prolonged oxygen lack in experimental atherosclerosis led to a marked increase in the blood cholesterol concentration and to the rapid development of atherosclerosis in rabbits.

Investigations of the effects of various drugs showed that the specific activity of the liver cholesterol is increased by insulin, cortisone, or drug-induced sleep and is appreciably decreased by the action of caffeine [5]. N.G. Kritsman and M. B. Bavina [2] found that methionine, choline, biotin, and adenosinetriphosphoric and pantothenic acids had no significant effect on the biosynthesis of cholesterol in the liver after this has been depressed in rabbits by cholesterol feeding.

We have studied the effect of oxygen on the total cholesterol concentration and the endogenous cholesterol synthesis in certain tissues of rabbits fed on cholesterol.

EXPERIMENTAL METHOD

Investigations were carried out on 34 male chinchilla rabbits weighing 1.7-2.4 kg. kept on an identical diet, between April and June of one year.

The rabbits were divided into groups. The first (control) group consisted of 6 rabbits which received neither cholesterol nor oxygen. The second group consisted of 14 rabbits which received pure cholesterol with their diet in a daily dose of 0.2 g/kg body weight for 2 or 3 weeks. The third group, also of 14 rabbits, received cholesterol daily and in addition were kept in an oxygen tent with an oxygen concentration of 60-65% for 1.5-3 h each day.

Three hours before the animals were sacrificed they received an intraperitoneal injection of carbon-labeled acetate in a dose of 100 μ Ci/kg body weight. The rabbits were electrocuted and the organs for testing were extracted immediately. Weighed samples (each of 1 g) were taken of the heart, liver, and lungs and both adrenals also were weighed.

Cholesterol was extracted by the method of Sperry and Webb [8]. The cholesterol extracted from the weighed samples of the organs was precipitated with 1% digitonin solution. The activity of the extracted cholesterol was investigated by means of an end-type counter and a type B apparatus. The total cholesterol content of the test organs was determined by a colorimetric method.

EXPERIMENTAL RESULTS

It will be seen in Table 1 that as a result of daily feeding on cholesterol the content of this substance in all the test organs rose by comparison with its level in the control animals. A more marked increase in the total cholesterol was observed in the rabbits receiving cholesterol for 3 weeks. When the effect of oxygen was studied the changes in the level of the total cholesterol in the different organs were found to be varied in direction. For instance, after inhalation of oxygen for 2 weeks, the cholesterol concentration in the heart muscle (64-111 mg%) was slightly lower than in the experimental rabbits which did not inhale oxygen (51-147 mg%). This tendency was seen more clearly in the animals receiving cholesterol for 3 weeks.

TABLE 1. Total Cholesterol Concentration in Heart Muscle, Liver, Lungs, and Adrenals

Experimental conditions	Rabbit No.	Total cholesterol (in mg ^g)						
		heart muscle	liver	lungs	adrenals			
Control	13	60	161	242	—			
	23	102	181	201	1 671			
	24	100	168	330	1 235			
	31	54	120	90	1 164			
	32	90	220	210	2 193			
	41	90	220	300	909			
Feeding with cholesterol	14 days	21	99	240	273	2 585		
		25	66	283	162	4 131		
		27	51	308	185	3 474		
		33	147	235	282	3 741		
		40	114	276	300	4 650		
	21 days	2	150	213	191	2 235		
		3	133	200	190	2 910		
		5	65	211	—	1 950		
		7	123	335	543	1 583		
		9	60	398	300	2 530		
		11	68	312	214	2 448		
		16	132	344	450	2 154		
		17	155	458	330	1 385		
		19	105	350	330	4 374		
		Feeding with cholesterol + inhalation of oxygen	14 days	22	111	246	330	4 818
				25	105	222	177	8 421
				28	54	200	210	7 830
				29	93	100	240	1 911
				30	78	123	243	2 325
21 days	1		63	400	230	3 500		
	4		63	405	243	1 251		
	6		91	272	272	1 290		
	8		21	259	334	1 505		
	10		48	—	225	1 395		
	12		36	390	481	1 392		
	14		48	244	252	5 645		
	18		30	240	480	10 272		
	20		54	390	420	1 507		

In the rabbits receiving cholesterol alone, the total cholesterol concentration in the heart muscle was relatively high (60-156 mg%), whereas after administration of oxygen its level fell significantly (21-91 mg%) below the values observed in the control animals (54-102 mg%).

In the rabbits fed on cholesterol for 14 days the total cholesterol concentration in the liver (240-308 mg%) was higher than in the animals receiving cholesterol and kept in an oxygen tent (100-246 mg%). The total cholesterol level in the liver rose higher in the experiments lasting 3 weeks and became identical in both groups of animals. The total cholesterol concentration in the lungs was not significantly changed after inhalation of oxygen. Daily feeding of the rabbits with cholesterol affected its level in the adrenals: the total cholesterol concentration in the control animals was 909-2196 mg% compared with 2586-4650 and 1386-4675 mg% in animals fed on cholesterol for 2 and 3 weeks, respectively. In the animals kept in the oxygen tent the total cholesterol level in the adrenals was higher (1941-10,272 mg%).

The results given in Table 2 show that the specific activity of the cholesterol in the myocardium, liver, lungs, and adrenals was much lower in the rabbits receiving cholesterol in their diet than in the control animals. It was higher in the myocardium in the rabbits receiving oxygen; the levels of specific activity of cholesterol in the liver were even lower in the animals of this group than in the rabbits only receiving cholesterol. A small difference was observed in the changes in specific activity of cholesterol in the lungs and adrenals depending on the duration of the experiments. For instance, in the rabbits inhaling oxygen for 14 days the activity was lower than in the animals receiving only cholesterol during this period. Inhalation of oxygen for 21 days slightly increased the specific activity of the cholesterol in the lungs while leaving that in the adrenals practically unchanged. Con-

sequently, following administration of oxygen, the total cholesterol concentration fell in the myocardium and liver, rose in the adrenals, and remained unchanged in the lungs.

It is possible that these differences in the trend of the changes in the cholesterol concentration are due to the fact that the myocardium, liver, lungs, and adrenals behave differently in relation to lipid metabolism (synthesis, deposition, and excretion of lipids). The investigations of V. F. Zatishev and L. V. Myasnikov [4] showed that in rabbits with experimental atherosclerosis thyroid extract caused a sharp increase in the absorption of C^{14} -labeled cholesterol by the liver and, at the same time, lowered its level in the aorta. Apparently administration of oxygen is followed by a redistribution of cholesterol: an increase in its content in the adrenals leads to a decrease in the amount of cholesterol entering the myocardium. Interesting results in this connection were obtained by S. S. Khalatov [6], who observed that patients with cutaneous xanthomatosis have a less marked degree of atherosclerosis of the arteries.

SUMMARY

Endogenous cholesterol synthesis was studied in 64 rabbits by administering carbon labeled acetate to them. Total cholesterol level and its specific activity in the heart muscle, lungs, liver and adrenal glands were investigated. Fourteen rabbits received cholesterol with 100-110 mg or 1300 mg daily; 14 rabbits not only received cholesterol, but also were placed into an oxygen tent for 14-21 days; 6 rabbits served as a control to which there was

TABLE 2. Specific Activity of Cholesterol in Heart Muscle, Liver, Lungs, and Adrenals of Rabbits

Experimental conditions	Rabbit No.	Specific activity of cholesterol (impulses/min/mg)						
		heart muscle	liver	lungs	adrenals			
Control	23	81	194	95	43			
	24	114	579	310	91			
	31	38	244	16	24			
	32	14	152	20	25			
	41	40	212	59	37			
Feeding on cholesterol	14 days	21	6	29	15	9		
		25	4	128	34	41		
		27	3	38	25	35		
		33	—	27	26	76		
		40	4	9	27	10		
	21 days	2	4	8	3	61		
		3	11	—	2	4		
		9	14	21	10	13		
		11	—	12	7	13		
		16	12	132	5	32		
		17	—	74	24	44		
		19	12	16	34	29		
		Feeding on cholesterol + inhalation of oxygen	14 days	22	9	11	6	9
				26	—	2	10	16
28	16			9	9	20		
29	31			2	1	8		
30	13			57	28	49		
21 days	1	4	3	4	7			
	4	11	1	2	—			
	10	22	—	52	59			
	12	4	—	7	14			
	14	27	23	27	21			
	18	12	2	98	22			
	20	8	1	234	56			

a reduction of specific cholesterol activity as compared with controls. Oxygen breathing was followed by a drop in the total cholesterol content of the myocardium and a rise of its level in the adrenal glands. As compared with the animals which received cholesterol alone, in the group of those giving oxygen, the specific activity indices in the myocardium were somewhat increased, and in the liver, lowered.

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