

A Note on the Synthesis of Cholesterol in the Animal Organism

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Recent work has shown that cholesterol is synthesized not only in the liver but also in the extra-hepatic tissues. Srere, Chaikoff, Treitman and Burstein¹ found cholesterol synthesis from C—14 labeled acetate in the eviscerated rat and in *in vitro* experiments they demonstrated conversion of C—14 acetate to cholesterol by the following isolated tissues of adult rat: liver, kidney, testis, small intestine and skin. The most rapid synthesis occurred in skin and liver. Srere, Chaikoff and Dauben² had earlier shown the adrenal cortex to be a site for cholesterol synthesis.

The synthesis of cholesterol in the rabbit has been studied by Popjak and Beeckmans³ with the aid of deuterium oxide and C—14 acetate. They found the D and C—14 content of the cholesterol of the small intestine and ovaries higher than that of the liver indicating a synthesis of cholesterol in the former organs. They also found the interesting fact that the specific activity of the free cholesterol was higher than that of esterified cholesterol, being about 1.5 times higher in liver and about 3 times higher in small intestine.

In connection with a study of the metabolism of C-14-1-stearic acid in the rat⁴ we have made similar observations. We determined the specific activities of the free cholesterol of liver, small intestine and blood, and of total cholesterol of heart, kidney, lung, brain and carcass at different intervals after peroral administration of C-14-1-stearic acid to adult rats (Table 1). The highest specific activities were found in the free cholesterol of the small intestine, indicating that part of the absorbed stearic acid is degraded in the intestinal mucosa presumable to acetate that is utilized for cholesterol synthesis. The specific activities of the cholesterol of all other organs tested were lower than that of the intestine, the liver having the next highest activity.

Table 1. Specific activity of free cholesterol in counts per min. after a single peroral administration of l-C 14-stearic acid to rats: 1/20 mmole/sq dm² body surface. Specific activity 90000 c/min./mg as BaCO₃.

Standard deviation in counting < ± 7 %. Background 20 c/min.

	Hours after administration				
	2	6	12	24	48
Liver	8	13	25	39	25
Small intestine	11	17	34	65	24
Blood	(2)	9	23	38	21

In another type of experiment we found that the intestinal wall contributed a quantitatively important part of the blood cholesterol via the lymphatic system at least during fat absorption and that part of this cholesterol is synthesized in the intestinal wall from ingested fatty acids.

Two adult rats with the intestinal lymphatics cannulated according to Bollman *et al.*⁵ were given C-14 labeled fat and the intestinal lymph was collected for 24 hours. The free and esterified cholesterol were separated on columns of aluminum oxide⁶. After saponification of the esterified cholesterol, the two cholesterol fractions were precipitated as digitonides according to Srere *et al.*² and the C-14 activities assayed after wet combustion. The results are summarized in Table 2.

Table 2. C¹⁴ content of esterified and free cholesterol and neutral fat fatty acids of intestinal lymph in rat after peroral administration of 0.5 ml corn oil + 18.0 mg C¹⁴-l-stearic acid (specific activity 150000 c/min./mg as BaCO₃). Total administered activity about 2.7 · 10⁶ c/min. Specific activity of the fatty acid mixture after hydrolysis about 7000 c/min./mg as BaCO₃.

	Weight mg	Specific activity c/m	Per cent of administered activity
Esterified cholesterol	6.8	109	0.027
Free cholesterol	9.4	112	0.039
Neutral fat fatty acids	367	5360	73.8
Esterified cholesterol	3.6	58.5	0.0078
Free cholesterol	5.8	107	0.016
Neutral fat fatty acids	117	4050	17.5

The findings here reported are in accord with the results of Popjak and Beeckmans³ on rabbit and show the active part played by the small intestine in the metabolism of fatty acids and cholesterol. However, Popjak and Beeckmans found higher activities of esterified than of free cholesterol of small intestine. Our figures for intestinal lymph cholesterol show about the same or lower specific activities for esterified cholesterol compared with those for free cholesterol.

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