3.0 mg/kg of diet.

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Effect of Exclusion of Hepatic Circulation on Oxidation of Octanoic Acid in the Rat.* (29229)

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The ability of the liver to synthesize and oxidize long chain fatty acids and triglycerides has been well established. It has also been shown that peripheral tissues are capable of oxidizing long chain fatty acids for energy, although the tendency to regard the liver as the major oxidative site for lipids *in vivo* has persisted. Some excellent studies in recent years have challenged this entrenched, older concept and have yielded an ever increasing role to the peripheral tissues, especially muscle, in direct utilization of long chain fatty acids(1). There have however been conflicting reports(1,2,3) concerning the oxidation of short chain fatty acids by extrahepatic tissues. The studies presented here were designed to explore the extent to which peripheral tissues of rats, in which the liver had been excluded from the circulation are capable of oxidizing a C^{14}-labeled, 8-carbon fatty acid.

Method. Ten fasted male albino rats weighing 300-475 g were anesthetized intraperitoneally with sodium pentobarbital (30 mg/kg), divided into 2 equal groups and prepared for surgery.

Group 1. In each animal a 1½ cm inguinal incision was made, the femoral vein was isolated and a small polyethylene catheter was inserted through this vein for a distance of 1.5 cm into the inferior vena cava. The catheter, which was attached to a 2 ml syringe, was secured and maintained in place throughout the experiment.

Group 2. A 4 cm median abdominal incision was made in each rat and the following steps taken in the order listed: 1) ligatures were tied around mesenteric and hepatic arteries; 2) portal vein was ligated at the hilus of the liver; 3) a catheter was inserted into the inferior vena cava just above the entrance of the common iliac veins and maintained in place. Throughout the experiment a slow infusion of 5% dextrose in water at the rate of 2 ml per hour was administered.

A 10% solution of sodium octanoate was prepared at a pH of 7.5. Each milliliter of this solution contained 90 mg of sodium octanoate and 2 microcuries of carboxyl-C^{14} sodium octanoate, prepared by the New England Nuclear Corp. with a specific activity of 13.7 millicuries per millimole. After completion of the surgery, each rat was immediately placed in a clear plastic container, which was connected to a system for continuous analysis of expired radioactive CO_2 as described pre-

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TABLE I. Recovery Rates of $C^{14}O_2$ Following Sodium Octanoate Infusion in 5 Normal Rats.

Animal	Wt (g)	Amt of sodium octanoate (mg)	Dose of RAO (μc)	Delay time (min)	% dose recovered
9E	350	90	2	2	34.6
41A	475	90	2	3	24.0
10C	370	90	2	3	25.0
17E	310	90	2	1	30.6
34	330	90	2	1	23.0
				Avg	27.4

TABLE II. Post-Infusion Recovery Rates of $C^{14}O_2$ in 5 Rats with Exclusion of Hepatic Circulation.

Animal	Wt (g)	Amt of sodium octanoate (mg)	Dose of RAO (μc)	Delay time (min)	% dose recovered
1E	340	90	2	2	26.0
12E	350	90	2	1	21.1
14D	370	90	2	1.5	29.4
17E	300	90	2	2	20.5
34	290	90	2	3	21.4
				Avg	23.7

viously (Fig. 1)(4). A 1 cc infusion of the above solution was administered to each animal over a period of 5-6 minutes through the catheter into the inferior vena cava. A microburet was used to assure a slow and uniform rate of injection. From the time activity was first observed on the recorder chart, the expired radioactive CO_2 was continuously measured for 60 minutes. Total amount of $C^{14}O_2$ recovered during this period was expressed as percentage of the administered dose.

Results. In the 5 control rats in Group I an average of 27.4% (range 23.0-34.6%) of the administered dose of radioactivity was recovered as $C^{14}O_2$ in 60 minutes (Table I). In the 5 rats in Group II, in which the liver had been excluded from circulation, an average of 23.7% (range 20.5-29.4%) of $C^{14}O_2$ was recovered (Table II). The delay time, *i.e.,* the interval from the point at which infusion of the labeled fatty acid was begun until the point at which radioactivity was first observed on the recorder chart, was identical for both groups, ranging from 1 to 3 minutes.

Discussion. A number of *in vitro* experiments have shown that extrahepatic tissues, such as skeletal muscle, heart and adipose tissue, are capable of oxidizing long chain fatty acids(1,6,7,8). *In vivo* studies of extrahepatic fatty acid oxidation, however, remain incomplete and controversial. Goldman *et al* have shown that the exclusion of the liver from the circulation considerably depresses the oxidation of palmitic acid in the dog(9). Other studies with short chain fatty acids also emphasize the importance of the liver in fatty acid metabolism(2,10). Geyer *et al* on the other hand, using short chain as well as long chain fatty acids and comparing their oxidation in normal and partially and totally hepatectomized rats, were unable to demonstrate a significant difference in fatty acid utilization(3).

Our results indicate that, when the liver is excluded from the circulation, rat peripheral tissues are capable of oxidizing octanoic acid

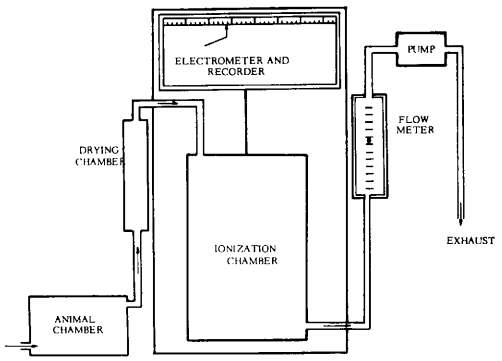

FIG. 1. Apparatus for continuous analysis of expired radioactive CO_2.

at nearly the same rate as rats with intact livers. The method of hepatic exclusion used in these experiments has been previously shown to reproduce the effects of a total hepatectomy in their entirety(11). The slightly lower rate of $C^{14}O_2$ recovery in Group 2 may be due to (1) reduced ventilation because of the more extensive abdominal incision or (2) reduction of total tissue, potentially capable of oxidizing the octanoate and subsequent reduction in CO_2 production(3) or (3) the sparing action of the infused glucose on fatty acid oxidation. Previous experiments in our laboratory have shown that the intact rat can completely oxidize a maximum of 90-100 mg of octanoic acid in one hour. It is quite likely therefore that by excluding the liver, pancreas and intestine from the circulation, the oxidative capacity of the tissues was exceeded by the 90 mg dose of octanoate administered. A slight inhibition of octanoate oxidation after administration of large doses of glucose was noted in rats by Lossow and Chaikoff(12). The continuous infusion of small amounts of glucose to our animals to prevent hypoglycemia induced by the hepatic exclusion procedure, may therefore theoretically also have contributed to the slight difference in octanoate oxidation. These results are at variance with those of Dye and Marsters, who noted a marked depression of octanoate oxidation in dogs, in which the liver, intestines and kidneys had been removed(2). In our studies as well as in those of Geyer *et al,* nephrectomies were not performed(3). The absence of the kidneys may be responsible for the differences observed.

In many ways octanoic acid would seem to be an ideal fatty acid to determine the oxidative capacity of peripheral tissues, since it does not enter the adipose tissue and is oxidized completely at a steady rate in the fasted animal(13). These facts coupled with our studies suggest that the oxidative potential of the peripheral tissues is similar if not identical to that of the liver in the case of octanoic acid. It is not possible, however, to estimate from these studies to what extent peripheral tissues normally utilize fatty acids as an energy source *in vivo.*

Summary. The oxidation of intravenously administered carboxyl-labeled octanoic acid was estimated in 2 groups of rats by continuously measuring and recording the expired $C^{14}O_2$ in a carbon-14 analyzer. In 5 normal rats an average of 27.4% of the administered dose of radioactivity was recovered in the expired air in one hour. In 5 rats in which the liver had been excluded from the circulation an average of 23.7% was recovered. These results suggest that extrahepatic tissues of the rat are capable of oxidizing octanoic acid at nearly the same rate as the intact animal.

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