Journal of Clinical Investigation
Vol. 42, No. 10, 1963

FATTY-ACID METABOLISM BY HUMAN ADIPOSE TISSUES *

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(Submitted for publication April 11, 1963; accepted July 3, 1963)

The metabolic activity of rat and mouse adipose tissues has been much investigated and the work extensively reviewed (1–3). Work on human adipose tissue, on the other hand, has been very limited and has chiefly dealt with its composition as affected by various diets (4–6). A study of the metabolic activity of human adipose tissues has been reported by Gellhorn and Marks (7). They compared the incorporation of acetate-1-C^{14} into lipids of human subcutaneous adipose tissue with that of lipomas and found a much higher activity in the latter tissue.

The tissue most easily obtained by biopsy from humans for metabolic studies is the subcutaneous adipose tissue (5, 6). It has to be established whether the analysis of the metabolic activity of this type of tissue yields results representative of the over-all activity of adipose tissues. We therefore undertook to compare the metabolic activity and composition of two types of human adipose tissues, subcutaneous and omental, obtained during surgical intervention.

METHODS

Adipose tissues were obtained from surgical patients with normal liver tests and normal blood glucose, cholesterol, and FFA. Twenty-two patients (nine men and thirteen women) ranging in age from 25 to 62 years were studied. After a fast of 8 to 12 hours, surgery was performed under general anesthesia consisting of pentobarbital, nitrous oxide, and cyclopropane. No ether was used. The adipose tissues obtained were kept in calcium-free Krebs-Ringer-phosphate buffer (8) at room temperature. Preliminary experiments with rat adipose tissues have shown that tissues kept on ice before the incubation showed decreased palmitate uptake and esterification. Preservation at room temperature for 3 hours did not cause any measurable decrease in activity (Table I). Usually 1 to 2 hours elapsed between the operative removal of the tissue and the beginning of the incubation.

Assimilation of palmitate was determined by incubation of 200- to 250-mg pieces of adipose tissue, sliced free-hand about 2 mm thick, at 37° C in 1.2 ml of a medium containing 2 to 3 μc sodium palmitate-1-C^{14} with 1.0 to 1.2 μmoles sodium palmitate carrier and 10 μmoles glucose dissolved in a 5% solution of bovine serum albumin in calcium-free Krebs-Ringer-phosphate buffer at pH 7.4 (8). At the end of the indicated incubation periods, the fatty acids in the medium and tissues and the tissue glycerides were extracted and analyzed as described by Kerpel, Shafrir, and Shapiro (9).

Release of FFA by the tissues was measured by incubation, as above, of 200- to 250-mg pieces of tissue in calcium-free Krebs-Ringer-phosphate solution containing 5% fatty acid-poor bovine serum albumin.[1] Extraction and analysis were performed as described by Dole (10).

Neutral lipid synthesis from uniformly labeled glucose-C^{14} or acetate-1-C^{14} was determined by incubation of 200- to 250-mg pieces of tissue in 1.2 ml Krebs-Ringer-phosphate solution containing 5% serum albumin and 12 μmoles glucose or sodium acetate with an activity of about 2 μc; in a few experiments, the buffer was Krebs-Ringer-bicarbonate. The activity in the long-chain fatty acids and glycerides was determined as above (9).

Nitrogen was determined by a modification of Lang's method (11) after tissue was defatted as described by Itzhaki and Wertheimer (12).

RESULTS

The neutral fat and FFA content of human omental and subcutaneous adipose tissue was identical, and only a small difference was found in their nitrogen content (Table II).

In contrast to this similarity in composition, the two adipose tissues differed markedly in their abilities to synthesize fatty acids. Lipid synthesis from acetate-1-C^{14} was twenty times greater in omental than in subcutaneous tissue. Conversion of glucose into neutral lipids was only twice as great in omental as in subcutaneous adipose tissue; the results were similar whether the

* Investigation supported in part by research grant A-3038 from the National Institute of Arthritis and Metabolic Diseases, Bethesda, Md., and by the Hebrew University-Hadassah Research Committee Fund, Jerusalem, Israel.

[1] Pentex Corp., Kankakee, Ill.

TABLE I

Effect of storage on rat adipose-tissue metabolism

Storage time	FFA release by epididymal adipose tissue			
	Storage at room temp. (20–23° C)		Storage in crushed ice (2–4° C)	
	No addition	+ Epinephrine 3 μg/ml	No addition	+ Epinephrine, 3 μg/ml
min	*μEq/100 mg tissue*		*μEq/100 mg tissue*	
0	0.079	0.90	0.050	0.56
30	0.080	0.70	0.055	0.57
60	0.087	0.75	0.075	0.61
120	0.060	0.59	0.078	0.50
180	0.075	0.67	0.073	0.58
	Palmitate-1-C^{14} uptake by adipose tissue			
	Epididymal	Mesenteric	Epididymal	Mesenteric
	%/100 mg tissue		*%/100 mg tissue*	
0	30.0	39.0	33.0	43.0
30	31.0	44.0	15.0	41.5
60	28.5	47.0	13.5	33.0
120	29.2	43.7	11.2	12.5
180	27.8	45.6	12.4	12.0

incubation was carried out in Krebs-Ringer-phosphate or Krebs-Ringer-bicarbonate buffer (Table III).

The uptake from the medium of palmitate-1-C^{14} (Figure 1) was much higher in omental adipose tissue. This difference was mainly due to the relative inactivity of the subcutaneous tissue in esterifying the fatty acids taken up by the tissue. FFA rapidly accumulated in subcutaneous tissue, but their removal into the ester fraction was very slow (Table IV).

Release of FFA from both types of human adipose tissue was low (Table V) when compared to that of rat or mouse adipose tissues (13), and it fluctuated widely from one specimen to another when compared with the other species. Addition of epinephrine at a final concentration of 3 or 15 μg per ml had only a very small effect. Storage of the adipose tissues in Krebs-Ringer-phosphate-Ca^{++} solution and subsequent incubation in that buffer caused no change in the amount of FFA released nor in the susceptibility of the tissue to stimulation by epinephrine.

DISCUSSION

The nearly identical composition of the two human adipose tissues, omental and subcutaneous, contrasts sharply with the marked differences in their metabolic activity.

Our results showed that incorporation of acetate into neutral lipids was twenty times greater in omental than in subcutaneous tissue. Similar results with rat adipose tissues were reported by Benjamin, Gellhorn, Wagner, and Kundel (14). They also report unpublished experiments with human adipose tissue in which they found lipid synthesis from acetate to be ten to seventy times greater in the omental than in the subcutaneous fat from the same subject. Similar differences in metabolic activity were found in fatty acid incorporation and esterification. It could be shown that the physical penetration of FFA into sub-

TABLE II

*Adipose-tissue composition**

Tissue	No. of samples	Neutral lipids	FFA	Nitrogen
		% wet wt tissue		*mg/g tissue*
Omental	10	66.5 ± 5.5	0.161 ± 0.031	3.95 ± 0.51
Subcutaneous	16	70.6 ± 3.5	0.147 ± 0.024	3.17 ± 0.36

* Values ± SEM.

TABLE III

*Incorporation of acetate-1-C^{14} and glucose-C^{14} into neutral lipids**

	Subcutaneous adipose tissue			Omental adipose tissue		
	No. of experiments	Per 100 mg wet wt	Per mg N	No. of experiments	Per 100 mg wet wt	Per mg N
		mμmoles	*mμmoles*		*mμmoles*	*mμmole*
Acetate 1-C^{14}	14	10.8 ± 1.85	45.0 ± 7.5	9†	232 ± 78	588 ± 120
				2‡	295	
Glucose-C^{14}	14	131 ± 15.4	540 ± 60	9†	234 ± 33.5	735 ± 121
				2‡	176	

* Values ± SEM.
† Incubation in Krebs-Ringer-phosphate buffer.
‡ Incubation in Krebs-Ringer-bicarbonate buffer.

cutaneous adipose tissue does not lag behind that of omental tissue. The active assimilation by means of esterification, however, is very slow in the first type of tissue, and FFA accumulate rapidly and check uptake from the medium.

It may be assumed that each tissue fulfills different functions in the organism, with subcutaneous adipose tissue acting mainly as insulation and support and contributing little to the metabolic tasks of the adipose tissues. Release of FFA was low in both types of tissue. Susceptibility to stimulation by epinephrine was also very low, compared to that found with rat tissues. The low activity of human adipose tissues in the release of FFA raises the question whether this function is sluggish in these tissues per se, or whether the conditions were unsuitable for revealing it. Gordon (15), who showed, with Cherkes (16), large negative a-v differences in the blood obtained from the greater saphenous

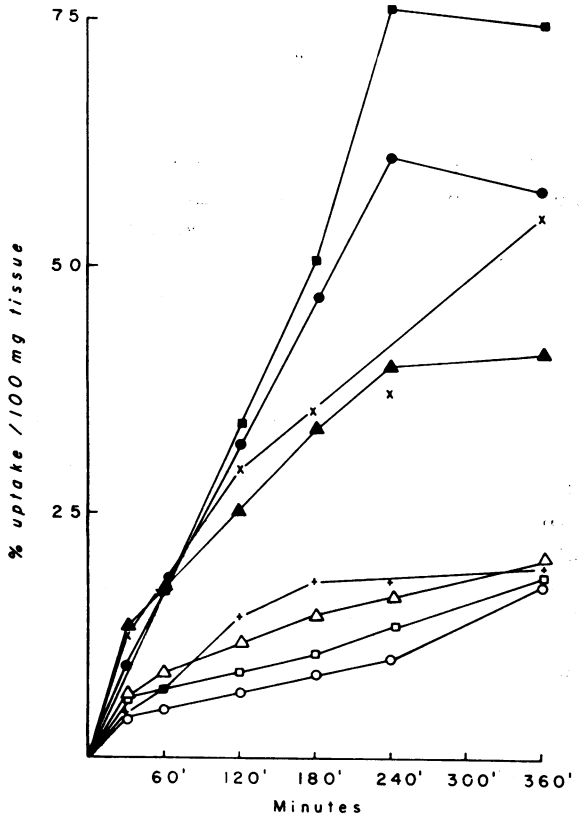

FIG. 1. TIME CURVE OF PALMITATE-1-C^{14} UPTAKE BY HUMAN ADIPOSE TISSUES. For experimental details, see Methods. Each curve represents a separate experiment; solid figures represent data with omental adipose tissue, and open figures, data with subcutaneous adipose tissue.

TABLE IV

Percentage of palmitate-1-C^{14} from medium incorporated into tissue glyceride and FFA fractions

Incubation time	No. of experiments	FFA	Glycerides
hours		%	%
Omental adipose tissue			
.5	4	2.70 ± 0.49	9.82 ± 0.86
1	4	1.96 ± 0.57	15.70 ± 0.55
2	4	2.10 ± 0.49	27.80 ± 2.05
3	4	3.46 ± 0.22	40.0 ± 3.02
4	4	4.22 ± 0.15	50.5 ± 8.90
6	4	3.26 ± 0.75	51.75 ± 5.80
Subcutaneous adipose tissue			
.5	10	3.03 ± 0.25	1.35 ± 0.13
1	9	3.18 ± 0.36	2.52 ± 0.57
2	10	2.95 ± 0.38	6.42 ± 0.82
3	10	2.82 ± 0.28	10.40 ± 1.65
4	10	3.21 ± 0.50	12.20 ± 1.33
6	8	2.64 ± 0.47	17.20 ± 2.40

TABLE V

*Release of FFA from adipose tissue after 2-hour incubation**

Adipose tissue source of FFA	No. of experiments	FFA released		
		No addition	+ Epinephrine 3 μg/ml	+ Epinephrine 15 μg/ml
			μEq/100 mg tissue	
Omental				
In tissue	6	0.250 ± 0.10	0.332 ± 0.114	0.294 ± 0.098
In medium	9	0.072 ± 0.011	0.181 ± 0.034	0.230 ± 0.055
Subcutaneous				
In tissue	13	0.200 ± 0.087	0.254 ± 0.075	0.262 ± 0.061
In medium	17	0.108 ± 0.016	0.146 ± 0.015	0.184 ± 0.010

* Values ± SEM.

vein as well as a considerable increase in plasma FFA after iv infusion of epinephrine to human subjects, has results supporting the second assumption.

Excision of a lipoma was performed in one of the patients in our series, and we compared the metabolism of the adjacent normal subcutaneous adipose tissue with that of the tumor. Our results were similar to those reported by Gellhorn and Marks (1). The synthesis of long-chain fatty acids was twenty times greater in the lipoma than in the subcutaneous adipose tissue. Also, the tumor nitrogen content was lower than that of the subcutaneous adipose tissue. No difference was found in palmitate-1-C^{14} uptake and esterification rate between the lipoma and subcutaneous adipose tissue. These results support the hypothesis of Gellhorn and Marks that a disturbance in lipid synthesis is a major factor leading to fat accumulation in the lipoma.

SUMMARY

The composition and metabolic activity of human omental and subcutaneous adipose tissues were compared. There were no significant differences in nitrogen, free fatty acid, and neutral fat content of the omental and subcutaneous tissues. The uptake of palmitate-1-C^{14} was much higher in omental than in subcutaneous adipose tissue. A considerably higher percentage of palmitate-1-C^{14} taken up was esterified by the omental than by the subcutaneous tissue. Synthesis of long-chain fatty acids was ten to twenty times greater in omental than in subcutaneous adipose tissue when tested with acetate-1-C^{14} and about two times greater with glucose-C^{14}. Free fatty acid release was low from both types of adipose tissue.

ACKNOWLEDGMENTS

The authors wish to thank Prof. B. Shapiro for his valuable assistance in the experimental part of this work as well as for his helpful suggestions in the preparation of the manuscript. Thanks are also due to Drs. T. Wishnitzer and N. Benhur for providing adipose tissues.

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