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Functional capacity of adipose tissue in human obesity and hyperlipidaemia

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1. Fifteen 'constitutionally' obese subjects, eleven hyperlipidaemic subjects of mixed-type and fourteen normal subjects were studied.

2. With a reduction in energy intake (range 3·3–4·2 MJ) for 21 d, there was no change in the levels of plasma total cholesterol (TC) and triglyceride (TG) of obese subjects, but the free fatty acid levels increased. However, in hyperlipidaemic subjects there was a reduction in levels of TC and TG with no increase in levels of free fatty acids.

3. There was a significant increase in the serum ketone levels of obese subjects but not in those of hyperlipidaemic subjects. The reduction of the respiratory quotient to a value of 0·7 was more rapid in the obese than in hyperlipidaemic subjects.

4. After administration of a fat load (0·5 g/kg gross body-weight) there was no change in plasma TG levels in obese subjects but there was an increase in those of normal subjects.

5. After administration of a glucose load (1 g/kg ideal body-weight) there was a significant reduction in plasma TG levels in obese subjects but no change in those of hyperlipidaemic subjects.

6. Hyperlipidaemic subjects eating their normal diet were found to have a hydroxybutyrate: acetoacetate ratio three- to fivefold that of obese and normal subjects.

7. These results suggest that obese subjects have an increased ability to store fatty acids, to mobilize them quickly and to generate fatty acid metabolites in the form of ketone bodies, while these same metabolic functions are reduced in hyperlipidaemic subjects.

The main function of adipose tissue is the storage and redistribution of plasma fatty acids (FA). Their storage is one method of clearing lipoprotein from the plasma. Lipoprotein lipase activity and glycolysis to provide α-glycerophosphate for re-esterification in adipocytes, are the main regulators of this clearance system. The redistribution of FA is regulated through adipocyte hormone-sensitive lipase activity. Under conditions in which utilization of FA for oxidation and lipoprotein biosynthesis can be experimentally modified and controlled, i.e. reduction of energy intake, or triglyceride (TG) or glucose load, the functional capacity of adipose tissue is reflected in the variations of FA and their metabolites in the plasma.

There is no classification of human obesity based on metabolic or biochemical measurements. 'Constitutionally' or 'metabolically' obese subjects were defined as those maintaining a stable body-weight from 1 to 6 months with a diet (determined by interview) providing less than 20% energy above their basal metabolic rate (BMR). The total cholesterol (TC) levels in these subjects are low and the plasma TG are at the upper limit of the normality range.

The purpose of this work was to explain the functional capacity of adipose tissue in regulating FA and their metabolites in the plasma, comparing a group of 'constitutionally' obese (group 1), to hyperlipidaemic subjects of mixed-type (group 2)

and normal subjects (group 3). In each group, variations in total lipids (TL), TC, TG, free fatty acids (FFA), β-hydroxybutyrate (β-HOB), acetoacetate (AcAc), lactate and pyruvate levels were examined after: (*a*) a reduction in energy intake for 21 d in groups 1 and 2; (*b*) a glucose load of 1 g/kg ideal body-weight in groups 1 and 2 and (*c*) a triglyceride load of 0·5 g/kg gross body-weight in groups 1 and 3. We also measured respiratory exchanges to estimate the lipid: carbohydrate ratio in oxidation or lipogenesis.

METHODS

Normal group. Subjects were fourteen laboratory workers, average age 43 years (range 25–57), average weight 64·8 kg (range 51·5–82) exceeding their ideal body-weight (Geigy, 1959) by an average of 10% (range −2 to +14). Their normal diet, determined by interview, provided daily (mean ± SD) 9·25 ± 0·88 MJ; 86 ± 5·1 g protein; 89 ± 13 g fat. On the day before administration of a glucose load, ten subjects (five male, five female) were given a diet providing (mean ± SD) 8·82 ± 0·64 MJ; 74 ± 5·6 g protein; 74 ± 12 g fat and before administration of the TG load, four male subjects received a diet providing (mean ± SD) 10·5 ± 0·11 MJ; 99 ± 17 g protein; 80 ± 12·7 g fat.

'*Constitutionally*' obese group. These were thirteen female and two male subjects, average age 35 years (range 18–51). Their normal diet (by interview) provided daily 5·6 ± 0·88 MJ; 66 ± 1·9 g protein; 43 ± 8·7 g fat. Their actual mean body-weight was 87 kg (range 81–96) exceeding their ideal body-weight (Geigy, 1959) by 51% (range 35–62%).

Before administration of the glucose load, seven subjects (one male, six female) received for 8–21 d a diet providing 3·96 ± 0·56 MJ/d. Before administration of the lipid load, four female subjects received 2·94 MJ/d.

Hyperlipidaemic group. Eleven subjects with mixed-type hyperlipidaemia (eight male, three female), average age 52 years (range 34–63), were studied. The mean body-weight was 61 kg (range 52·8–72) exceeding their ideal body-weight by 6% (range −2 to +2·7). Their previous diet had provided daily 7·3 ± 1·51 MJ; 74 ± 10·4 g protein; 73 ± 14·5 g fat.

The glucose load was administered to four subjects (three male, one female) after 21 d on a diet providing daily 5·7 ± 0·5 MJ; 74 ± 6·6 g protein; 67 ± 11·3 g fat. Seven subjects (five male, two female) were given the load after being given a diet providing 3·3 MJ/d for 21 d.

Experimental procedure

At 08.00 hours after 12–14 h fasting, subjects rested for 15 min and gas-exchange measurements were done. A blood sample was taken at 08.30 hours. At 09.00 hours, a load of 1 g glucose/kg ideal body-weight or 0.5 g oil (peanut or rapeseed)/kg actual body-weight was administered orally. Blood samples were taken 45 and 120 min after the glucose load, and 150 and 210 min after the oil load.

Analytical procedures

Lipid metabolites were separated by agarose gel electrophoresis by the method of Lees & Hatch (1963) modified by Noble (1968). TL content was estimated by the colorimetric method of Zöllner & Kirsch (1962). FFA levels were estimated using the method of Duncombe (1963, 1964) and TG levels by the method of Schmidt & von Dahl (1968). β-HOB and AcAc levels were estimated by the enzymic method of Williamson, Mellanby & Krebs (1962).

The amounts of glucose metabolites were estimated as follows: glucose by the glucose-oxidase method of Keston (1956), lactate and pyruvate by the enzymic method of Hohorst, Kreutz & Bücher (1959) using the neutralized filtrate obtained after deproteinization with 10% perchloric acid (1 ml perchloric acid: 2 ml plasma), alanine by the method of Pfleiderer (1965), and free glycerol by the method of Schmidt & von Dahl (1968).

Respiratory exchange was determined using the technique of Trémolières, Dontcheff & Huot (1966), in which CO_2 output was estimated by a weighing method.

Statistical analysis

Results are given as mean and standard error of the mean after verifying that the values have a 'normal' or 'log-normal' distribution (Lowy & Manchon 1968–9). The between-group variation was determined using the '*F*' test (Lowy & Manchon 1968–9).

RESULTS

Plasma levels after 12 h fasting. Table 1 indicates that in obese subjects given a 'spontaneous' reducing diet ($5{\cdot}7 \pm 0{\cdot}9$ MJ/d) there was a significant increase in TG, FFA, β-HOB and AcAc levels compared with those of normal subjects. Hyperlipidaemic subjects given a diet providing more energy ($7{\cdot}3 \pm 1{\cdot}5$ MJ/d) than that of the obese group but less than that of the normal group, were found to have a higher level of TL, TC, TG, FFA but not of ketone bodies.

Effect of reduction of energy intake in obese subjects compared to that in hyperlipidaemic subjects. Table 2 shows that after 21 d on a diet providing $3{\cdot}96 \pm 0{\cdot}56$ MJ/d, β-HOB and AcAc levels of obese subjects increased, TL levels decreased while TC and TG levels remained unchanged. The mean FFA level increased but the variation was not statistically significant. In the hyperlipidaemic subjects given a diet providing 3·3 MJ/d, there was a significant decrease in TL, TC, TG and FFA levels. There was no increase in the plasma levels of β-HOB or AcAc.

These results suggest an inability of the adipose tissue of the hyperlipidaemic group to mobilize its FA on a reduced diet, and to control the level of plasma lipoprotein on a higher energy intake. The reverse occurs in 'constitutionally' obese subjects, and can be related to the rapid reduction in respiratory quotient (RQ) found in these subjects after a 12 h fast (Table 5). Our thesis is that adipose tissue failed in its storage and mobilization functions in the hyperlipidaemic group, these functions being augmented in the obese.

Table 1. *Amounts of lipid and glucose metabolites in plasma of eleven normal, six 'constitutionally' obese and eleven hyperlipidaemic subjects after a* 12 h *fast*

(Mean values with their standard errors; no. of subjects in parentheses)

	Normal (11)		Obese (6)		Hyperlipidaemic (11)	
	Mean	SE	Mean	SE	Mean	SE
Plasma metabolite						
Total lipid (g/l)	7·66	0·41	7·03	0·47NS	11·51	0·66**
Total cholesterol (mmol/l)	5·18	0·22	4·69	0·34NS	8·24	0·41**
Triglycerides (g/l)	1·11	0·11	1·81	0·11*	2·79	0·22**
Free fatty acids (μequiv./l)	652	63	1050	219**	1330	188**
β-hydroxybutyrate (μmol/l) (β-HOB)	164	25	568	54**	134	21NS
Acetoacetate (μmol/l) (AcAc)	23·1	7·6	119	11**	31·9	5·7NS
β-HOB: AcAc	7·3	1·2	4·75	0·63*	4·19	0·13*
Glucose (mmol/l)	5·36	0·21	4·60	0·89NS	5·10	0·24NS
Lactate (mmol/l) (L)	1·529	0·165	1·424	0·170NS	1·600	0·131NS
Pyruvate (μmol/l) (P)	64·2	4·3	61·9	6·4NS	74·2	7·5NS
L:P	23·8	2·4	23·6	2·2NS	21·6	1·7NS
Alanine (μmol/l)	563	71	780	186NS	627	84NS

NS, not significant; * $P < 0.05$; ** $P < 0.01$.

Table 2. *Effects of reducing energy intake for* 21 *d, on levels of lipid and glucose metabolites in plasma of seven mixed-type hyperlipidaemic and seven 'constitutionally' obese subjects*†

(Mean values with their standard errors)

Energy intake (MJ/d) ...	Hyperlipidaemic 3·3				Obese 3·96 ± 0·56			
	Day 0		Day 21		Day 0		Day 21	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Plasma metabolite								
Total lipid (g/l)	10·96	0·58	8·69	0·42**	7·51	0·26	5·63	0·26**
Total cholesterol (mmol/l)	8·00	0·52	5·83	0·36**	5·21	0·29	4·69	0·29NS
Triglycerides (g/l)	2·66	0·22	1·92	0·32**	1·61	0·17	1·54	0·17NS
Free fatty acids (μequiv./l)	1551	322	650	122*	998	240	1600	240NS
β-hydroxybutyrate (β-HOB) (μmol/l)	146	22	149	15NS	362	65	733	65**
Acetoacetate (AcAc) (μmol/l)	40·9	7·6	51·0	9·7NS	57	16	145	16**
β-HOB:AcAc	3·5	0·47	2·9	0·4NS	6·3	1·3	5·0	0·5
Glucose (mmol/l)	5·27	0·27	5·00	0·24NS	5·05	0·27	4·77	0·27NS
Lactate (mmol/l)	1·559	0·132	1·034	0·065NS	1·315	0·161	1·151	0·161NS
Pyruvate (μmol/l)	70·7	9·6	65·3	5·0NS	73·4	4·6	79·6	4·6NS

NS, not significant; * $P < 0.05$; ** $P < 0.01$.

† For details of previous diets see p. 274.

Table 3. *Effects of administration of a glucose load* (1 *g/kg ideal body-weight*) *on levels of lipid and glucose metabolites in plasma of eleven normal* (*N*), *ten mixed-type hyperlipidaemic* (*H*) *and six 'constitutionally' obese* (*O*) *subjects* 0, 45 *and* 120 *min after loading*

(Mean values with their standard errors)

		Sampling time after administration of load (min)					
		0		45		120	
		Mean	SE	Mean	SE	Mean	SE
Total cholesterol (mmol/l)	H	8·24	0·42	7·93	0·44NS	7·64	0·42NS
	O	4·69	0·35	4·64	0·34NS	4·53	0·35NS
	N	5·18	0·22	4·92	0·23NS	4·82	0·22NS
Triglycerides (g/l)	H	2·79	0·22	2·53	0·12NS	2·52	0·12NS
	O	1·81	0·11	1·65	0·09*	1·64	0·09NS
	N	1·11	0·11	0·95	0·12**	0·79	0·12**
Free fatty acids (μequiv./l)	H	1330	188	1003	286NS	1006	298NS
	O	1050	219	467	87**	375	87NS
	N	652	63	451	55**	330	55**
β-hydroxybutyrate (μmol/l)	H	134	21·3	134	32·8NS	123	17·8NS
	O	568	53·7	573	53·7NS	330	60·7*
	N	164	24·6	135	27·7NS	150	18·2NS
Acetoacetate (μmol/l)	H	31·9	5·70	15·4	2·54*	9·89	0·80*
	O	11·9	11·3	132	11·3NS	93	13·4*
	N	23·1	7·53	11·9	2·08NS	8·6	1·21NS
Glucose (mmol/l)	H	5·10	0·25	7·88	0·62**	5·82	0·46*
	O	4·55	0·91	7·38	0·91**	6·55	0·91NS
	N	5·36	0·21	7·71	0·59**	5·54	0·22**

NS, not significant; * $P < 0·05$; ** $P < 0·01$.

Effects of administration of a glucose load. Table 3 shows that in hyperlipidaemic subjects, compared with obese and normal subjects, administration of a glucose load did not produce a significant decrease in TG or FFA levels but did produce a decrease in AcAc levels. In obese subjects under similar hyperglycaemic conditions there was a decrease in plasma TG and FFA levels.

Effects of administration of an oil (*TG*) *load.* Table 4 shows that in obese subjects, there was no significant increase in TG levels compared with normal subjects, but glycerol levels were increased and glycaemia was reduced.

Therefore, with this energy intake, the obese subject has a greater ability to store FA, i.e. remove FA from plasma.

Effects of a reduced energy intake and of glucose load on respiratory exchanges. Table 5 shows that in obese subjects given a low-energy diet, RQ was reduced more rapidly than in hyperlipidaemic patients. In all subjects energy expenditure was the same, and a glucose load produced an increased glucose oxidation when RQ was lowered by reducing energy intake.

DISCUSSION

Figs. 1 and 2 summarize the results and suggestions for a physiopathological explanation for the information obtained.

Table 4. *Effects of administration of an oil load (rapeseed or peanut oil, 0·5 g/kg gross body-weight) on plasma levels of lipid and glucose metabolites in four normal male and four obese female subjects, 0, 150, and 210 min after loading*

(Mean values with their standard errors; no. of subjects in parentheses)

Time after loading (min) ...	Normal (4)						Obese (4)					
	0		150		210		0		150		210	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Glucose (mmol/l)	4·93	0·082	4·48	0·082**	4·81	0·082NS	4·09	0·133	3·89	0·150NS	3·74	0·159NS
Total lipids (g/l)	9·36	0·236	10·34	0·236*	10·34	0·236*	9·09	0·728	8·86	0·826NS	9·08	0·826NS
Cholesterol (mmol/l)	6·69	1·06	6·90	1·07NS	6·78	1·07NS	6·32	0·383	6·14	0·435NS	6·09	0·435NS
Triglycerides (g/l)	1·33	0·159	1·71	0·159NS	1·89	0·159*	1·22	0·154	1·44	0·175NS	1·22	0·173NS
Free glycerol (mg/l)	5·6	1·10	6·9	1·10NS	6·7	1·10NS	5·6	1·70	9·2	1·70NS	5·7	1·70NS
Free fatty acids (μequiv./l)	897	76·8	914	78·8NS	1283	109·6*	1655	210·9	1643	239·2NS	2019	239·2NS
Lactate (mmol/l) × 10	0·98	0·119	1·21	0·119NS	1·05	0·119NS	1·12	0·165	1·37	0·187NS	1·22	0·197NS
Pyruvate (μmol/l)	84·2	4·14	76·3	4·14NS	73·6	4·14NS	69·1	5·90	68·1	6·68NS	78·3	7·05NS
β-hydroxybutyrate (μmol/l) (β-HOB)	45·4	3·42	65·9	5·02**	125	9·39***	910	305·2	840	244·9NS	1245	258·0NS
Acetoacetate (μmol/l) (AcAc)	22·3	2·32	36·3	3·82**	59·4	6·19**	228	53·0	265	69·1NS	365	98·4NS
β-HOB:AcAc	2·04	0·206	1·83	0·212NS	2·14	0·219NS	3·47	0·312	3·08	0·297NS	3·37	0·358NS

NS, not significant; * $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

Table 5. *Changes in respiratory quotient (RQ) and energy expenditure of obese, hyperlipidaemic and normal subjects, 0, 45 and 120 min after administration of a glucose load (1 g/kg ideal body-weight)*

(Mean values with their standard errors; no. of subjects in parentheses)

	RQ						Energy expenditure (MJ/m² per d)					
Time after loading (min) ...	0		45		120		0		45		120	
Energy intake (MJ)	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Obese												
(12) 5·0–6·25 (habitual)†	0·70	0·021	0·75	0·030NS	0·80	0·036*	4·317	0·220	4·184	0·157NS	3·907	0·225NS
(5) 2·77–3·56 (after 21 d reduced intake)	0·72	0·06	0·76	0·017NS	0·74	0·036NS	4·083	0·151	4·184	0·176NS	3·786	0·250NS
Hyperlipidaemic												
(11) 5·5–6·76 (habitual)†	0·82	0·03	0·80	0·02NS	0·82	0·02NS	4·251	0·194	4·606	0·199NS	4·510	0·143NS
(9) 3·3–4·12 (after 21 d reduced intake)	0·71	0·02	0·81	0·03*	0·82	0·03**	4·242	0·212	4·171	0·159NS	4·251	0·136NS
Normal												
(9) 9·25±0·88 (habitual)†	0·79	0·039	0·81	0·028NS	0·79	0·042NS	4·188	0·219	4·543	0·245NS	4·284	0·300NS

NS, not significant; * $P < 0·05$; ** $P < 0·01$. † 'Normal' diet determined by interview.

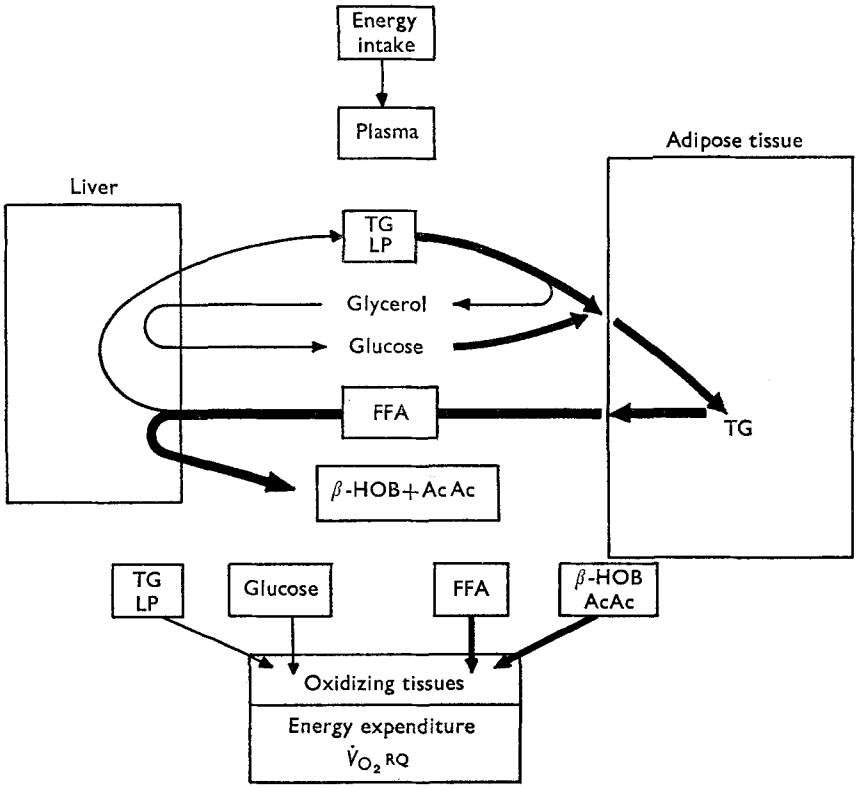

Fig. 1.* Administration of a triglyceride (TG) load (0·5 g/kg) results in no change in TG levels but a reduction in glucose levels. Administration of a glucose load produces a decrease in TG levels. Reducing energy intake resulted in an increase in free fatty acids (FFA) β-hydroxybutyrate (β-HOB) and acetoacetate (AcAc) levels. ➡, enhancement of pathway; LP, lipoprotein, $\dot{V}_{O_2}$, oxygen consumption; RQ, respiratory quotient. * From Trémolières (1973).

The results suggest that 'constitutionally' obese subjects at the energy level intake studied have an increased ability (*a*) to oxidize FA, particularly ketone bodies; (*b*) to store FA after receiving a TG load, therefore reducing glycaemia, and (*c*) to store plasma TG under conditions of hyperglycaemia.

In mixed-type hyperlipidaemic subjects, the opposite situation was found. Hyperlipidaemia was reduced when energy intake was reduced, and there was a deterioration of the process of FA mobilization from adipose tissue under fasting conditions and, as a result, an inability to generate FA metabolites in the form of ketone bodies. The increased ability of obese subjects to increase levels of ketone bodies under fasting conditions is subject to controversy.

Cahill, Owen & Morgan (1968) found that in ten obese subjects receiving only 1500 ml water/d for 5 weeks and expending 7·9 MJ energy/24 h (95 % derived from FA), the plasma levels of β-HOB, AcAc and FFA (nmol/ml) were 6330, 1110 and 2037 respectively. The rate of ketosis is six times higher than the values we obtained, but the β-HOB: AcAc ratio is the same.

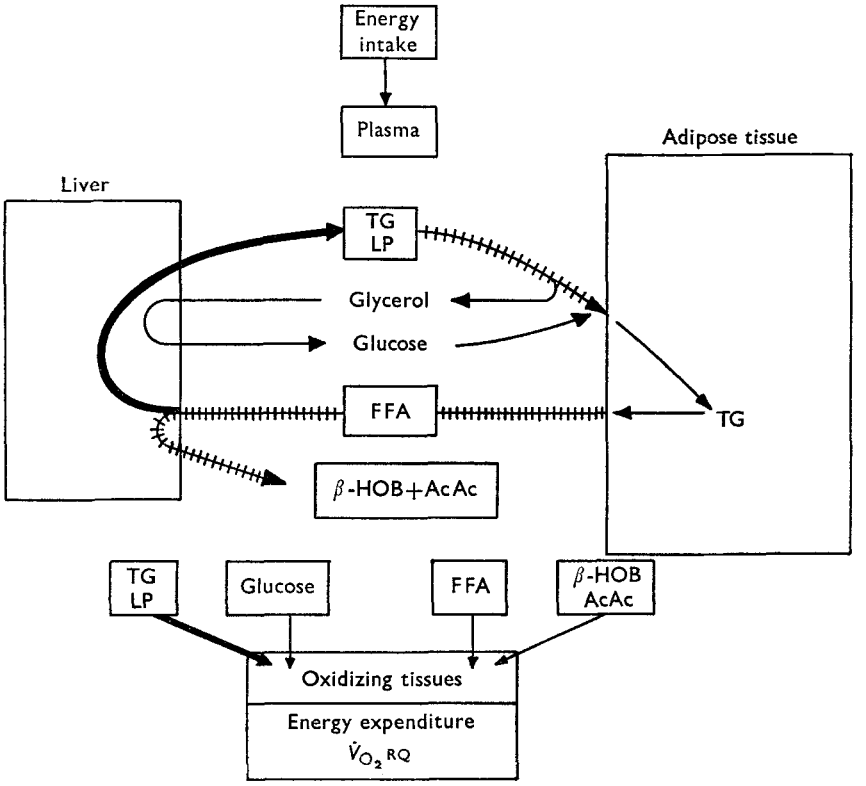

Fig. 2.* Administration of a glucose load (1 g/kg ideal body-weight) produced no reduction in triglycerides (TG) or free fatty acid (FFA) levels. Reducing energy intake resulted in a reduction in TG and total lipid levels but no increase in FFA or β-hydroxybutyrate (β-HOB) and acetoacetate (AcAc) levels. ➡, enhancement of the pathway; ⫞⫞→, diminution of the pathway; LP, lipoprotein. $\dot{V}_{O_2}$, oxygen consumption; RQ, respiratory quotient. * From Trémolières (1973).

Kekwick & Pawan (1957) reported contradictory results from experiments with ten obese subjects given a diet providing 4·2 MJ/d (90 % derived from FA, 5 % from glucose). Ketosis was apparently much slower and much lower than in normal subjects. After intravenous infusion of β-HOB (30 mg/kg body-weight) their ability to oxidize ketone bodies was unchanged. Either the type of obesity, or the composition of the pre-experimental diet may have been responsible for these different observations.

The effect of administration of a glucose load in lowering serum TG levels apparently depends on numerous factors. Waterhouse & Kemperman (1966) and Waterhouse, Baker & Rostami (1969) reported that an intravenous infusion of 0·5 g glucose/kg body-weight resulted in a reduction of 65 % in the oxidation of FA to CO_2. Barter & Nestel (1972) and Barter, Nestel & Carrol (1972) found that plasma TG levels decreased after glucose ingestion and that there was an increase in FA turnover when the glucose intake was the same as the energy expenditure. The lower plasma TG levels after glucose ingestion could be related to a temporary change in the equilibrium between the inflow and outflow of FA in adipose tissue.

Tamir, Grant, Fosbrooke, Segall & Lloyd (1968) were unable to confirm this in experiments with four men who had fasted overnight.

A reduction in blood glucose levels after administration of a TG (medium chain length FA) load, was reported by Debry, Laurent, Drouin, Méjean, Gonand & Cherrier (1969) and by Tamir *et al.* (1968) with 1 g/kg (−13 to −23 m/gl).

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