The control of fatty acid metabolism in adult diabetes

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Introduction

In diabetes mellitus there is frequently an elevation of the levels of plasma fatty acids (FA) (Hales & Randle, 1963), and even when these are normal there is an increase in their turnover (Lewis, Mancini, Mattock, Chait & Fraser, 1972). The abnormality of plasma FA metabolism may contribute to a variety of complications. For example an increase in plasma FA flux stimulates hepatic triglyceride synthesis and may therefore predispose to the hypertriglyceridaemia of diabetes. A raised level of plasma FA may compete with glucose for oxidation by various tissues such as cardiac muscle and therefore enhance the hyperglycaemia of this condition (Randle, Garland, Hales & Newsholme, 1963). It has also been proposed that increased plasma FA have a direct 'toxic' effect on the ischaemic myocardium, predisposing to cardiac arrythmias (Oliver, 1973). For these reasons it is important to define the factors responsible for the abnormality of plasma FA in diabetes with a view to possible therapy. In juvenile diabetes the major factor is considered to be insulin deficiency with loss of the antilipolytic action of insulin on adipose tissue. In adult diabetes the causes are not so clear; and hyperglycaemia with raised circulating levels of insulin would be expected to favour antilipolysis and a reduction in plasma FA. This does not occur in adult diabetes and suggests that there may be tissue rather than hormonal factors predisposing to the increase in plasma FA. Since adipose tissue is a major source of plasma FA we have investigated the regulation of lipolysis in this tissue in adult diabetes to see if a defect here could account for the abnormality of plasma FA metabolism.

Source of plasma FA

The adipose organ is a major, if not the only, source of plasma FA, and arteriovenous differences across other organs such as liver and muscle do not show a net output of FA. Furthermore the fall in plasma FA during a glucose load correlates closely with the reduction in release of FA from adipose tissue (Fig. 1), and it is found that plasma levels of FA following a glucose load correlate with the release of FA from adipose tissue (r 0·67, n=11, P<0·05) but not with the release of glycerol (Fig. 2). The fact therefore that the plasma levels of FA change in parallel with the release of FA from adipose tissue suggests that the tissue is a major determinant of plasma levels of FA.

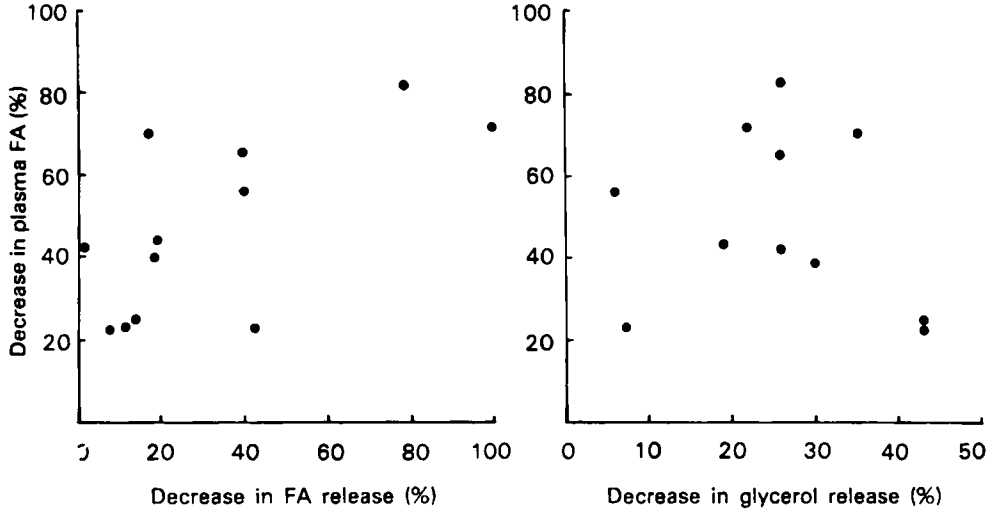

Fig. 1. Decrease in plasma fatty acids (FA) and in release of FA and glycerol from adipose tissue of diabetics during a glucose-tolerance test. Blood and adipose tissue were taken at zero-time and at 1 h after a glucose load. The percentage fall in plasma FA is related to the percentage fall in tissue release of glycerol and FA. (For plasma FA *v.* tissue release of FA, r 0·67, n=12, P<0·05. For plasma FA *v.* release of glycerol, r −0·09, n=11.)

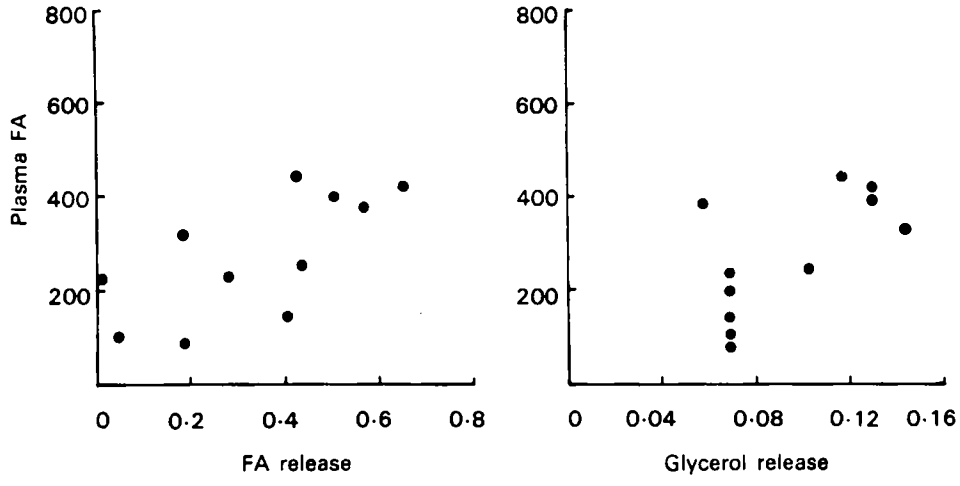

Fig. 2. Release of fatty acids (FA) and glycerol from adipose tissue (nmol/mg tissue per h) related to levels of plasma FA (μmol/l) in diabetics. Blood and adipose tissue was taken at 1 h from the start of a glucose-tolerance test and the plasma FA and tissue release of FA and glycerol were measured. Points represent individual patients. (For plasma FA *v.* tissue release of FA, r 0·67, n=11, P<0·05.)

Adult diabetes

Lipolysis. Adipose tissue from obese adult diabetics shows increased basal release of FA into an incubation medium compared to obese non-diabetic controls. However, there are no significant differences in the basal release of glycerol (Table

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1) between the two groups. When tissue is stimulated by a variety of lipolytic agents (isoprenaline, noradrenaline, noradrenaline plus phentolamine) there are no significant differences in the release of glycerol (Table 2) or in the tissue levels of cyclic AMP between diabetic and non-diabetic obese patients. In particular there is no evidence for loss of α-receptor activity or enhanced β-receptor activity on the diabetic adipocyte.

Table 1. *The release of glycerol and fatty acids (nmol/mg tissue per h) from human adipose tissue (200 mg portions) incubated for 1 h in 0·5 ml Earle's bicarbonate buffer with 10 mg bovine serum albumin/ml and no glucose*

(Mean values with their standard errors for twelve observations)

Patient group	Fatty acid release	Glycerol release
Non-diabetic obese	0·258±0·055	0·098±0·009
Diabetic obese	0·609±0·054**	0·130±0·010

Significance of difference from non-diabetic obese patients, calculated by Student's *t* test: $^{**}P<0.001$.

Table 2. *The effect of various lipolytic agents on the release of glycerol (nmol/mg tissue per h) from human adipose tissue (50–100 mg portions) incubated at 37° for 1 h in 0·5 ml Earle's bicarbonate buffer with 10 mg bovine serum albumin/ml and additions as indicated*

(Mean values with their standard errors for two incubations/patient; no. of patients in parentheses)

Patient group	Basal	+Adrenaline (10^{-4}M)	+Adrenaline (10^{-4}M), phentolamine (10^{-4}M)	+Noradrenaline (10^{-4}M)	+Noradrenaline (10^{-4}M), phentolamine (10^{-4}M)	+Isoprenaline (10^{-5}M)
Non-diabetic obese	0·191± 0·025 (10)	0·375± 0·114 (3)	0·610± 0·073 (3)	0·385± 0·038 (10)	0·658± 0·094 (10)	0·632± 0·076 (9)
Diabetic obese	0·204± 0·026 (11)	0·395± 0·056 (11)	0·543± 0·102 (11)	0·397± 0·042 (11)	0·537± 0·057 (11)	0·608± 0·093 (13)

Antilipolysis. After stimulation of lipolysis in adipose tissue the pathway is inactivated, probably by the action of prostaglandins. These are synthesized by the tissue and released with FA from the cell after stimulation of lipolysis (Shaw & Ramwell, 1968). They are potent antilipolytic agents, probably inhibiting the pathway at the level of adenylate cyclase (*EC* 4.6.1.1). It could be postulated therefore that the excessive release of FA by diabetic adipose tissue was due to loss of inhibition of the lipolytic pathway by prostaglandins. However, when this is tested in vitro, tissue from adult diabetics appears to respond normally to prostaglandins (Table 3). Another antilipolytic agent, insulin, has been tested in a similar tissue preparation and diabetic tissue was found to respond normally to the antilipolytic action of insulin. It is concluded therefore that lipolysis in adipose tissue of diabetics is regulated normally by both lipolytic and antilipolytic agents.

Table 3. *The effect of prostaglandin E_1 on the intracellular accumulation of cyclic AMP (pmol/mg tissue after 5 min) in human adipose tissue in vitro after submaximal stimulation by isoprenaline**

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

				+Isoprenaline (10^{-7}M) and prostaglandin E_1:				
Patient group	Basal	+Isoprenaline (10^{-5}M)	+Isoprenaline (10^{-7}M)	3×10^{-9}M	3×10^{-11}M	3×10^{-12}M	3×10^{-13}M	3×10^{-14}M
Non-diabetic obese	0·154±0·039 (20)	1·901±0·237 (16)	0·514±0·065 (22)	0·294±0·062 (6)	0·349±0·051 (17)	0·329±0·046 (20)	0·335±0·043 (18)	0·284±0·029 (12)
Diabetic obese	0·142±0·023 (29)	1·957±0·294 (25)	0·462±0·052 (37)	0·221±0·027 (5)	0·313±0·036 (23)	0·277±0·030 (27)	0·284±0·055 (18)	0·283±0·040 (15)

*Adipose tissue samples (50–100 mg) were preincubated at 37° for 30 min in Earle's bicarbonate buffer with 10 mg bovine serum albumin/ml and 10^{-2}M-theophylline. Samples were then incubated at 37° for 5 min in further buffer (with albumin and theophylline) with appropriate additions as indicated. Accumulation of cyclic AMP was terminated by the addition of 200 µl ice-cold 0·7 M-HCl: cyclic AMP was estimated by a competitive protein-binding assay.

Re-esterification. An alternative and more likely explanation of the increased release of FA from adipose tissue of diabetics is that there could be a defect in the re-esterification of FA by the intracellular glyceride–FA cycle. If lipolysis were unaffected, as it appears to be, the result would be an increase in the availability of free FA for release from the cell. It would also account for the increased FA output from the cell with normal release of glycerol. Measurements of the rate of esterification of palmitate to di- and triglycerides by diabetic and non-diabetic tissue are shown in Table 4. There is impaired esterification to triglycerides and a similar tendency to impaired esterification to diglycerides in diabetic tissues, confirming previous observations of Carlson & Ostman (1963) and Galton, Wilson & Kissebah (1971). The difference is not due to pool dilution of FA since the intracellular levels of FA in non-diabetic and diabetic tissues were 49·6 (SE 12·5, n =9) and 62·9 (SE 12·2, n=12) pmol/cell respectively (difference not significant). Although the esterification pathway has not been studied in detail in tissue from diabetics, as has been done for adipose tissue in states of starvation (Galton & Wilson, 1970), it is possible that a metabolic defect here could underlie the increased output of FA and hence the abnormality of plasma FA metabolism in adult diabetes.

Table 4. *The esterification of [1-^{14}C]palmitate to glycerides by human adipose tissue (35–45 mg portions) incubated for 1 h in 1 ml Earle's bicarbonate buffer*

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

	Esterification of palmitate to:			
	Triglycerides		Diglycerides	
Patient group	nmol/10^5 cells per h	nmol/g lipid per h	nmol/10^5 cells per h	nmol/g lipid per h
Non-diabetic obese (9)	5·72±1·03	93·1±13·2	3·0 ±0·53	52·7±11
Diabetic obese (12)	3·06±0·59*	60·3± 8·2*	1·95±0·23	40·7±3·4

Significance of difference from non-diabetic obese patients: *P<0·05.

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