

## Effect of diet on human adipose tissue metabolism

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Adipose tissue is, in one sense, the tissue most affected by diet. As the ultimate reservoir for energy storage, its mass reflects an integration of energy imbalance during the bearer's life. Diet also has qualitative effects on adipose tissue: for instance, the pattern of adipose tissue triacylglycerol (TAG)-fatty acids reflects the dietary fatty acid pattern (Hirsch, 1965; Jacobsen *et al.* 1983; van Staveren *et al.* 1986), and fat-soluble xenobiotics (such as pesticides) accumulate in adipose tissue fat (Handelman *et al.* 1988). Only the energy storage aspect will be considered here.

Long-term changes in body-weight involve a change in the amount of TAG stored in adipose tissue; there is a very strong relationship between the body-weight and the body fat content (both corrected for height; Webster *et al.* 1984). (The associated changes in non-fat tissue will not be considered here.) The processes of fat deposition and fat mobilization are, therefore, in a metabolic sense, the final common pathways for procedures influencing body-weight. The general principle of energy balance, that energy consumed equals energy expended plus the change in body energy stores, cannot be contradicted. But the link between a change in body energy stores and a change in the amount of fat (TAG) stored in adipose tissue is not so obvious. Our studies over the past few years have been aimed at elucidating some of the regulatory aspects of fat deposition and mobilization in humans, and attempting to relate these to energy balance.

### ROUTES OF FAT MOBILIZATION AND DEPOSITION

There are, in principle, two routes by which fat may be deposited in the form of adipose tissue TAG: uptake of preformed fatty acids, and uptake of other substrates which can be converted to TAG. In practice, the former means fatty acids derived from circulating TAG, either chylomicron-TAG or very-low-density lipoprotein (VLDL)-TAG. Adipocytes will take up labelled extracellular non-esterified fatty acids (NEFA) (Abumrad *et al.* 1984; Sorrentino *et al.* 1989), but the mass gradient of NEFA *in vivo* is always in the direction of NEFA release (Coppack *et al.* 1990*a,b*). Circulating TAG is hydrolysed by lipoprotein lipase (LPL; EC 3.1.1.34) situated in the capillary lumen. The action and regulation of this enzyme have been thoroughly reviewed recently (Eckel, 1987, 1989; Williamson, 1990). In brief, it is synthesized within adipocytes, modified intracellularly, and exported to its site of action (bound to the endothelium via heparan sulphate chains). Its synthesis, activation and possibly transport to the endothelium are all stimulated by insulin, the whole process of stimulation taking a matter of hours (Sadur & Eckel, 1982). The fate of the fatty acids released by LPL action is not entirely clear. At least a proportion will reach the adipocytes, where they may be taken up for esterification and storage; various models for the 'microanatomy' of adipose tissue which allow them to make this journey have been reviewed recently (Frayn, 1992). Some

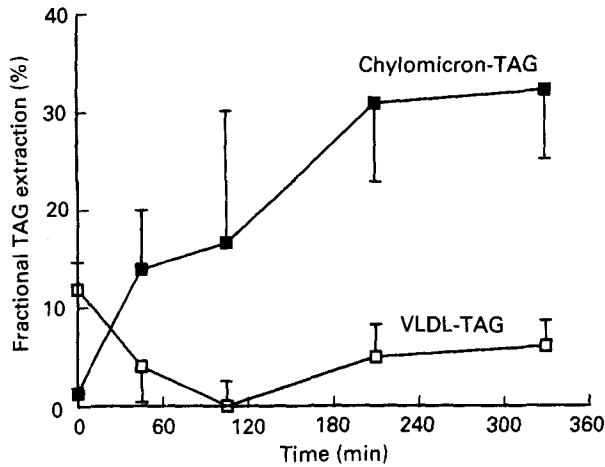


Fig. 1. Fractional extraction of triacylglycerol (TAG) during passage through human subcutaneous adipose tissue for nine normal subjects. Values at time 0 are each means of three measurements after an overnight fast. Between 0 and 20 min a mixed meal (composition given on p. 415) was eaten. (■), Chylomicron-TAG; (□), very-low-density lipoprotein (VLDL)-TAG. Reproduced from Potts *et al.* (1991a) with permission of Portland Press.

fatty acids released by LPL will, however, 'escape' into the venous plasma. This escape is particularly prominent in the postprandial phase when there is a high rate of hydrolysis of chylomicron-TAG (Coppack *et al.* 1990a). It is still not clear (in teleological terms) whether this represents simple 'inefficiency' or whether the body gains by such a tactic, for instance by directing fatty acids from dietary fat to other tissues for possible oxidation or storage. LPL has certain substrate preferences. It is specific for the 1- and 3- linkages in acylglycerols (Nilsson-Ehle *et al.* 1973) and its action thus leaves a 2-monoacylglycerol (MAG). This has to isomerize to a 1(3)-MAG before hydrolysis, and MAG will accumulate during rapid hydrolysis *in vitro* (Scow & Olivecrona, 1977). The possibility of MAG uptake by adipocytes (as in enterocytes) has occasionally been suggested (Small, 1991) but not, so far as we are aware, tested. It would presumably be followed by hydrolysis since adipose tissue contains a very active MAG lipase, whereas the MAG esterification pathway (active in enterocytes) is not thought to be important in adipose tissue. LPL also has preferences amongst the TAG-rich lipoproteins. Chylomicrons are much better substrates than VLDL, to the extent that they compete for hydrolysis postprandially, causing a rise in the plasma VLDL-TAG concentration (Potts *et al.* 1991a,b; Fig. 1).

The other possible route of fat deposition, via *de novo* lipogenesis, has attracted much experimental attention, especially in the rat. In experimental animals on high-carbohydrate, low-fat diets it may well be important, although even in the rat a large proportion of adipose tissue TAG arises from uptake of preformed fatty acids (Williamson, 1990). In humans, there is little evidence for *de novo* lipogenesis during normal life as a route of net fat deposition (Acheson *et al.* 1982), and some doubt about the enzyme capacity for carrying it out, at least in adipose tissue (Shrago *et al.* 1969). The correspondence, discussed earlier, between fatty acid patterns in adipose tissue TAG

and diet also points towards direct uptake of dietary fat as the most important route of adipose tissue TAG deposition under normal conditions.

The process of fat mobilization (liberation of NEFA from adipose tissue for use as a substrate in other tissues) has been well reviewed by others (Fain, 1980; Belfrage, 1985; Vernon & Clegg, 1985). The stored TAG is hydrolysed by the so-called hormone-sensitive lipase (HSL; EC 3.1.1.3). This interesting enzyme has been very difficult to study in detail since it is largely hydrophobic and difficult to solubilize. Its gene has recently been cloned (Holm *et al.* 1988), however, and its cellular and molecular biology are now being unravelled. Removal of the first fatty acid by HSL is the rate-limiting step in lipolysis; HSL also removes the second fatty acid, and the third is removed by an active MAG lipase (EC 3.1.1.23). The products are, thus, glycerol and NEFA. Glycerol does not appear to be utilized to a significant extent in adipose tissue (Lin, 1977) and is largely exported, whereas the fatty acids may be re-esterified after activation by condensation with acetyl-CoA. The activity of HSL is regulated on a rapid basis by phosphorylation–dephosphorylation, the former stimulated (via cyclic-AMP) by glucagon and  $\beta$ -adrenergic agents. Dephosphorylation is brought about by insulin (at least in part by activation of a phosphodiesterase activity and reduction of cyclic-AMP levels (Belfrage, 1985)) and by agents inhibiting adenylate cyclase (EC 4.6.1.1) via  $G_i$  proteins (e.g. adenosine, prostaglandin  $E_2$ , nicotinic acid and analogues). Control of HSL activity via these mechanisms appears to be the major short-term regulatory mechanism for lipolysis. Release of NEFA, on the other hand, is controlled also by the rate of re-esterification. Thus, insulin reduces lipolysis and also increases the proportion of fatty acids re-esterified and, thus, retained in the tissue (Fig. 2), presumably via increased provision of glycerol-3-phosphate. In terms of diet and adipose tissue metabolism, the role of insulin in regulating NEFA release is probably paramount. In the postprandial period, with a high insulin concentration, fatty acids are retained within the adipocyte both by reduced HSL activity and by increased re-esterification (Coppack *et al.* 1992). As the postprandial phase leads into the post-absorptive phase and insulin levels fall, fatty acid release returns (Coppack *et al.* 1990a).

#### EXPERIMENTAL APPROACHES

In an attempt to provide more direct information about the processes of fat deposition and mobilization in human adipose tissue, we developed a few years ago a technique for measurement of arterio–venous concentration differences across a subcutaneous adipose depot, that of the anterior abdominal wall (Frayn *et al.* 1988, 1989). This site has some unique features: it has a reasonably well-defined system of venous drainage, accessible for cannulation (albeit with difficulty), and its vasculature is completely separated from that of the underlying muscle bed by an avascular fibrous sheath, the aponeurosis of the *external oblique* muscle. Blood sampled from the major veins draining this depot, the superficial circumflex iliac and the superficial epigastric, represents drainage from adipose tissue with a contribution (which we believe to be small in most subjects) from the overlying skin. We have compared this blood with that taken from a vein draining a warmed hand ('arterialized') or from a radial artery, and, in some studies, with blood taken from a deep antecubital vein draining mainly forearm muscle. In our later studies, adipose tissue blood flow was measured using the  $^{133}\text{Xe}$  clearance technique (Larsen *et al.* 1966).

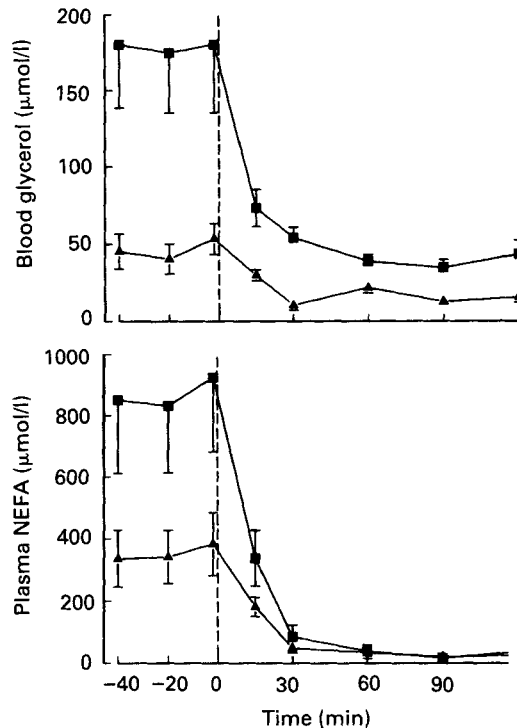


Fig. 2. Plasma non-esterified fatty acid (NEFA) and blood glycerol concentrations for eight normal subjects, after overnight fast ( $-40$  to  $0$  min) and then during infusion of insulin at  $35$  mU/m<sup>2</sup> per min, with the plasma glucose concentration 'clamped' at  $5$  mmol/l. (▲), Arterialized blood; (■), venous drainage from subcutaneous adipose tissue. The difference between arterialized and venous thus represents the release from adipose tissue, which is completely suppressed by insulin in the case of NEFA, less so in the case of glycerol. Based on data in Coppack *et al.* (1989), and reproduced from Frayn (1992) with permission of Raven Press Ltd.

Human adipose tissue *in vivo* does not have the simple metabolic pattern that might be expected from studies of adipocytes *in vitro*. Even in the post-absorptive state (taken here to mean after an overnight fast), it is engaged in a variety of metabolic exchanges. TAG, glucose, oxygen, acetoacetate and 3-hydroxybutyrate and acetate are all extracted from the blood, and NEFA, glycerol, lactate and carbon dioxide are released. (Pyruvate exchange is variable and not significant in either direction amongst a group of subjects.) Also amino acid metabolism is not negligible, although it will not be considered in detail in the present review; the tissue releases both alanine and glutamine, and takes up glutamate, at rates that may give it an appreciable role in the whole body (Frayn *et al.* 1991). In terms of overall balance of substrates (assessed by the 'carbon atom balance' in all these substrates), adipose tissue is a considerable exporter of substrate carbon in the post-absorptive state. The forearm, in contrast, whilst engaged in exchange of many of the same substrates, takes up rather than releases NEFA, and thereby remains nearly in 'carbon balance' after overnight fast (Fig. 3).

The export of material in the post-absorptive state must be balanced (if body-weight is relatively steady) by import of carbon-containing substrates in the fed state. From the

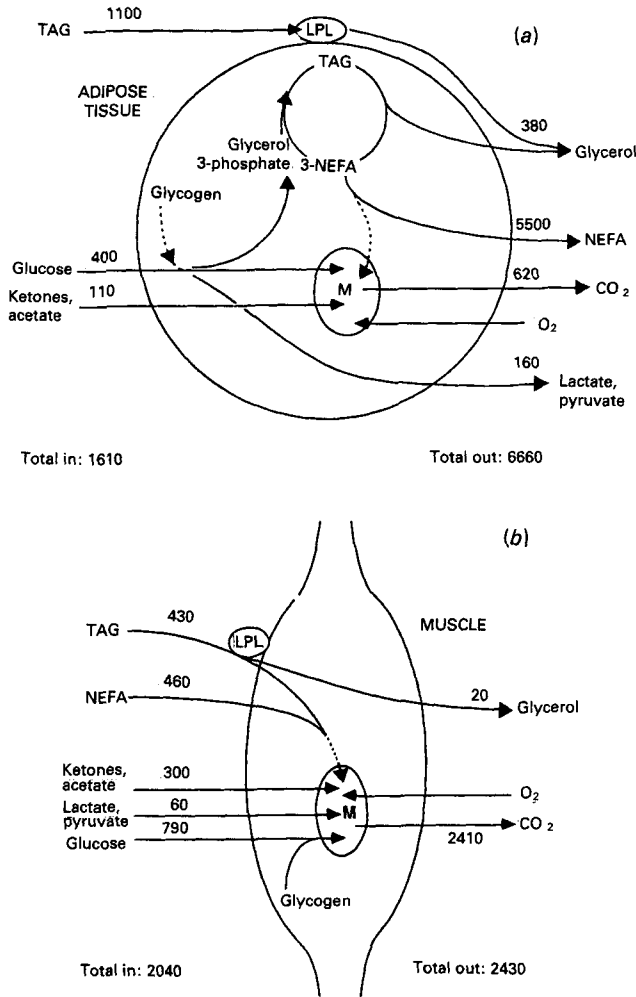


Fig. 3. Carbon atom balances (μg atoms/l whole blood) across (a) subcutaneous adipose tissue and (b) forearm muscle after overnight fast. Results are mean values from twenty-five studies of normal subjects. LPL, lipoprotein lipase (EC 3.1.1.34); M, mitochondrion; NEFA, non-esterified fatty acids; TAG, triacylglycerol. Reproduced from Coppack *et al.* (1990b) with permission of W. B. Saunders Co.

description of fat deposition given previously, it is to be expected that the main sources will be TAG and (to a lesser extent) glucose. We investigated the change in adipose tissue substrate balance produced by giving an oral glucose load (75 g glucose monohydrate, 1160 kJ). Much as expected (Fig. 4(b)), after the glucose there was a change to net carbon uptake in both adipose tissue and forearm (more pronounced and more sustained in the latter). It can then be asked: what was the major change in substrate exchange bringing about this switch from carbon export to import? The biggest single change was not a positive uptake of any one substrate, but a suppression of the

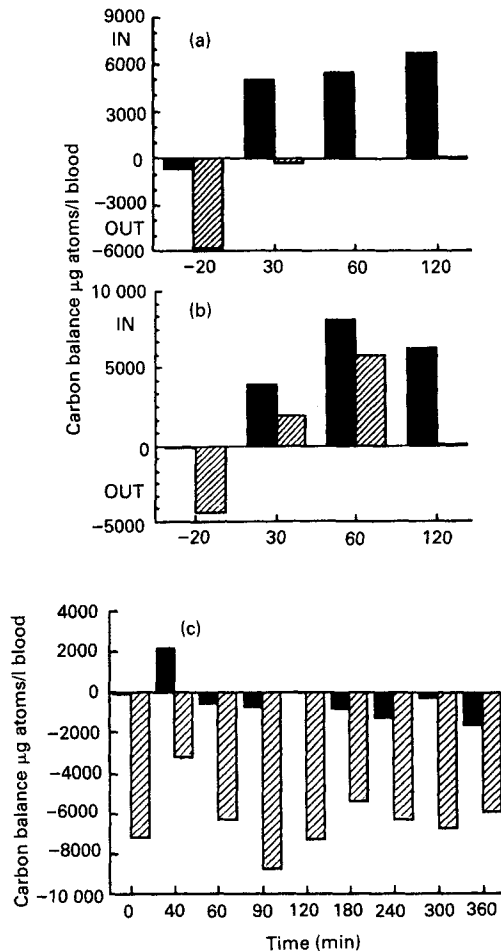


Fig. 4. Net carbon atom balances across human subcutaneous adipose tissue (▨) and forearm muscle (■), after overnight fast (-20 or 0) and then: (a) during infusion of insulin (see Fig. 2); (b) after ingestion of 75 g glucose monohydrate; (c), after ingestion of 47.5 g ethanol. Positive values represent net uptake of carbon atoms by the tissue, negative values represent net export. Based on data in Coppack *et al.* (1989) and Frayn *et al.* (1990b); reproduced from Frayn (1992) with permission of Raven Press Ltd.

release of NEFA. Thus, net nutrient uptake into adipose tissue after a glucose load is brought about mainly by suppression of fat mobilization (Frayn *et al.* 1990a).

The role of insulin in bringing about this change was investigated by infusing insulin, using a euglycaemic (5 mmol/l) clamp procedure (Coppack *et al.* 1989). Insulin was infused for 2 h at 35 mU/m<sup>2</sup> per min, producing plasma insulin concentrations of about 50 mU/l, similar to the peak reached after oral glucose. The effect on net substrate storage in adipose tissue was much less pronounced than that of glucose ingestion (Fig. 4(a)), although the effect in the forearm was very similar. In terms of individual substrate exchanges, insulin infusion completely suppressed NEFA release from adipose tissue (see Fig. 2), but produced only a slight stimulation of glucose uptake.

Ethanol is another energy-providing substrate, at least in so far as energy is released when it is burnt in a bomb calorimeter ( $\Delta H = -30$  kJ/g). There are some features of ethanol ingestion which are not, however, clear. Some dietary studies show that increased ethanol consumption is not accompanied by the expected change in body-weight (Pirola & Lieber, 1972; Colditz *et al.* 1991). Pathways have been suggested by which ethanol may be oxidized without generation of useful energy, via a microsomal oxidation system with concomitant peroxisomal oxidation of NADPH (Pirola & Lieber, 1972, 1976) or via futile cycling between ethanol and acetaldehyde (Lands & Zakhari, 1991). On the other hand, in experiments designed to look at the 'thermic effect' of ethanol consumption, no evidence for excessive thermogenesis was found (Shelmet *et al.* 1988; Reinus *et al.* 1989). From a biochemical point of view, ethanol illustrates very clearly the difficulty of linking the 'energy value' of a nutrient (as assessed in a bomb calorimeter) with the (net) storage of TAG in adipose tissue. Ethanol is metabolized via acetaldehyde to acetate in the liver. Clearly the NAD(P)H or ATP thus generated cannot be transferred directly to adipose tissue; and yet, it would seem that there must be a mechanism which results in the net retention of fatty acids within adipose tissue, corresponding on a 'joule for joule' basis to hepatic ethanol oxidation. What could be the nature of such a link? Acetate may have an anti-lipolytic effect (Crouse *et al.* 1968); but, if this is the explanation, it would seem to be 'fortuitous' rather than a necessary consequence of hepatic oxidation of an energy-bearing substrate. In any case, the evidence for acetate and anti-lipolysis is not strong, and there is no evidence *in vivo* for increased acetate uptake by adipose tissue after ethanol ingestion (Frayn *et al.* 1990b). Other acute studies have suggested that ethanol ingestion spares carbohydrate rather than fat oxidation (Sonko *et al.* 1991). In an attempt to investigate the link between ethanol and adipose tissue fat stores, normal subjects were given 47.5 g ethanol (in the form of gin and low-energy tonic) after overnight fast: this is a rather larger energy load than the 75 g glucose monohydrate used in our earlier studies (1400 kJ *v.* 1160 kJ). The 'carbon balance' was followed across the adipose tissue for 6 h after ethanol ingestion. There was no tendency for 'net substrate storage' in the tissue as there had been after glucose ingestion (Fig. 4(c)). These experiments cannot rule out a steady, slow sparing of NEFA release from adipose tissue, but if this occurred, the mechanism by which it was brought about was not obvious. Clearly, the effects of 'ethanol energy' on adipose tissue metabolism are qualitatively very different from the effects of 'glucose energy'.

At a more complex level, the responses to ingestion of a 'real meal' (chicken, vegetables, biscuits, fruit and ice cream) containing 3.1 MJ, of which 41% were from fat and 47% from carbohydrate (Coppack *et al.* 1990a, 1992), were studied. The comparison of forearm muscle and adipose tissue in these studies was very revealing. Both tissues changed to net carbon intake after the meal. In the forearm, this was brought about almost entirely by increased glucose uptake (the time-course of which mirrored very closely the plasma insulin concentration). In adipose tissue, uptake of fat was predominant. (The avid extraction of chylomicron-TAG shown in Fig. 1, based on the same experiments, reflects this.) The carbon balance across adipose tissue depended largely on the interplay between NEFA release and TAG uptake (Fig. 5). These studies emphasize the metabolic 'ease' with which dietary fat is taken up for storage in adipose tissue, but again highlight the subtle regulation of net fat storage by regulation of both fat uptake and fatty acid release.

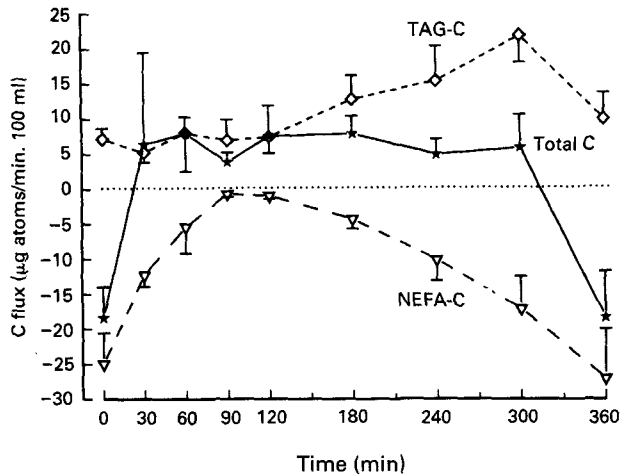


Fig. 5. Net carbon atom fluxes (arterio-venous difference  $\times$  blood flow) across human subcutaneous adipose tissue after overnight fast (time 0) and after ingestion of a mixed meal (see Fig. 1). ( $\star$ ), Total C flux (sum of C atoms in eight major substrates); ( $\diamond$ ), C atom import from plasma TAG; ( $\nabla$ ), C atom export as NEFA. Reproduced from Coppack *et al.* (1990a) with permission of Portland Press.

#### CONCLUSION

There is a challenge facing those interested in the interactions between diet, metabolism and adiposity. At a whole-body level, the relationship between energy intake, energy expenditure and energy storage is clear (indeed, incontrovertible). The translation of this energy storage into a change in body fat stores, on a joule for joule basis, is not clear. There is much to be learned about the precise quantitative regulation of intermediary metabolism, and adipose tissue is a tissue in which we, as nutritionists, should have a special interest.

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