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Fatty acid metabolism in adipose tissue, muscle and liver in health and disease

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Abstract

Fat is the largest energy reserve in mammals. Most tissues are involved in fatty acid metabolism, but three are quantitatively more important than others: adipose tissue, skeletal muscle and liver. Each of these tissues has a store of triacylglycerol that can be hydrolysed (mobilized) in a regulated way to release fatty acids. In the case of adipose tissue, these fatty acids may be released into the circulation for delivery to other tissues, whereas in muscle they are a substrate for oxidation and in liver they are a substrate for re-esterification within the endoplasmic reticulum to make triacylglycerol that will be secreted as very-low-density lipoprotein. These pathways are regulated, most clearly in the case of adipose tissue. Adipose tissue fat storage is stimulated, and fat mobilization suppressed, by insulin, leading to a drive to store energy in the fed state. Muscle fatty acid metabolism is more sensitive to physical activity, during which fatty acid utilization from extracellular and

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intracellular sources may increase enormously. The uptake of fat by the liver seems to depend mainly upon delivery in the plasma, but the secretion of very-low-density lipoprotein triacylglycerol is suppressed by insulin. There is clearly cooperation amongst the tissues, so that, for instance, adipose tissue fat mobilization increases to meet the demands of skeletal muscle during exercise. When triacylglycerol accumulates excessively in skeletal muscle and liver, sometimes called ectopic fat deposition, then the condition of insulin resistance arises. This may reflect a lack of exercise and an excess of fat intake.

Introduction

Triacylglycerol (or triglyceride) is a concentrated form in which to store energy. Triacylglycerol circulates in the plasma in lipoproteins and is also present as lipid droplets within cells. The 'energy density' of lipid stored in cells in this way is approx. 37 kJ/g. The energy density of whole adipose tissue (with cytoplasm, connective tissues etc.) is approx. 30 kJ/g. In contrast, glycogen in pure form has an energy density of approx. 17 kJ/g, but when stored in hydrated form with about three times its own weight of water (as it is in cells), this reduces to approx. 4 kJ/g. There are three main organs that store triacylglycerol in a regulated way and hydrolyse it to release fatty acids, either for export or for internal consumption. These are, in order of amount of triacylglycerol typically stored, adipose tissue, skeletal muscle and the liver. Recent years have seen an enormous increase in our understanding of
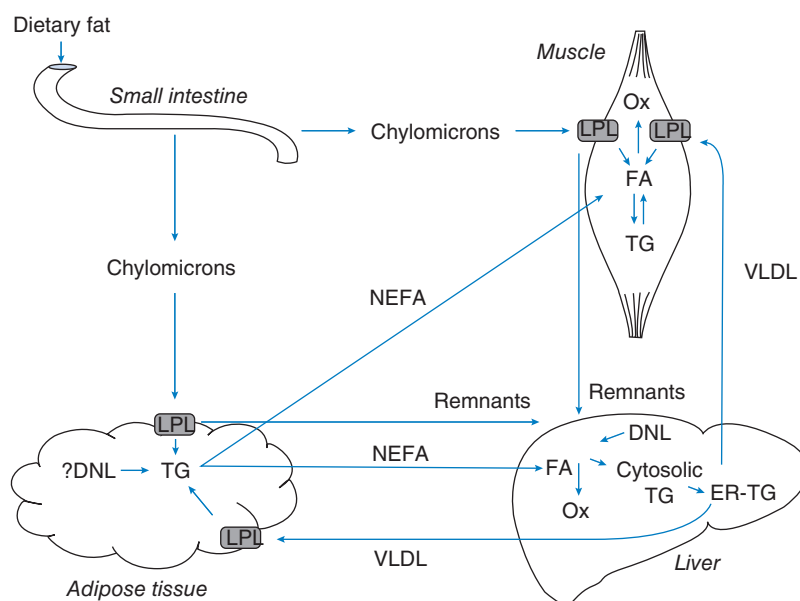

Figure 1. Lipid exchanges between gut, adipose tissue, skeletal muscle and liver
Note that adipose tissue LPL also releases NEFA into the plasma, making further fatty acids available for uptake by muscle and liver. ER, endoplasmic reticulum; FA, fatty acids; Ox, β-oxidation.

Table 1. Characteristics of fatty acid and TG metabolism compared in adipose tissue, skeletal muscle and liver

	Adipose tissue	Skeletal muscle (at rest)	Liver
Input	LP–TG ~ 45 g/day	NEFA ~ 20 g/day	NEFA ~ 20 g/day
	NEFA ~ 5 g/day	LP–TG ~ 10 g/day	Remnant-LP–TG ~ 25 g/day
			DNL ~ 1 g/day
Stimulation of uptake	Feeding/insulin	Fasting (high NEFA supply) Exercise	Delivery
FA transporters	FAT	FAT	FAT
	FATP-1, 4	FATP-1, 4	FATP-2, 5
Typical whole-body TG store	15 kg	300 g	100 g
Half-life of store	250 days	24 h	100 h
Lipolysis of TG store	HSL - stimulated lipolysis	HSL ?	Unknown
	ATGL - basal lipolysis		
	MGL - monoacylglycerol hydrolysis		
Releases mainly	NEFA into plasma	FA for oxidation	FAs re-esterified in ER and released as VLDL-TG

Quantitative data involve some estimates and should be taken as representative only. ER, endoplasmic reticulum; FA, fatty acids; LP, lipoprotein; MGL, monoacylglycerol lipase; TG, triacylglycerol.

triacylglycerol and fatty acid metabolism in these organs, and of its relationship to health and disease.

There is a continual flow of fatty acids between the three tissues described above, outlined in Figure 1 with some quantitative estimates in Table 1. Dietary fat enters the plasma from the small intestine in the form of chylomicron-triacylglycerol. The chylomicrons are the largest of the lipoprotein particles and have a very fast turnover (the half-life of chylomicron-triacylglycerol in the circulation is around 5 min). They deliver triacylglycerol-fatty acids to tissues expressing the enzyme LPL (lipoprotein lipase), an enzyme bound to the endothelial cells lining capillaries of a number of tissues including adipose tissue, skeletal and cardiac muscle (more details are given in Figure 2).
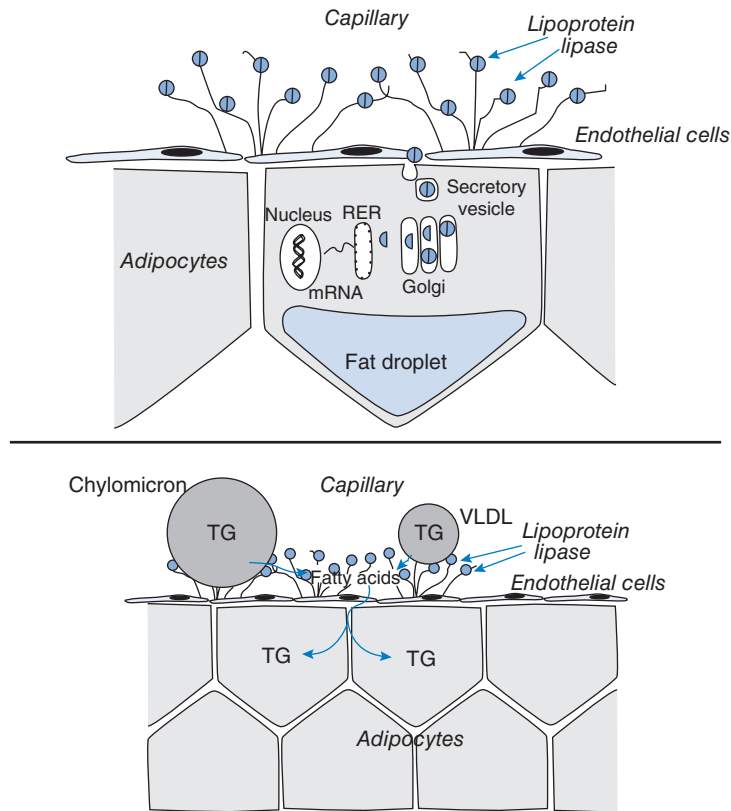
Figure 2. Regulation and action of LPL

This is shown for adipose tissue but aspects of the regulation and action are likely to be similar in other tissues. Top panel: LPL is synthesized in the rough endoplasmic reticulum (RER) and post-translationally modified, becoming active in the Golgi apparatus. An important aspect of activation is dimerization. From the Golgi, LPL is secreted via the vascular endothelial cells to proteoglycan chains attached to the endothelial cell membrane. The lipid droplet of the mature adipocytes has been reduced in size in this diagram for clarity. In principle, regulation of LPL activity could occur at many points. In fact, up-regulation of adipose tissue LPL activity in the fed state occurs with little change in mRNA or intracellular enzyme mass. It appears mainly to involve the mobilization of active enzyme to the capillary-luminal aspect of the endothelial cells. There is no evidence for reversible phosphorylation as a means of regulation of LPL activity. In fasting, more LPL becomes inactive (perhaps via monomerization). Note that, in contrast, LPL in skeletal and cardiac muscle is activated during fasting. Lower panel: LPL acts via binding to the triacylglycerol-rich lipoprotein particles, chylomicrons (carrying dietary fat) and VLDL (secreted from the liver). It hydrolyses the triacylglycerol to liberate fatty acids, that can be taken up by the adipocyte (or muscle cell) and esterified to form new triacylglycerol. In skeletal or cardiac muscle, these fatty acids might also be a substrate for oxidation. Lower panel taken from Frayn, K.N. (2003) *Metabolic Regulation : a Human Perspective*, 2nd edn. Published by Blackwell Publishing.

The remaining 'remnant' particles (that have lost perhaps two-thirds of their triacylglycerol) are mainly taken up by the liver. This is the starting point for fatty acid metabolism in the tissues.

Adipose tissue takes up fatty acids via the action of LPL. It releases fatty acids by the hydrolysis (lipolysis) of stored (intracellular) triacylglycerol, by

the action of the enzyme known as HSL (hormone-sensitive lipase) and other lipases, to liberate NEFA (non-esterified fatty acids) into the plasma. Plasma NEFA circulate bound to albumin. The turnover of plasma NEFA is also rapid, with a half-life of 4–5 min. The liver takes up fatty acids in various forms and liberates triacylglycerol-fatty acids as VLDL (very-low-density lipoprotein) particles. In this scenario, skeletal and heart muscle (and other oxidative tissues not considered here) are the only pure consumers, taking up fatty acids either from lipoprotein-triacylglycerol or from the plasma NEFA pool and using them ultimately for oxidation.

Regulation of triacylglycerol and fatty acid metabolism at rest

Overview

The pattern of flow of fatty acids between the tissues changes with nutritional state. In the fed, or postprandial, state there is a drive to store excess nutrients and as part of this, adipose tissue LPL is up-regulated, probably by the action of insulin released in response to carbohydrate in the meal. This diverts chylomicron-fatty acids to adipose tissue rather than muscle, where LPL is somewhat down-regulated by insulin (muscle LPL becomes particularly active with physical training or during fasting, conditions when the muscle has a greater need for fatty acids). Since adipose tissue is acquiring fatty acids in the postprandial period, it makes sense that fat mobilization is suppressed at this time, again by the action of insulin. Both the liver and skeletal muscle take up fatty acids largely according to their availability. The rate of removal of plasma NEFA is, under most conditions, fairly closely proportional to their plasma concentration. The removal by the liver of remnant-particle triacylglycerol-fatty acids is also probably determined by their delivery in plasma. The abundance of the different sources of fatty acids in plasma varies with nutritional state, with the highest supply of NEFA in the fasting state and chylomicron-remnant triacylglycerol fatty acids becoming more prominent in the fed state. As mentioned earlier, muscle LPL is up-regulated during fasting although its activity does not seem to vary greatly during the normal day. The secretion of VLDL-triacylglycerol by the liver is undoubtedly subject to nutritional regulation. Insulin acutely suppresses hepatic VLDL-triacylglycerol secretion. VLDL particles are secreted with a range of sizes, and it is especially the secretion of the larger, more triacylglycerol-rich particles that is suppressed by insulin. The mechanism by which insulin suppresses VLDL-triacylglycerol secretion is 2-fold. First, it suppresses delivery of NEFA to the liver from adipose tissue as described above. But there is a further, and more important, effect on VLDL particle secretion from the hepatocytes. Whether insulin has this effect in the normal daily feeding situation is not so clear: it is difficult to study *in vivo* in humans because the non-steady state of feeding is not ideal for the tracer experiments that have mostly been used to study regulation of VLDL secretion.

Tissue-specific features of triacylglycerol and fatty acid metabolism

Adipose tissue

Adipose tissue triacylglycerol storage varies widely between individuals. The 'standard' adult female has approx. 30% of body weight as fat and the male approx. 20%, most of which is in adipocytes [1]. The adipocyte is a cell highly specialized for fat storage, although we now also appreciate that it has important protein secretory functions secreting hormones such as leptin, adiponectin and a range of other so-called 'adipokines'. The specific fatty acids stored in human adipose tissue (saturated, monounsaturated and unsaturated) reflect dietary intake. There is debate about the contribution of DNL (*de novo* lipogenesis) to adipose tissue fat stores but, at the whole-body level, DNL only operates significantly when carbohydrate intake exceeds energy requirements. Isotopic data suggest that approx. 10% of adipose tissue triacylglycerol fatty acids arise from DNL [2]. Most of the triacylglycerol-fatty acids in human adipose tissue therefore arise from plasma, mainly from the triacylglycerol fraction of plasma lipids with a small contribution of direct uptake from NEFAs [3].

The control of fatty acid uptake by adipocytes is not well understood. Up-regulation of adipose tissue LPL activity in the fed state is brought about by multiple mechanisms (Figure 2). LPL is synthesized within adipocytes and exported to its site of action, the luminal side of the capillary endothelial cells. Of the large pool of LPL in adipose tissue, only a portion becomes active endothelial-bound LPL. An important mechanism for up-regulation in the fed state is the diversion of LPL away from the degradative, into the secretory pathway [4]. LPL acts on circulating lipoprotein-triacylglycerol and generates fatty acids in the local area close to the endothelium. Chylomicrons are the pre-ferred substrate for adipose tissue LPL. Chylomicron-triacylglycerol is hydro-lysed considerably more rapidly than VLDL-triacylglycerol. Nevertheless, both substrates may contribute fatty acid under appropriate circumstances. The fatty acids released by LPL migrate across the endothelial wall and into the underlying adipocytes. The mechanisms involved in this process are not clear, although there is increasing evidence for the involvement of specific fatty acids transporters including FAT (fatty acid translocase, also known as CD36) in facilitating fatty acid movement across the adipocyte cell membrane. There is also non-regulated diffusion through the cell membrane. Within the adipocyte, fatty acids are 'activated' by esterification to CoA in an ATP-requiring process that seems to be intimately linked to fatty acid transport into the cell, at least when mediated by a member of the FATP (fatty acid transport protein) family (FATP1) [5].

Adipose tissue LPL generates an excess of fatty acids. The adipocytes then take up a proportion, depending upon nutritional state. There is always an 'overspill' of fatty acids into the plasma. Insulin increases the proportion of LPL-derived fatty acids taken up by the tissue but even in the postprandial state
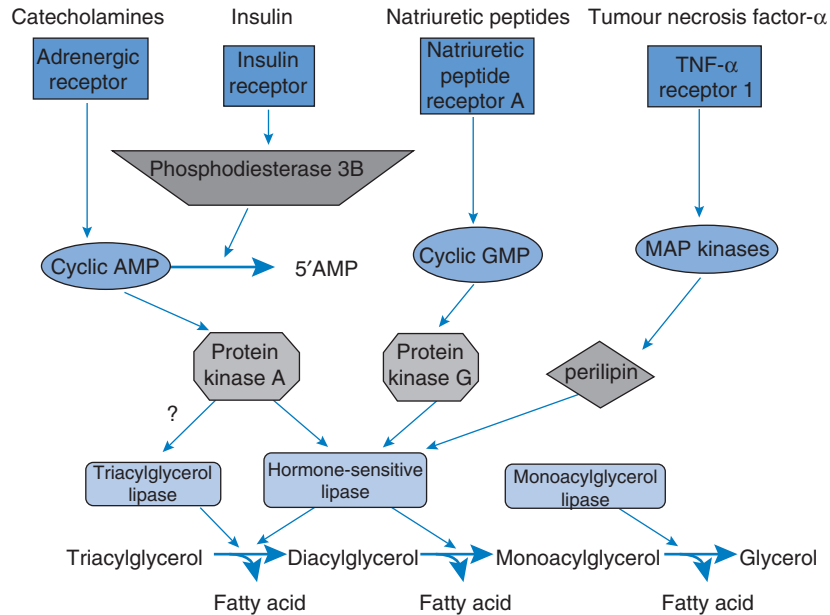
Figure 3. Regulation of lipolysis in white adipose tissue
For more detail please refer to the text.

typically approx. 50% may be released as NEFA, clearly shown by enrichment of the plasma NEFA pool with dietary fatty acids soon after a meal. These fatty acids are then available for uptake by other tissues including muscle and liver. The control of fatty acid uptake into the adipocyte may involve recruitment of the fatty acid transporters CD36 and FATP1 to the cell surface upon insulin stimulation [5]. It also involves stimulation of fatty acid esterification to make new triacylglycerol within the adipocyte. Regulation of the enzymes of triacylglycerol synthesis is still not understood in detail although the pathway as a whole is certainly stimulated by insulin [6]. In addition, insulin may stimulate glucose uptake and glycolysis, which supplies the glycerol 3-phosphate necessary for fatty acid esterification. The ability of fat cells to take up acylglycerols directly is very limited.

Adipose tissue fat mobilization has been studied in detail [7] and is summarized in Figure 3. Until recently it was considered that the only major regulatory point was the enzyme HSL. HSL has triacylglycerol-lipase activity directed at two fatty acids on a triacylglycerol molecule, but is not active against monoacylglycerols, whereas it is especially active against diacylglycerols. There is a separate, and unrelated, monoacylglycerol lipase that is consitutively expressed in adipose tissue and catalyses the last step in triacylglycerol hydrolysis. HSL is regulated in the long-term by transcriptional control: HSL mRNA abundance increases during starvation, and is decreased in obesity. But the most important aspect of HSL on a day-to-day basis is its regulation by reversible

phosphorylation [7]. HSL has three phosphorylation sites that are substrates for PKA (protein kinase A), phosphorylation of which greatly increases its activity. Adipocyte fat mobilization is brought about by signals that increase the cAMP concentration. Typically, catecholamines would act by binding to β-adreno-ceptors in the cell membrane, linked by G-proteins to adenylate cyclase. Insulin suppresses HSL activity by activation of a particular phosphodieste-rase, PDE3B, which reduces the cAMP concentration. These effects are rapid and potent. However, the increased rate of lipolysis seen upon stimulation of fat cells with β-adrenergic agents is far greater than would be predicted from the increase in activity of HSL *in vitro*. It is now clear that phosphorylation of HSL is accompanied by phosphorylation of a protein, perilipin, that coats the adipocyte fat droplet. This dual phosphorylation allows HSL to translocate from the cytosol to the surface of the fat droplet to achieve lipolysis. Under non-stimulated conditions, HSL is excluded from the fat droplet surface.

A further system of human-specific regulation has been described, involv-ing the circulating peptides known as ANF (atrial natriuretic factor) and BNF (brain natriuretic factor) [8]. These factors are released during stress states including exercise and bind to specific cell-surface receptors that are cou-pled to synthesis of cGMP and activation of cyclic GMP-dependent protein kinase. Finally, there is an autocrine regulation of lipolysis by tumour necrosis factor-α. This cytokine acts on perilipin through MAPK (mitogen-activated protein kinase) signalling pathways.

The primary role of HSL in lipolysis has been challenged by findings in mice deficient in HSL. These mice have relatively normal adipose tissue mass, and lipolysis is preserved, although β-adrenergic responsiveness is almost or completely lost, depending upon the model. This has led to a search for other lipases in the adipocyte. One candidate, ATGL (adipose triglyceride lipase), has marked specificity for triacylglycerols compared with di- or mono-acylglycerols, and may be of great importance for lipolysis in rodents. It now seems likely that ATGL is responsible for 'basal' lipolysis in human adipose tissue, with HSL responsible for the majority of catecholamine- or ANF-stimulated lipolysis [9].

Liver

The normal triacylglycerol content of the liver is around 1–10% by weight [1] but can expand considerably in the condition generally called 'fatty liver'. The liver receives plasma fatty acids as NEFA, from hydrolysis of circulating triacylglycerol and from the uptake of remnant lipoprotein particles. Uptake of NEFA appears to be similar to the process described in adipose tissue: FAT/CD36, FATP2 and FATP5 are expressed in liver. The adult liver does not express LPL, but a related enzyme, HL (hepatic lipase) which acts preferentially upon smaller particles than LPL. It will remove triacylglycerol from small VLDL particles and from particles on their way to becoming LDL (low-density lipoprotein) and also from HDL (high-density lipoprotein) particles. It also has a major role in 'docking' with particles that are being

internalized bound to specific receptors expressed in the liver. The liver is the main organ for uptake of the remnant particles formed from the action of LPL on triacylglycerol-rich chylomicrons and VLDL. The chylomicron remnant particle is thought to contain typically about one-third of its original triacylglycerol content. This is still appreciable (a typical chylomicron particle contains approx. 10^6 molecules of triacylglycerol), and would lead to delivery to the liver of around 20–30 g/day of dietary triacylglycerol.

In addition, the liver has the enzymatic capacity for DNL, the synthesis of fatty acids from glucose and other non-lipid precursors. DNL makes a small contribution in people on a typical, western relatively high-fat diet, but it becomes activated during a high-energy diet rich in carbohydrate [10]. The pathway involves export of acetyl-CoA formed in the mitochondrion (in the case of glucose as the precursor, by pyruvate dehydrogenase) to the cytosol (in the form of citrate), conversion of acetyl-CoA to malonyl-CoA by acetyl-CoA carboxylase and then sequential addition of two carbon units by fatty acid synthase.

Fatty acids taken up into the hepatocytes are activated by esterification to CoA. The long-chain acyl-CoA may then enter the mitochondria for oxidation or be a substrate for glycerolipid synthesis (triacylglycerol and phospholipids). This is a key regulatory point, determined largely by regulation of entry into the mitochondria, via the enzyme CPT 1 (carnitine palmitoyltransferase 1, the 'overt' isoform, expressed in the outer mitochondrial enzyme). This enzyme is allosterically regulated by the cytosolic malonyl-CoA concentration. Malonyl-CoA (an intermediate in fatty acid synthesis) is a very potent inhibitor of CPT 1. Its concentration is high when insulin levels are high and glucose is readily available, conditions when fatty acid synthesis should be favoured over fatty acid oxidation. In the fasting state, when insulin levels are low, fatty acid oxidation is therefore favoured. There is a further branch point in fatty acid oxidation when acetyl-CoA may either enter the tricarboxylic acid cycle or may be directed into ketone body synthesis. Less is known about regulation of this 'metabolic branch point'. A suggested regulation of ketone body synthesis is by reversible succinylation of the mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase [11].

The cytosolic triacylglycerol pool within the hepatocyte is the precursor for VLDL-triacylglycerol. Lipolysis of this cytosolic pool is necessary to generate fatty acids that are then esterified to make new triacylglycerol within the endoplasmic reticulum, where VLDL particles are assembled. The identity of the lipase responsible, and its regulation, are not clear. VLDL-triacylglycerol secretion is acutely inhibited by insulin, although hepatic fatty acids are preferentially stored as triacylglycerol when insulin levels are high. This implies that the hepatocyte triacylglycerol store fluctuates in size, increasing after meals and then discharging during fasting as VLDL are secreted. This has recently been visualized directly in healthy humans where approx. 10% of the fat from a meal was stored in the liver in the few hours following feeding [12].

Muscle

The total triacylglycerol store in a healthy human liver is approx. 100 g (or less). The typical triacylglycerol content in whole-body skeletal muscle might be approx. 300 g (estimated making various assumptions, see [13]).

There are two major triacylglycerol stores in muscle: in adipocytes inter-leaved with the muscle fibres (seen, for instance, as 'marbling' in a cut of meat) and triacylglycerol stored within the muscle fibre itself ('intramyocellular tria-cylglycerol'). Here we will discuss only the latter. It is still not clear whether there is any direct metabolic relationship between adipocytes and skeletal muscle fibres even when they are located in close proximity.

Intramyocellular triacylglycerol is present as lipid droplets, often in close contact with mitochondria. Some of the enzymatic machinery for fatty acid and triacylglycerol metabolism in the muscle fibre is similar to that in the adipocyte. Fatty acids can be taken up from the plasma, either from the albumin-bound NEFA pool or, as in adipose tissue, from the pool of fatty acids generated by the action of LPL on circulating triacylglycerol. In either case it seems that the fatty acids enter the cells at least in part by facilitated diffusion, as both FAT/CD36 and FATP1 are expressed in skeletal muscle. Muscle has the enzymatic machinery to synthesize malonyl-CoA from glucose utilization, the first stage of the biosynthesis of fatty acids. However, expression of fatty acid synthase (which makes fatty acids from malonyl-CoA) is very small or non-existent. Therefore the triacylglycerol present in muscle can be assumed to arise entirely from plasma fatty acids (NEFA or triacylglycerol). The role of malonyl-CoA appears to be in the regulation of fatty acid oxidation, as described above for the liver.

The intramyocellular triacylglycerol is hydrolysed to make fatty acids available for oxidation. HSL is likely to be the key lipase controlling this proc-ess, although there is no direct evidence for this other than the fact that HSL is expressed in muscle and becomes activated on muscle contraction [14]. This is reinforced by the accumulation of large lipid droplets in skeletal muscle of HSL-deficient mice [15]. Fatty acids made available from muscle triacylgly-cerol lipolysis would be a substrate for oxidation after activation and entry into the mitochondria. Muscle lipolysis is less sensitive to hormone regula-tion than adipocyte lipolysis, at least in humans. Insulin is not effective but catecholamines stimulate muscle lipolysis [14,16].

It is not clear whether, as in the adipocyte, fatty acids may be released from the cell into the plasma. Certainly this does not happen in a net sense: muscle always extracts NEFA from plasma, never adds them. Some measure-ments suggest that fatty acids are released from muscle beds, in larger amounts than could be accounted for by the adipocytes likely to be present [17]. Nevertheless, it is clear that adipose tissue is the only tissue that contributes NEFA to the plasma in a net sense.

The processes of fatty acid uptake by muscle, and of mobilization of muscle triacylglycerol stores, are covered in detail in Chapter 4 and will not be covered here in further detail.

The heart muscle (myocardium) is also involved in fatty acid metabolism; in fact, as a continuously contracting oxidative muscle, it has a very high demand for fatty acids. These fatty acids are acquired from plasma both as NEFA and through the LPL-route. Many features of myocardial fatty acid metabolism are similar to skeletal muscle, although the major isoform of the FATP family expressed in the heart is FATP6, which co-localizes on the plasma membrane with CD36.

Metabolic interactions during exercise

Fat is an important fuel for skeletal muscle during exercise. Its importance is greater at lower intensities of exercise and as the duration of exercise increases. In any exercise lasting more than approximately 2 h, fat becomes the major fuel (once muscle glycogen stores are exhausted). Most of the fatty acids oxidized in muscle during exercise come from the plasma NEFA pool. Hence coordination between adipose tissue (activation of lipolysis) and muscle (fatty acid utilization) is crucial. The contribution of VLDL-triacylglycerol fatty acids during exercise is small, but in the fed state chylomicron-triacylglycerol fatty acids might make a greater contribution [18]. Regarding the role of the intramuscular triacylglycerol store, early studies involving muscle biopsies before and after exercise were generally uninformative. New approaches have increased our understanding of muscle triacylglycerol. Isotope infusion studies show that muscle triacylglycerol utilization makes a substantial contribution to fatty acid oxidation at moderate intensity of exercise (approx. 55–65% VO_2max), almost equal to the contribution from plasma NEFA, but less at lesser or greater intensity [19,20]. The measurement of IMCL (intra-myocellular lipid) by magnetic resonance spectroscopy also shows muscle triacylglycerol utilization during exercise, at rates comparable with those observed with tracer techniques [21,22].

The activation of adipose tissue lipolysis during exercise is largely β-adrenergic, responding presumably to circulating adrenaline or perhaps activation of the sympathetic outflow to adipose tissue (studies in people with spinal cord injuries suggest mainly the former [23]). The technique of microdialysis of adipose tissue involves a small probe of semi-permeable membrane, which is used both to introduce agents and to sample the interstitial glycerol concentration (as a marker of lipolysis). Introduction of propanolol (a non-specific β-adrenergic blocker) largely, but not completely, inhibits the stimulation of lipolysis by exercise [24]. The remaining, non-β-adrenergic component, may represent activation by the ANF pathway [8].

If activation of adipose tissue lipolysis relies on signals that are part of the exercise response, how is it that the rate of fatty acid delivery so closely matches the rate of utilization by skeletal muscle? This would seem to require some direct signal from the muscle to the adipose tissue. If someone exercises whilst lipolysis is suppressed, e.g. using the drug acipimox which acts on the so-called

nicotinic acid receptor on adipocytes and potently blocks NEFA release, then the muscles use more IMCL and also more glucose. That implies that NEFA delivery from adipose tissue is a 'preferred' fuel and the muscles will use other fuels to make up any lack of NEFA. An alternative view is that adipose tissue lipolysis normally operates at a greater rate than is necessary for fatty acid oxidation in other tissues. The 'excess' fatty acids are re-esterified, for instance in the liver, and returned to adipose tissue in VLDL. Then, at the onset of exercise, a greater proportion of the NEFA delivered from adipose tissue will be oxidized and a correspondingly lower portion re-esterified [25]. However, this view is not supported by all studies [17].

Tissue triacylglycerol metabolism in health and disease

The systems described above function efficiently in health to maintain appropriate delivery of fatty acids when they are needed. Dysfunction of these systems may underlie some specific disorders of lipid metabolism. For instance, in the relatively common condition known as familial combined hyperlipidaemia, there is evidence that the primary defect is an over-production of small VLDL particles from the liver. This may be combined with a low rate of lipolysis in adipose tissue [26].

We will discuss here one very common condition which may arise from a dysfunction of these systems: the 'metabolic syndrome' or 'insulin resistance syndrome'. This is a collection of inter-connected adverse metabolic changes including insulin resistance (with some degree of glucose intolerance), elevated blood triacylglycerol concentrations and low concentrations of the 'protective' HDL-cholesterol. This condition is usually associated with central (abdominal) obesity. It has become clear in recent years that insulin resistance is closely associated with increased concentrations of triacylglycerol in liver and skeletal muscle. An increase in triacylglycerol deposition in the pancreatic β-cell may lead, in time, to impairment of insulin secretion, therefore explaining why this syndrome is an important precursor to development of type 2 diabetes. This has been termed 'ectopic fat deposition', i.e. deposition of triacylglycerol in tissues other than adipose tissue. It may arise from a dysfunction of the adipose tissue, leading to exposure of other tissues to excess flux of fatty acids (both NEFA and triacylglycerol-rich remnant particles) [27]. One possible mechanism is that abdominal fat, including the visceral fat within the abdominal cavity, is less efficient than is lower-body adipose tissue at 'sequestering' excess dietary fat and thereby protecting other tissues. There is evidence for this view from tracer studies showing a high rate of turnover of triacylglycerol stores in abdominal, especially intra-abdominal adipose tissue [28] and indirectly from the strong protective effect of lower-body adipose tissue against insulin resistance, dyslipidaemia and hypertension [29].

Why should an increased triacylglycerol concentration in liver and skeletal muscle be associated with insulin resistance? The difficulty is in dissociating

cause and effect. It is possible that the persistent high insulin concentrations that characterize insulin resistance lead to altered partitioning of fatty acids, with more going towards esterification at the expense of oxidation. In that view, ectopic fat deposition would be a consequence of insulin resistance rather than a cause. But there are also strong suggestions of a causal relationship. There are many demonstrations, especially in skeletal muscle (which is more accessible to study than the liver), that elevated fatty acid availability reduces the efficiency of insulin signalling (e.g. to stimulate glucose metabolism). The underlying mechanisms are discussed in Chapter 4 of this volume. The potential mechanisms by which regular exercise and training prevent insulin resistance despite large intramyocellular triacylglycerol stores in muscle are discussed in several of the essays in this volume.

It is also clear that treatments that reduce 'ectopic' fat content improve insulin resistance. For instance, the TZD (thiazolidinedione) insulin-sensitizing drugs that are now in clinical use for the treatment of type 2 diabetes improve insulin sensitivity and reduce hepatic fat content [30]. The interesting point is that the TZDs are agonists to the nuclear receptor/transcription factor PPARγ (peroxisome-proliferator-activated receptor γ), which is most highly expressed in adipose tissue and not expressed in liver. This suggests that TZDs reduce liver fat and improve hepatic insulin sensitivity by effects on adipose tissue, possibly increasing the capacity of adipose tissue to 'entrap' fatty acids and thus protect the liver.

There are further links between the tissues that are the subject of this chapter. It is now recognized that adipose tissue secretes a large number of peptides and other factors, some of which may function as hormones and affect metabolism in other tissues. One of these is a protein called adiponectin. It is abundant in the circulation (typical plasma concentration 10 mg/l). Adiponectin is most highly secreted by small adipocytes. As adipocytes increase in size, adiponectin expression and secretion are so highly down-regulated (the mechanism is unknown) that plasma concentrations are actually lower in obese than in lean people. There are strong relationships between high adiponectin concentrations and a 'healthy' metabolic profile, or conversely between low adiponectin and features of the metabolic syndrome. At least some of these effects may be mediated by adiponectin-induced reduction in liver fat content. The molecular mechanism may involve activation of the AMP-activated protein kinase [31]. It is also noteworthy that a strong effect of TZD administration is to raise adiponectin expression, secretion and plasma concentration, and that the reduction in liver fat content observed with TZD treatment is closely related to the increase in adiponectin concentration [30].

Summary

- *Fat is the most important stored fuel in mammals.*
- *Three tissues play major roles in fatty acid and triacylglycerol metabolism: adipose tissue, skeletal muscle and liver.*
- *Each of these tissues has a store of triacylglycerol that can be hydrolysed (mobilized) in a regulated way to release fatty acids.*
- *There is clearly cooperation amongst the tissues, so that, for instance, adipose tissue fat mobilization increases to meet the demands of skeletal muscle during exercise.*
- *When triacylglycerol accumulates excessively in skeletal muscle and liver, sometimes called ectopic fat deposition, then the condition of insulin resistance arises. This may reflect a lack of exercise and an excess of fat intake.*

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