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Reviews

Adipose tissue as a buffer for daily lipid flux

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Abstract

Insulin resistance occurs in obesity and Type II (non-insulin-dependent) diabetes mellitus, but it is also a prominent feature of lipodystrophy. Adipose tissue could play a crucial part in buffering the flux of fatty acids in the circulation in the postprandial period, analogous to the roles of the liver and skeletal muscle in buffering postprandial glucose fluxes. Adipose tissue provides its buffering action by suppressing the release of non-esterified fatty acids into the circulation and by increasing triacylglycerol clearance. In particular, the pathway of 'fatty acid trapping' (adipocyte uptake of fatty acids liberated from plasma triacylglycerol by lipoprotein lipase) could play a key part in the buffering process. If this buffering action is impaired, then extra-adipose tissues are exposed to excessive fluxes of lipid fuels and could accumulate these in the form of triacylglycerol, leading to insulin resistance. These tissues will include liver, skeletal muscle and the pancreatic beta cell, where the long term effect is to impair insulin secretion. Adipose tissue buffering of lipid fluxes is impaired in obesity through defects in the ability of adipose tissue to respond rapidly to the dynamic situation that occurs after meals. It is also impaired in lipodystrophy because there is not sufficient adipose tissue to provide the necessary buffering capacity. Thus, the phenotype, at least with regard to insulin resistance, is similar with both excess and deficiency of adipose tissue. Furthermore, this concept could provide a framework for understanding the action of the thiazolidinedione insulin-sensitizing agents. [Diabetologia (2002) 45:1201–1210]

Keywords Adipose tissue, Insulin resistance, Obesity, Lipodystrophy, Fatty acids.

Adipose tissue: not just an inert repository for excess energy

In the last few years we have begun to appreciate that adipose tissue is more than just a passive repository for excess energy. The discovery that adipocytes express and secrete a large number of proteins and other molecules, including the hormone leptin, has changed our view of this previously under estimated tissue. Alongside these developments, it has also become clear that even the processes of fat storage and mobilization are themselves regulated in a highly coordinated manner, with minute-to-minute control and rapid, dramatic shifts in metabolic flux, for instance in the period following a meal [1]. Even in its role as an energy storage organ, adipose tissue is far from 'inert' as it is sometimes described [2].

At the same time, attention has been focussed on the role of adipose tissue in pathophysiology. The excess adipose tissue of obesity is associated with insulin resistance. There are correlations between adiposity and insulin resistance even over relatively normal

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Abbreviations: ASP, Acylation stimulating protein; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; PPARγ, peroxisome proliferator activated receptor-γ; TZD, thiazolidinedione; TG, triacylglycerol; VLDL-TG, very low density lipoprotein-triacylglycerol

ranges of fatness [3, 4, 5]. Paradoxically, a deficiency of adipose tissue, as in lipodystrophy or lipoatrophy in humans [6, 7] and rodents [8, 9, 10], is also associated with insulin resistance. These observations suggest that adipose tissue in health is carrying out some active function that maintains normal insulin sensitivity. The aim of this review is to propose a view of adipose tissue as a highly active, efficient buffer against the daily flux of fatty acids in the circulation, which will inevitably impinge upon other tissues with adverse consequences should the buffering action of adipose tissue fail.

The concept of tissue buffering of substrate fluxes

A typical Western diet provides around 300 g per day of carbohydrate and 100 g per day of fat. A typical meal, then, might contain 100 g carbohydrate and 30–40 g fat.

The argument for buffering of glucose flux is well understood. The amount of free glucose in the body is small, typically around 12 g in the circulation and extravascular space. When a meal containing 100 g carbohydrate is ingested, the influx of glucose could potentially increase the plasma glucose concentration eightfold. This does not happen, because coordinated mechanisms come into play to increase the disposal of glucose from plasma and to suppress the entry into the circulation of endogenous glucose [11]. By these means, the excursion in plasma glucose concentration and the exposure of tissues to hyperglycaemia are minimized. The main tissue involved in 'buffering' the influx of glucose is the liver, absorbing the influx of glucose and switching off glucose production. Skeletal muscle plays a subsidiary role in taking up glucose under the influence of insulin.

Exactly the same arguments can be made for fat. The amount of triacylglycerol in the circulation is around 3 g (for a plasma triacylglycerol concentration of 1 mmol/l). Therefore absorption of a typical meal could in principle raise the plasma triacylglycerol concentration tenfold. Again, this does not happen. Typically, after a meal containing 33 g fat and 96 g carbohydrate, the plasma triacylglycerol concentration will rise somewhat less than 100% in healthy subjects [12]. This implies that, just as for carbohydrate metabolism, there must be mechanisms that 'buffer' the influx of triacylglycerol into the circulation and prevent the exposure of tissues to excessive triacylglycerol flux. Just what these mechanisms are will be discussed below.

The somewhat imprecise term 'fatty acid flux' has been used deliberately. The triacylglycerol concentration increases from for example, 1 mmol/l to somewhat less than 2 mmol/l after a meal. Most of this rise will be accounted for by chylomicron-triacylglycerol, although endogenous very low density lipoprotein-triacylglycerol (VLDL-TG) will also contribute [13]. But at the same time, the plasma NEFA concentration will be suppressed, typically from 600 μmol to less than 100 μmol/l. Therefore the increase in total fatty acid concentration in both NEFA and triacylglycerol is 'buffered' to a greater extent than might be expected initially. When we consider the more rapid turnover of NEFA compared with triacylglycerol-fatty acids (typical half-lives: NEFA, 3 min; chylomicron-triacylglycerol, 5 min [14]; non-chylomicron-triacylglycerol around 120 min), it is apparent how the potential exposure of tissues to fatty acid flux (in both NEFA and triacylglycerol) is minimized in the postprandial period.

In real daily life, one postprandial period merges into the next with successive meals. There is a regular circadian rhythm of plasma NEFA and triacylglycerol concentrations, NEFA concentrations in particular fluctuating with each meal [15, 16]. It seems likely that these variations reflect changes in the activity of adipose tissue hormone-sensitive lipase (HSL) and lipoprotein lipase (LPL), although these have not been assessed in humans.

Adipose tissue and the buffering of lipid flux

The major mechanisms that contribute to the buffering of fatty acid flux in the postprandial period are probably threefold and not unrelated: (i) suppression of NEFA release, (ii) increased clearance of circulating triacylglycerol, and (iii) suppression of endogenous triacylglycerol secretion.

Suppression of NEFA release clearly lies within adipose tissue. The rapidity with which insulin suppresses fatty acid release from adipose tissue is illustrated in the period following a meal, when NEFA release from adipose tissue can go from its highest rate in the 24-h cycle, after overnight fast, to virtually zero within 90 min [1, 12].

Clearance of triacylglycerol in adipose tissue also increases in the postprandial period. Insulin up-regulates adipose tissue expression of LPL, through multiple mechanisms [17]. The time-course of this effect is quite different from that of suppression of NEFA release. Insulin-activation of adipose tissue LPL is a slow effect, seen during insulin infusions lasting several hours [18]. Peak triacylglycerol clearance in adipose tissue is seen around 3 to 5 h following a meal [12, 19], a time that coincides perfectly with the peak triacylglycerol concentrations in plasma. This increased clearance will reflect both activation of LPL, and the increased concentration of chylomicron-triacylglycerol in the circulation, since chylomicron-triacylglycerol is hydrolysed more avidly by LPL than is VLDL-TG [20, 21]. The latter mechanism is somewhat analogous to glucose uptake by the liver by the high-Km transporter GLUT-2 followed by the high-

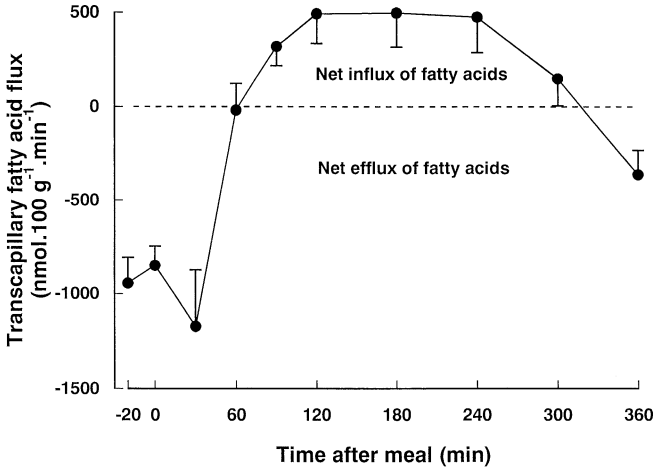

Fig. 1 Net transcapillary flux of fatty acids in adipose tissue in the postabsorptive and postprandial states. A negative value indicates net efflux of fatty acids from the tissue (i.e. fat mobilization); positive values indicate net influx of fatty acids into the tissue (i.e. fat deposition). Calculated from arteriovenous difference measurements across human subcutaneous abdominal adipose tissue, together with measurement of blood flow, [23], using pooled data from 35 healthy subjects. Original data are in [19, 113, 114, 115]. The figure illustrates the rapid changes in direction of net flux of fatty acids in and out of adipose tissue in response to feeding and fasting

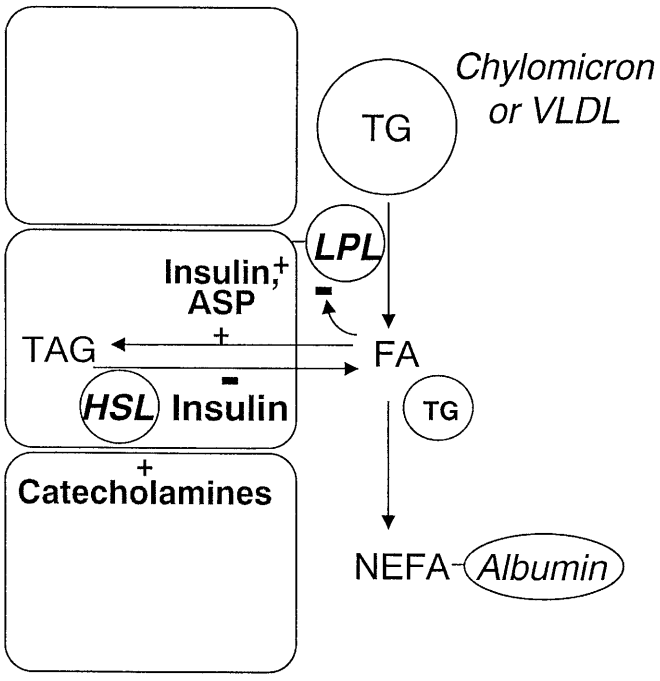

Fig. 2 A model for the regulation of fatty acid fluxes in and out of adipocytes. During fasting, HSL (intracellular) is highly active and the net flow of fatty acids is 'outward' from adipocytes to capillaries. In the fed state, insulin activates LPL and stimulates the pathway of fatty acid esterification, reinforced by ASP. HSL is suppressed by insulin. The result is a net inward flow of fatty acids from capillaries to adipocytes, part of the 'buffering' action of adipose tissue against lipid fluxes in the circulation. Based on [116] with permission of Portland Press

Km glucokinase: as glucose concentrations rise in the portal vein, so glucose moves 'passively' into the hepatocytes, independently of regulation of enzyme activity. The dynamic nature of fatty acid fluxes out of and into adipose tissue, reflecting the switch between fasting and fed states, is summarised in Figure 1.

NEFA release and triacylglycerol clearance in adipose tissue are closely related. Recently, it has been recognized that the uptake and release of fatty acids by adipocytes reflects a series of coordinated events [22]. LPL in adipose tissue capillaries generates a surplus of fatty acids, a proportion of which will be taken up by adipocytes for esterification with glycerol 3-phosphate and storage as triacylglycerol. A proportion of the LPL-generated fatty acids, however, always enters the plasma as NEFA [23], as indicated by the rapid entry of dietary fatty acids into the NEFA pool [24, 25, 26, 27]. The proportion of 'LPL-derived fatty acids' taken up by the adipocyte seems to be regulated by intracellular events. In the fasting state, when the intracellular enzyme HSL is active, there is a large net outward flow of fatty acids from adipocytes into the plasma, and the concentration gradient will not favour fatty acid uptake: LPL-derived fatty acids in that state are almost quantitatively released as NEFA [23, 28]. In the postprandial state, HSL is suppressed by insulin and the pathway of fatty acid esterification is stimulated, and LPL-derived fatty acids are 'drawn into' the adipocyte by the resultant concentration gradient [28] (Fig. 2). (Intracellular fatty acid binding proteins and acyl-CoA synthase are, of course, also involved in this process, as also are the putative fatty acid transporters [29]). Thus, the pathway of fatty acid uptake, or 'fatty acid trapping' [30], plays an important part in regulating NEFA delivery from adipose tissue in the postprandial state. It probably also regulates triacylglycerol-fatty acid flux. Local accumulation of fatty acids at the site of LPL action can lead to premature detachment of LPL together with the remnant particle [31, 32], which will then deliver an increased fatty acid load in the form of triacylglycerol-rich remnants to the liver and other tissues.

The pathway of fatty acid trapping is regulated by insulin, as noted above, and also by the acylation-stimulating protein (ASP) derived from components of the alternative complement pathway produced by adipocytes [33]. The activity of fatty acid trapping (reflected in the proportion of LPL-derived fatty acids taken up by the tissue) varies with time in the postprandial period, going from close to zero after overnight fast to around 90% (the exact figure depending on meal carbohydrate and fat contents) within 1 to 2 h after a meal [23]. Again, the dynamic pattern of regulation of lipid metabolism in adipose tissue is apparent.

It was suggested, by analogy with glucose metabolism, that endogenous triacylglycerol secretion might be suppressed in the postprandial period. Direct evidence for this in man is lacking, partly because of the difficulty of making isotopic tracer measurements in such a rapidly-changing non-steady state. However, the ability of insulin to acutely suppress VLDL-TG secretion both in rodent cellular systems [34, 35] and in humans in vivo [36, 37] is well established. Although this is a hepatic effect, the suppression of hepatic VLDL-TG secretion by insulin is likely to be reinforced by suppression of NEFA release from adipose tissue. There is a close relation between NEFA production rates and triacylglycerol secretion, measured isotopically, in a range of conditions [38], although the effects of acute reduction of NEFA concentrations are not as marked as are the effects of insulin per se on VLDL secretion [39]. Thus, adipose tissue again participates in the events that minimise excursions in plasma fatty acid flux in the postprandial period. It might be noted that NEFA delivery from adipose tissue is now seen also as a major determinant of hepatic glucose output [40], thus giving adipose tissue a role in signalling nutrient requirements to the liver [41, 42].

We do not claim that adipose tissue is the only tissue involved in 'buffering' of lipid fluxes. The liver is clearly involved as discussed above, and in addition the liver will receive and hence 'buffer' an influx of triacylglycerol in triacylglycerol-rich remnant particles in the postprandial period. Similarly, skeletal muscle will remove triacylglycerol from the circulation [12], which could be stored within the myocytes [43] in the postprandial period. However, adipose tissue is the only major tissue in which triacylglycerol clearance and fatty acid trapping is specifically up-regulated in the postprandial period, and furthermore it is the only site of release of NEFA. Hence, we believe that it has a special place in 'buffering' of lipid fluxes.

Adipose tissue and insulin resistance

There is much evidence showing that the function of adipose tissue is disturbed in insulin-resistant states. The ability of insulin to suppress fatty acid release is impaired in obesity and other insulin-resistant states [19, 44, 45, 46, 47, 48]. This was shown clearly in a study of insulin dose-response curves, which showed an insulin concentration for half-maximal suppression of lipolysis of 101 pmol/l in lean, but 266 pmol/l in obese subjects [48]. Similarly, the ability of insulin to up-regulate LPL activity and hence triacylglycerol clearance in adipose tissue is impaired in obesity [19, 49, 50, 51]. For instance, LPL activity, measured in adipose tissue biopsies, increased following a meal by 124% in lean, but only by 27% (NS) in obese subjects (data estimated from figure) [50]. The pathway of fatty acid trapping in adipose tissue could also be defective in insulin resistance, thus adding to impaired buffering of fatty acid flux [52]. These and similar studies involving meal feeding [19] show that the hyperinsulinaemia associated with obesity is not sufficient to produce normal adipose tissue metabolism in the postprandial period. These impairments in adipose tissue function will lead to less effective buffering of fatty acid fluxes in the circulation, manifest as increased postprandial NEFA and triacylglycerol concentrations.

It is increasingly recognized that insulin resistance is associated with increased triacylglycerol concentrations in insulin-responsive tissues including skeletal muscle (in humans and rodents) [53, 54, 55] and the liver [56, 57, 58, 59]. In addition, prolonged exposure of pancreatic islets to fatty acids results in impairment of insulin secretion [60, 61], and (in rodents) lipid accumulation in pancreatic islets is characteristic of states associated with insulin resistance and Type II diabetes [62, 63].

Interestingly, the same pattern of insulin resistance and tissue triacylglycerol accumulation is seen in lipodystrophy. Human lipodystrophy, whether total or partial, is an insulin-resistant state, often severely so, and is usually associated with Type II diabetes [7]. In rodent models, adipose tissue deficiency is also associated with insulin resistance and diabetes [8, 58, 64] and again with accumulation of triacylglycerol in skeletal muscle, liver and pancreas [58, 65]. These and other observations have led to the concept of 'lipotoxicity' in the pathogenesis of Type II diabetes [66].

The key point of our hypothesis is that this lipotoxicity reflects impairment of the normal ability of adipose tissue to buffer excessive fatty acid flux, especially in the period following meals. Since we, as humans eating Western diets, spend most of our days in a postprandial state, loss of adipose tissue's ability to buffer the incoming flux of fatty acids will inevitably lead to increased exposure of other tissues to this increased flux. This can then lead to triacylglycerol deposition in tissues, which is associated with, and could well be a causal factor of insulin resistance and, in the case of the beta cell, eventual failure of insulin secretion. This hypothesis provides a unifying concept for obesity-associated insulin resistance and the insulin resistance associated with deficiency of adipose tissue (lipodystrophy or lipoatrophy). In obesity, adipose tissue function is altered so that buffering is less effective: effectively, it could be argued that the adipocytes are full and are resisting further fat storage. Indeed, the argument has been made that 'insulin resistance' in obesity is an adaptation tending to prevent further fat storage [67, 68]. Of course, most excess dietary fatty acids will ultimately be deposited in adipose tissue, but they could go through several metabolic cycles (e.g. via hepatic VLDL-TG) before they reach their destination. During that time, other tissues are

exposed and will take up a proportion of the fatty acid flux. In lipodystrophy, there could simply be insufficient adipose tissue to carry out the normal buffering function.

Importance of adipocyte size and adipocyte differentiation

Larger adipocytes are generally found to be less sensitive to insulin in vitro, at least in rodents [69, 70, 71] and in some human studies [72]. Furthermore, the occurrence of larger adipocytes in the subcutaneous abdominal depot is a marker of risk of developing Type II diabetes [73, 74]. Much of our thesis would fit with the idea that, as adipocytes enlarge with fat storage, their efficiency as 'metabolic buffers' decreases. In this context, it is interesting that the thiazolodinedione insulin sensitizers act, via the nuclear receptor PPARγ, to stimulate adipocyte differentiation and to increase the number of small adipocytes (at least in rats) [75, 76]. It could well be that the new, smaller adipocytes thus formed act as powerful 'buffers', avidly absorbing fatty acids in the postprandial period. Indeed, it has been proposed that an inability to differentiate new adipocytes as required for storage of excess energy underlies the development of Type II diabetes [77].

Site-specific properties of adipose tissue

It is well recognized that the different adipose depots show individual metabolic characteristics. It is possible that the intra-abdominal fat depots, although relatively small in comparison with subcutaneous depots, play an important role in normal buffering. Rates of lipolysis from intra-abdominal adipocytes, when measured in vitro, tend to be high [78, 79, 80], and these high rates of lipolysis must be matched in the postprandial period by high rates of fat deposition [81]. There is some direct evidence for the latter in vivo [82]. However, an enlarged intra-abdominal store is associated in many studies with features of insulin resistance [83, 84], suggesting that large intra-abdominal adipocytes could be less efficient at buffering. It is difficult to reach firm conclusions because most of the evidence about the metabolic behaviour of intra-abdominal adipocytes has, of necessity, been obtained in vitro, under which conditions the many regulatory influences that operate to maintain fatty acid homeostasis in vivo are absent. It is interesting that estimates of the delivery of fatty acids either to the liver or to the systemic circulation suggest that the intra-abdominal depots do not explain excessive fatty acid flux in upper-body obesity [85]. The special role of the intra-abdominal depots in insulin resistance could therefore relate more to liberation of non-lipid factors such as cytokines.

Other aspects of this hypothesis

The hypothesis that impaired buffering of lipid fluxes in adipose tissue in obesity can lead to insulin resistance in insulin-responsive tissues could in principle be tested in various ways. One corollary of this hypothesis is that patients lacking adipose tissue should also develop insulin resistance. As discussed above, this is indeed so, and the phenotype in lipodystrophy also includes triacylglycerol deposition in other tissues just as expected.

Another test would be to show that an agent that improved the buffering capacity of adipose tissue (perhaps its capacity to take up fatty acids) would improve insulin sensitivity. This could be exactly what the thiazolidinedione (TZD) insulin-sensitizers do. It has been unclear how drugs that are thought to act mainly in adipose tissue, by binding to the nuclear receptor PPARγ, could enhance insulin sensitivity in glucose-metabolizing tissues. Common features of TZD action are that they rapidly reduce plasma NEFA concentrations (in rodents and humans) [86, 87] and that they require a longer period (days to weeks) to improve insulin sensitivity. These would fit exactly with the expected effects if indeed TZDs increase the effectiveness of fatty acid trapping in adipocytes, perhaps by stimulating adipocyte differentiation and hence creating new, smaller adipocytes with a high avidity for fatty acid uptake as described above. The TZDs also lead to weight gain whilst improving sensitivity to insulin, apparently a paradox but clearly explained under this hypothesis. Presumably TZD-induced improvement in fatty acid trapping in adipose tissue would lead gradually to a reduction in acylglycerol content in other tissues. This has been shown in rats [88, 89], although not yet tested in humans.

The present hypothesis also provides a way of unifying a number of apparently diverse observations about adipose tissue function in obesity. A key feature of this hypothesis is that effective buffering requires rapid alterations in adipose tissue metabolism to meet the changing flux of fatty acids, especially in the postprandial period. This emphasises the dynamic aspects of adipose tissue metabolism rather than the steady-state. Thus, a number of studies have shown that in obesity, adipose tissue LPL is not up-regulated normally in the postprandial period [19, 49, 50] It can always be argued that up-regulation is not necessary because the total amount of adipose tissue is such that even a relatively low activity of LPL is sufficient for normal triacylglycerol clearance. However, we suggest that the emphasis should be shifted to the dynamic adjustment of metabolism. Accordingly, a study [90] showed some years ago that, in obese subjects, adipose tissue LPL will, indeed, respond to a 'normal' extent to insulin stimulation, but that this process is considerably delayed compared with lean subjects. That delay could well result in sufficient impairment

of postprandial buffering that other tissues are exposed for some hours to excess lipid flux.

Another observation whose physiological relevance is not immediately clear, but that could fit this hypothesis, is that the normal postprandial increase in adipose tissue blood flow is blunted in obesity [19, 91]. As discussed elsewhere, the physiological relevance of the marked increased in adipose tissue blood flow seen after meals is not clear [92] but it could be a mechanism to increase triacylglycerol delivery to the tissue, and hence triacylglycerol clearance [93]. As in the case of LPL, it can be argued that whole body adipose tissue blood flow is probably greater in obese than in lean subjects because of their increased total adipose tissue. But again, the dynamic adjustment in the postprandial state is lost in obesity.

Other potential links between adipose tissue and insulin resistance

We are aware, of course, of many authors who have described links between obesity and insulin resistance, diabetes or cardiovascular disease in terms of increased NEFA flux and impaired fatty uptake by adipocytes [2, 94, 95, 96]. The novel aspect of our hypothesis is, we believe, the attention it draws to the highly active pattern of fatty acid metabolism in adipose tissue, and the widespread effects of this on other tissues. We do not wish to ignore other potential links between adipose tissue and insulin resistance, but these have been reviewed thoroughly by other authors [97, 98, 99].

In some models of lipoatrophy in rodents, replacement of leptin has dramatic effects in reducing skeletal muscle, liver and beta-cell triacylglycerol concentrations and reversing insulin resistance [100, 101]. Treatment of lipodystrophic patients with recombinant leptin also produced marked metabolic improvements [102], although probably mediated at least in part by reduction in food intake. It has been suggested, therefore, that an important causal role for leptin is the maintenance of fatty acid homeostasis in non-adipose tissues [63]. However, as summarised in reference [2], leptin replacement does not ameliorate metabolic abnormalities in all fat-deficient animal models. Furthermore, whilst lack of leptin could explain the link between adipose tissue deficiency and insulin resistance, it is not so easy to explain the link between obesity, usually with increased leptin concentrations, and insulin resistance.

The recent discovery of resistin [103], an additional protein hormone secreted by adipocytes, provides yet a further potential link, although as with all such molecules released from adipose tissue, it is less easy to see how deficiency of adipose tissue could lead to insulin resistance. Furthermore, the initial findings on resistin have been challenged [104, 105].

Among all the bioactive peptides secreted from the adipose tissue, adiponectin has recently attracted attention as a putative signal modulating insulin sensitivity. Adiponectin, also called Arcp30 and AdipoQ, was detected by subtractive cloning of transcripts exclusively expressed in adipose tissue [106, 107, 108]. Despite the tissue origin, obesity is associated with lower plasma concentrations of adiponectin and high concentrations are seen in lean, insulin-sensitive subjects [109]. Very low concentrations are seen in lipodystrophy. Accordingly, if adiponectin were to be a major determinant of insulin sensitivity it would also resolve the paradox of both lipodystrophy and obesity being insulin-resistant states. The mechanism of action of adiponectin is not entirely clear but recent animal studies suggest that adiponectin stimulates fatty acid oxidation in muscle [110]. Increased fatty acid oxidation is seen together with increased body temperature, which could suggest an uncoupling mechanism. The triacylglycerol engorgement of muscle and liver seen in insulin resistance is alleviated by adiponectin, with restoration of hepatic insulin sensitivity, which in turn leads to a normalisation of the insulin modulation of hepatic glucose production [111].

Conclusions

We have reviewed the evidence that adipose tissue, even in its ‘classical’ energy storage capacity, is a dynamic tissue with a very active pattern of metabolism. We propose that adipose tissue plays a crucial role in buffering the flux of fatty acids in the circulation in the postprandial period, just as the liver and, to a lesser extent, skeletal muscle buffer postprandial glucose fluxes. By buffering we mean that the postprandial excursion in circulating substrate flux is minimised. In the case of lipids, we have to consider both NEFA and triacylglycerol-fatty acids. Adipose tissue provides its buffering action by suppressing the release of NEFA into the circulation and by increasing triacylglycerol clearance. In particular, the pathway of ‘fatty acid trapping’ (adipocyte uptake of fatty acids liberated from plasma triacylglycerol by LPL) could be important in the buffering process. When this buffering action is impaired, then extra-adipose tissues are exposed to excessive fluxes of lipid fuels and could accumulate these in the form of triacylglycerol, which leads to insulin resistance. These tissues will include the liver, skeletal muscle and the pancreatic beta cell, where the long term effect is to impair insulin secretion. Adipose tissue buffering of lipid fluxes is impaired in obesity through defects in the ability of adipose tissue to respond rapidly to the dynamic situation that occurs after meals. It is also impaired in lipodystrophy because there is simply not sufficient adipose tissue to provide the necessary buffering capacity. Thus, the hypothesis explains why the phenotype, at

least as regards insulin resistance, is similar with both excess and deficiency of adipose tissue. Furthermore, this hypothesis can provide a framework for understanding the action of the TZD insulin-sensitising agents.

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