Symposium in recognition of the work of the late Mike Stock on ‘Human energy metabolism’

Fatty acid metabolism in obesity and type 2 diabetes mellitus

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Disturbances in pathways of lipolysis and fatty acid handling are of importance in the aetiology of obesity and type 2 diabetes mellitus. There is evidence that a lowered catecholamine-mediated lipolytic response may play a role in the development and maintenance of increased adipose tissue stores. Increased adipose tissue stores, a disturbed insulin-mediated regulation of lipolysis and subnormal skeletal muscle non-esterified fatty acid (NEFA) uptake under conditions of high lipolytic rate may increase circulating NEFA concentrations, which may promote insulin resistance and cardiovascular complications. In addition, a disturbance of NEFA uptake by adipose tissue postprandially is also a critical determinant of plasma NEFA concentration. Furthermore, evidence is increasing that insulin-resistant muscle is characterised by a lowered ability to oxidise fatty acids. A dysbalance between fatty acid uptake and fatty acid oxidation may in turn be a factor promoting accumulation of lipid intermediates and triacylglycerols within skeletal muscle, which is strongly associated with skeletal muscle insulin resistance. The present review describes the reported disturbances in pathways of lipolysis and skeletal muscle fatty acid handling, and discusses underlying mechanisms and metabolic consequences of these disturbances.

Fatty acid metabolism: Obesity: Type 2 diabetes mellitus

Obesity and type 2 diabetes mellitus frequently occur together, indicating that these conditions may share common pathological mechanisms. Both conditions are characterised by insulin resistance, disturbances in intermediary carbohydrate and fat metabolism and most often by an increased adipose tissue mass as well as increased triacylglycerol storage within skeletal muscle. Disturbances in the lipolytic pathways in adipose tissue and skeletal muscle and impairments of fatty acid handling in skeletal muscle may be important factors in the development and maintenance of increased triacylglycerol storage and accumulation of lipid intermediates within adipose tissue and skeletal muscle, thereby promoting obesity, insulin resistance and type 2 diabetes mellitus.

The present review discusses the evidence underlying a causal role of disturbed catecholamine-mediated lipolysis and skeletal muscle fatty acid handling in the aetiology of obesity and type 2 diabetes mellitus.

Adipose tissue lipolysis in obesity and type 2 diabetes mellitus

Several studies have shown that the development or maintenance of an increased adipose tissue mass might be promoted by a blunted lipolytic response after catecholamine stimulation. In several studies the increase in adipose tissue lipolysis, as measured by an increase in arterial glycerol (Blaak et al. 1994a) or rate of appearance of glycerol (Connacher et al. 1991) during β-adrenergic stimulation or during catecholamine infusion, was blunted in obese males. A similar disturbance in adrenaline-mediated lipolysis was shown in upper-body-obese women.

Abbreviations: CTP, carnitine palmitoyl transferase; HSL, hormone-sensitive lipase; NEFA, non-esterified fatty acids.
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as compared with lower-body-obese women (Jensen et al. 1989). Subsequent studies showed that this diminished lipolytic response could be ascribed to a diminished function of the $\beta_2$ adrenoceptor (Schiffelers et al. 2001). Also, there are indications from ‘in vitro’ adipose tissue biopsy studies that decreased $\beta_2$ adrenergically-mediated lipolysis may be related to a decreased number of $\beta_2$ adrenoceptors (Reynisdottir et al. 1994). In addition, in vitro studies in adipocytes from first-degree relatives of obese subjects (Hellstrom et al. 1996) and studies in adipocytes from elderly male subjects with several manifestations of the metabolic syndrome also indicate post-receptor alterations at the level of the protein kinase A–hormone-sensitive lipase (HSL) complex (Reynisdottir et al. 1994).

The molecular mechanisms underlying the activation of lipolysis are not known in detail. Stimulation of adipocytes with catecholamines triggers the translocation of HSL from the cytoplasmic compartment to the surface of lipid droplets, and in intact cells this translocation only takes place after phosphorylation of HSL (Holm et al. 2000). A complementary mechanism precluding HSL binding to the lipid droplet in intact cells seems to rely on perilipins. Under basal conditions non-phosphorylated perilipin resides on the lipid droplet. On stimulation of the adipocytes, perilipin phosphorylation would relieve this constraint and allow phosphorylated HSL free access to the lipid droplet (Souza et al. 1998). Interestingly, it was shown that a blunted lipolytic response in older rats may be related to blunted HSL translocation from the cytosol to the lipid droplet and a movement of perilipin away from the lipid droplet (Clifford et al. 2000). On the basis of these findings it seems a plausible option that defects in HSL translocation or perilipin function may also play a role in the catecholamine resistance of lipolysis in obese subjects.

Thus, conditions characterised by insulin resistance are associated with disturbances in the capacity to mobilise fatty acids. It is hard to differentiate between primary and secondary factors when the obese or insulin-resistant state has already developed. In vitro studies on adipose tissue biopsies indicated that a 20 % weight reduction partially-normalised lipolysis regulation in subcutaneous fat cells of obese women (Reynisdottir et al. 1995). In vivo studies indicate that the dysfunction in catecholamine-mediated (adipose tissue) lipolysis seems to persist after weight reduction (Blaak et al. 1994b), indicating that this disturbed lipolysis may play an important role in the aetiology of obesity and type 2 diabetes mellitus. In addition, evidence that altered catecholamine-mediated lipolysis may be an important primary factor comes from findings that polymorphisms in $\beta_2$ adrenoceptor genes (Arg16Gly, Glu27Gly) may be associated with obesity, obesity-related phenotype and diabetes mellitus, although these findings are controversial (Large et al. 1997; Ishiyama-Shigemoto et al. 1999; Meirhaeghe et al. 2000; Ukkola et al. 2000). Also, variations in CA$\Delta$ repeats in introns 6 (Magre et al. 1998) and 7 (Klannemark et al. 1998) and a 60C→G substitution in the promotor region of the HSL gene (Pihlajamaki et al. 2001) are associated with an obesity phenotype and type 2 diabetes mellitus. Presently, it is not known whether these polymorphisms are associated with an impaired lipolysis in abdominally-obese subjects and/or subjects with type 2 diabetes. In addition, disturbed lipolysis and HSL action have been reported in subjects with an inherited potential for obesity (Hellstrom et al. 1996).

**Skeletal muscle fatty acid utilization in obesity**

There are numerous indications that obesity is associated with a diminished capacity to use fat as a fuel. Impairments in the capacity to mobilise and oxidise fat have been reported in obese subjects during $\beta$-adrenergic stimulation (Blaak et al. 1994a; Fig. 1). Also, skeletal muscle fatty acid oxidation has been shown to be impaired in visceral-obese subjects during post-absorptive conditions, whereas glucose uptake and glucose oxidation were increased (Colberg et al. 1995; Mandarino et al. 1996). Wade et al. (1990) reported a

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**Fig. 1.** (a) Skeletal muscle fatty acid uptake (non-esterified fatty acid flux) and (b) glucose uptake (flux) in lean and obese and reduced-obese males (n 8) during post-absorptive conditions (---) and during infusion of the non-selective $\beta$-agonist isoprenaline (●). Values are means and standard deviations represented by vertical bars. Mean values were significantly different from those for the other two isoprenaline treatment groups: *P<0.05. (Data are adapted from Blaak et al. 1994a,b.)
positive relationship between percentage body fat and the RER during exercise in obese subjects, indicative of a lowered fat oxidation during exercise in obesity. However, this study has been criticised because most subjects were lean (percentage body fat < 25). Also, in this study subjects were exercising at a fixed work load of 100 W, which may have disturbed the relationship between fitness and fatness. Indeed, two subsequent studies (Geerling et al. 1994; Helge et al. 1999) did not confirm the results of the Wade et al. (1990) study. There are more recent indications that there may be differences in the source of fatty acids used during exercise in obese subjects as compared with controls. Abdominally-obese women have been shown to have an increased utilization of triacylglycerol-derived fatty acids during exercise (Horowitz & Klein, 2000). It is possible that increased triacylglycerol-derived fatty acid oxidation during exercise is driven by the mass of the muscle triacylglycerol stores, which have been reported to be increased in obese subjects (Levin et al. 2001; Malenfant et al. 2001).

Weight reduction did not improve the impaired capacity to utilise fatty acids in obese subjects (Blaak et al. 1994b; Kelley et al. 1999; Fig. 1), suggesting that these defects could be primary to the obese state rather than adaptational responses. This explanation is consistent with findings that a decreased reliance on lipid oxidation is a risk factor for weight gain in Pima Indians in Arizona, USA (Zurlo et al. 1990). In addition, in contrast to never-obese women, post-obese women showed decrements in postprandial and 24 h fat oxidation, and a high RQ has been correlated with weight gain in post-obese women (Froidevaux et al. 1993). Finally, in post-obese women it has been shown that fat oxidation during exercise (at 60–65 % VO2max) is subnormal for their high circulating level of fatty acids (Ranneries et al. 1998; Ezell et al. 1999). Overall, on the basis of the existing evidence it can be concluded that an impaired capacity to utilise fat as a fuel may be an important factor in the aetiology of obesity, leading to increased fat stores and weight regain after weight reduction.

**Skeletal muscle fatty acid utilization in type 2 diabetes mellitus**

As indicated earlier obesity and type 2 diabetes may share common pathological mechanisms. Indeed, in obese subjects with type 2 diabetes disturbances in skeletal muscle fatty acid utilization are similar to those present in obese subjects. Using the forearm balance technique in combination with infusion of the stable isotope tracer [U-13C]palmitate it was shown that the uptake and oxidation of NEFA were diminished in skeletal muscle of subjects with type 2 diabetes during post-absorptive conditions and during β-adrenergic stimulation (Fig. 2; Blaak et al. 2000b). Furthermore, in the diabetic subjects about 50 % of the fatty acids taken up by muscle were directly oxidised during β-adrenergic stimulation, whereas no oxidation was detected in diabetic muscle. This dysbalance between uptake and oxidation may lead to net triacylglycerol storage and accumulation of lipid intermediates within skeletal muscle, which may play a role in the development of skeletal muscle insulin resistance. These findings are in line with those of Kelley and coworkers (Kelley & Simoneau, 1994).
who used the leg-balance technique in combination with indirect calorimetry. They reported a diminished uptake and oxidation of NEFA in the post-absorptive state in subjects with type 2 diabetes mellitus. In another study in our laboratory subjects with type 2 diabetes had a diminished plasma NEFA oxidation and a higher triacylglycerol-derived fatty acid oxidation during moderate-intensity exercise (50 % VO_{2max}), indicating that the disturbed fatty acid utilization in the post-absorptive state is also present during physical exercise (Blaak et al. 2000). Less is known about substrate utilization during post-prandial conditions. Kelley and coworkers (Kelley & Simoneau, 1994) showed that after a high-fat meal skeletal muscle fatty acid uptake is less suppressed in subjects with type 2 diabetes compared with control subjects. During insulin-stimulated conditions, however, leg RQ was lower in insulin-resistant subjects compared with control subjects, indicating lower glucose oxidation and higher lipid oxidation. The authors discussed this mechanism of metabolic inflexibility and speculated that it may play an important role in lipid accumulation within the insulin-resistant muscle (Kelley & Mandarino, 2000).

In addition to the lowered capacity to oxidise fatty acids, disturbances in the regulation of skeletal muscle lipolysis may also contribute to the increased triacylglycerol storage. So far, little is known about the regulation of skeletal muscle lipolysis. Although it seems plausible that the key mechanisms involved in the regulation of the catecholamine-mediated lipolysis in skeletal muscle are the same as those in adipocytes, there are some recent data indicating differences in the regulation of skeletal muscle and adipose tissue lipolysis (Enoksson et al. 1998; Hagstrom-Toft et al. 2001). It was shown recently that HSL is also expressed in myocytes (Langfort et al. 1999) and can be activated by adrenaline and by muscle contraction (Langfort et al. 1998). Recent studies in our laboratory indicate that obesity is accompanied by a diminished capacity to regulate skeletal muscle lipolysis during in situ β_{2}-adrenergic stimulation, suggesting that an impaired ability to regulate skeletal muscle lipolysis may be involved in the development of increased muscle triacylglycerol storage (E Blaak, S Schiffelers, W Saris, M Mensink and E Kooi, unpublished results). So far, it is not known if this disturbed muscle lipolysis also extends to the type 2 diabetic state, as is the case for adipose tissue lipolysis.

The impaired capacity to take up and oxidise fatty acids during exercise persisted after weight reduction in subjects with type 2 diabetes (Blaak et al. 2001b) and was already present in obese subjects with impaired glucose tolerance (Mensink et al. 2001), indicating that these defects may play a primary role in the development from impaired glucose tolerance to type 2 diabetes mellitus. In a recent study it was shown that lifestyle intervention (a combined dietary–physical activity intervention) can prevent a further deterioration of disturbances in plasma NEFA oxidation in subjects with impaired glucose tolerance (M Mensink, E Blaak, A Wagenmakers and W Saris, unpublished results), indicating that the inclusion of physical activity in the programme compensates for the impaired ability to oxidise fat. It can be speculated that this factor may represent one of the mechanisms underlying the previously reported beneficial effects of this type of lifestyle intervention programme on glucose tolerance and insulin resistance (Tuomilehto et al. 2001).

**Underlying mechanisms for disturbed muscle fatty acid utilization**

Several mechanisms may explain the impaired capacity to take up and oxidise NEFA in skeletal muscle of insulin-resistant subjects.

Forearm lipolysis (as indicated by glycerol release) has been reported to be higher in muscle of subjects with type 2 diabetes during post-absorptive conditions and during β-adrenergic stimulation (Blaak et al. 2000b). In fact, increased forearm lipolysis may flood the muscle with NEFA and reduce the NEFA concentration gradient between blood and muscle, which is one of the primary determinants of plasma NEFA uptake and oxidation (van der Vusse et al. 2002).

Second, evidence from *in vitro* and whole-animal studies supports the existence of protein-mediated transport of NEFA that is likely to co-exist with passive diffusional uptake (Glatz et al. 2001a,b). Previous studies in our laboratory showed a lowered cytoplasmic fatty acid-binding protein (FABP) content in muscle of subjects with type 2 diabetes when compared with that of control subjects (Blaak et al. 2000b). However, in the study of Simoneau et al. (1999), neither the content of cytoplasmic FABP nor that of sarcoplasmic FABP was diminished in muscle biopsies from obese subjects. Nevertheless, it was shown recently that the ability to increase muscle cytoplasmic FABP was strongly correlated with weight loss, and with changes in fat oxidation following dietary intervention in obese subjects, also after correction for changes in the capacity for β-oxidation and oxidative capacity (Blaak et al. 2001a). In relation to these data, it remains to be determined whether there is a causal relationship between cytoplasmic FABP, weight loss and changes in fat oxidation or whether cytoplasmic FABP expression is merely an adaptive response to weight reduction. Evidence is emerging for concerted actions between membrane and cytoplasmic FABP that allow for efficient regulation of NEFA transport and metabolism. Thus, alterations in membrane fatty acid transporters such as fatty acid translocase/CD36 and fatty acid transport protein could also play a role in the lowered fat utilization. Indeed, muscle-specific cytoplasmic FABP has been reported to change concomitantly with fatty acid translocase/CD36 in insulin-deficient rats (Pelsers et al. 1999), indicating that the membrane-associated and cytoplasmic fatty acid transporters may be co-expressed in diabetes. Interestingly, the fatty acid translocase/CD36 gene has been implicated as one of the major genes in the aetiology of the disturbed fat metabolism in the spontaneously-hypertensive rat (Aitman et al. 1999), and has been associated with functionally important impairment of fatty acid transport (Coburn et al. 2000; Hajri et al. 2001). Furthermore, transgenic expression of CD36 in the spontaneously-hypertensive rat ameliorates insulin resistance and lowers serum fatty acids (Pravenec et al. 2001), perhaps by improving NEFA uptake in adipose tissue and skeletal muscle. CD36 deficiency is present in 2–3 % of the Japanese population.
and recent evidence suggests that it may be associated with insulin resistance, dyslipidaemia (Miyaoaka et al. 2001) and the absence of myocardial uptake of NEFA tracers in vivo (Nozaki et al. 1999). An association between mutations in CD36 and insulin resistance and diabetes has not, however, been reported in other human populations.

Skeletal muscle contains different types of fibre with a range of oxidative capacities. Type 1, slow-twitch, fibres have a high oxidative potential and have an excellent capacity for using lipid as a fuel. Type IIa fibres are intermediate, with an oxidative capacity that often overlaps that of type I fibres. An inverse relationship between percentage body fat and the percentage of slow-twitch fibres has been found (Wade et al. 1990; Helge et al. 1999), although data are not consistent (Simoneau et al. 1995; Kempen et al. 1998). Furthermore, several studies reported a lowered mitochondrial oxidative capacity, also independent of fibre type (Simoneau et al. 1995; Kempen et al. 1998; He et al. 2001), and a lowered capacity for β-oxidation (Astrup et al. 1996; Blaak et al. 2000b) in the obese or insulin-resistant muscle, although data are not entirely consistent (Simoneau et al. 1999). In general, the metabolic profile of enzymes and proteins involved in fat metabolism seems to be organised towards fat esterification rather than fat oxidation (Simoneau et al. 1999).

Another step that may possibly be rate-limiting for long-chain fatty acid oxidation is the transport of fatty acids into the mitochondria by means of carnitine palmitoyl transferase (CPT-1). In skeletal muscle of obese insulin-resistant subjects CPT-1 activity has been reported to be reduced (Simoneau et al. 1999). Also, CPT-1 activity has been shown to be correlated with post-absorptive NEFA uptake across the leg in visceral-obese subjects (Colberg et al. 1995). A recent study looking at the ‘in vitro’ fat oxidation in muscle biopsies of obese and lean subjects indicated that defects at both CPT-1 and post-CPT-1 (such as mitochondrial content) levels contribute to the reduced reliance on lipid oxidation in human skeletal muscle in obesity (Kim et al. 2000). An increased content of malonyl-CoA, as a result of a dysregulation by acetyl-CoA carboxylase and malonyl-CoA decarboxylase or by hyperinsulinaemia and hyperglycaemia, can lead to inhibition of CPT-1, and subsequently lower fatty acid oxidation. An increased content of malonyl-CoA has been reported in rodent models of obesity and insulin resistance in conjunction with a reduced lipid oxidation (Saha et al. 1997). At present, it is not certain whether a possible decrement in CPT-1 is mediated through malonyl-CoA or another mechanism such as a reduced expression of CPT-1.

The classic studies of Randle and coworkers (Randle, 1998) demonstrated that excessive fat oxidation in skeletal muscle interferes with insulin-mediated glucose uptake by muscle cells through an inhibition of pyruvate dehydrogenase. At first glance this factor seems at odds with the earlier considerations that indicate that a subnormal ability of muscle to oxidise fatty acids is an important contributor to the development of obesity and insulin resistance. Moreover, it has been proposed that the impairment in fat oxidation in muscle cells results from the glucose-induced inhibition of fatty acid oxidation (a reverse Randle cycle in which the intracellular availability of glucose regulates fatty acid oxidation). Superimposed on this regulatory effect of glucose availability may be the mass effect of NEFA availability. Skeletal muscle glucose oxidation has been reported to be higher in obese insulin-resistant subjects and subjects with type 2 diabetes during post-absorptive conditions (Kelley et al. 1999) and during β-adrenergic stimulation (Blaak et al. 1994a), and this situation does not change as a result of weight loss ((Blaak et al. 1994b; Kelley et al. 1999). In addition, Mandarino et al. (1996) showed that, at comparable arterial glucose concentration and higher arterial NEFA concentration, leg glucose uptake and oxidation are higher in obese subjects compared with lean subjects. Also, as indicated earlier hyperglycaemia and hyperinsulinaemia may increase malonyl-CoA concentrations, subsequently leading to an inhibition of CPT-1 and a diminished fatty acid oxidation (Saha et al. 1997). However, these findings do not exclude the possibility that glucose uptake is increased because of an impaired fatty acid uptake in muscle, especially in view of the fact that biochemical and physiological examinations of skeletal muscle in insulin-resistant subjects indicate a reduced capacity for fat oxidation and an increased tendency towards triacylglycerol storage.

**Metabolic complications associated with disturbances in fatty acid metabolism**

As indicated earlier, a diminished capacity to promote lipolysis during catecholamine stimulation may play an important role in the development and maintenance of increased adipose tissue stores. The increased adipose tissue mass and/or an impaired insulin-mediated suppression of lipolysis may increase circulating NEFA concentrations. In addition, the lowered capacity for NEFA uptake in skeletal muscle of obese insulin-resistant subjects and subjects with type 2 diabetes may contribute to the increased plasma NEFA concentrations, especially when the rate of lipolysis is relatively high (post-absorption, exercise, adrenergic stimulation). An increased delivery of NEFA to the liver may underlie many metabolic disturbances in obesity and diabetes such as decreased insulin binding to hepatocytes (Svedberg et al. 1990), diminished hepatic insulin clearance (Hennes et al. 1997) and increased VLDL-triacylglycerol output (Frayn et al. 1996). In addition, it has been proposed that chronically-elevated NEFA concentrations may reduce insulin secretion in type 2 diabetes (Pretkki & Corkey, 1996).

Furthermore, acute increases in NEFA concentrations may induce skeletal muscle insulin resistance (Boden, 1999). Randle and coworkers (Randle, 1998) proposed a mechanism in which excessive fat oxidation in skeletal muscle interferes with insulin-mediated glucose uptake. As discussed earlier, this mechanism does not seem to be consistent with increasing evidence of subnormal fatty acid oxidation in the insulin-resistant muscle. In addition, the finding of an early NEFA-induced defect in glucose oxidation without a concomitant decrease in insulin-mediated glucose uptake argues against an important role for the Randle cycle in skeletal muscle insulin resistance (Boden, 1999). Furthermore, an early decline in glucose-6-phosphate has been reported, indicating that NEFA may primarily inhibit glucose transport and/or phosphorylation (Roden et al. 1996, 1999).
The lowered fatty acid oxidation in the insulin-resistant muscle may lead to a dysbalance between fatty acid uptake and oxidation, possibly leading to increased intracellular long-chain fatty acid acyl-CoA concentrations resulting in diacylglycerol and triacylglycerol formation. Increased triacylglycerol storage within muscle is strongly related to skeletal muscle insulin resistance (Pan et al. 1997), reflecting the effect of the concomitantly increased diacylglycerol and long-chain fatty acid acyl-CoA concentrations on insulin signal transduction (Ellis et al. 2000; Itani et al. 2002), or interference with insulin-mediated glucose uptake through increased intramuscular fatty acid oxidation (Blak et al. 2000b). In addition to the lowered capacity to oxidise fatty acids, disturbances in the regulation of skeletal muscle lipolysis may also contribute to the increased triacylglycerol storage and to increased concentrations of lipid intermediates such as diacylglycerol. There is an urgent need for further studies on disturbances in the lipolytic pathways in insulin-resistant conditions.

Conclusion
Insulin-resistant conditions such as obesity and type 2 diabetes mellitus are characterised by disturbances in catecholamine-mediated lipolysis and skeletal muscle fatty acid handling. These disturbances may play an important role in the development and maintenance of increased adipose tissue stores, increased circulating NEFA concentrations and accumulation of lipid intermediates and triacylglycerols in skeletal muscle, all risk factors for the development of insulin resistance and diabetes mellitus. Increased adipose tissue stores, a disturbed insulin-mediated inhibition of lipolysis and a lowered ability of skeletal muscle to take up fatty acids under certain conditions may increase circulating NEFA concentrations, which is a risk factor in the development of insulin resistance and cardiovascular disease. Furthermore, there is increasing evidence that a dysbalance between fatty acid uptake and the (subnormal) ability of skeletal muscle to oxidise fatty acids may promote accumulation of lipid intermediates such as diacylglycerols and fatty acid acyl-CoA and triacylglycerols, which are strongly related to skeletal muscle insulin resistance. Further studies are necessary to elucidate disturbances in the pathways of lipolysis and fatty acid handling in adipose tissue and skeletal muscle in insulin-resistant conditions.

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