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Physiological factors that regulate the use of endogenous fat and carbohydrate fuels during endurance exercise

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Exercise causes a dramatic increase in energy requirements because of the metabolic needs of working muscles. Exercise-dependent factors regulate fuel use. Absolute exercise intensity determines the exercise-induced increase in energy demands, whereas exercise intensity relative to an individual's maximal aerobic capacity (VO_2max) determines the proportional contribution of different fuel sources (i.e. plasma glucose, plasma fatty acids, muscle glycogen and intramuscular triacylglycerols). Endurance training increases aerobic capacity in muscle and the oxidation of fat during exercise. In addition, exercise-independent factors, such as diet composition, sex, age, and body composition also influence substrate use during exercise. The present review discusses the regulation of substrate use during exercise in human subjects, with a focus on the role of exercise-independent factors.

Energy requirement: Fat metabolism: Carbohydrate metabolism: Endurance exercise

Introduction

During exercise there is a dramatic increase in energy requirements because of the metabolic needs of working muscles. During resting conditions, skeletal muscle consumes approximately 30 % of the body's total energy requirements, and most (about 80 %) of the muscles' energy needs at rest are derived from fat, the remainder being derived from carbohydrates (Andres *et al.* 1956; Dagenais *et al*. 1976). Exercise can induce up to a 10-fold increase in energy requirements and, therefore, fat and carbohydrate oxidation increase (Klein *et al*. 1994; Mendenhall *et al*. 1994) (Fig. 1). The relative contribution of carbohydrate and fat as fuel for working muscle is largely dependent on exercise intensity and duration. Fat is the predominant source of fuel during prolonged low- and moderate-intensity exercise (up to about 65 % of maximal O_2 consumption; VO_2max) (Jones *et al*. 1980; Romijn *et al*. 1993; van Loon *et al*. 2001); as exercise intensity increases there is a progressive decline in fat oxidation and the relative oxidation of carbohydrate increases (Jones *et al*. 1980; Coggan, 1991; Romijn *et al*. 1993; van Loon *et al*. 2001). Carbohydrate is also the predominant source of energy at the onset of exercise and during short-term exercise, such as sprints (for example, Trump *et al*. 1996; McKenna *et al*. 1997; Howlett *et al*. 1999*a*). Endurance training increases muscle oxidative capacity and fat oxidation (Horowitz & Klein, 2000*a*). In addition to these factors that are directly exercise-dependent (for example, exercise intensity, duration, training), exercise-independent factors such as an individual's sex (for example, Mittendorfer *et al*. 2002), age (for example, Sial *et al*. 1996), body composition (for example, Horowitz & Klein, 2000*b*), chronic diet composition (for example, Schrauwen *et al*. 2000), and exogenous or dietary fuel availability during exercise (for example, Horowitz *et al*. 1997; Odland *et al*. 1998) influence substrate use during exercise. Muscle fibre type might also be an important determinant of substrate metabolism during exercise because mitochondrial density is greater in slow-twitch than fast-twitch fibres (Ingjer, 1979*a*; Prince *et al*. 1981). However, Helge *et al*. (1999) were unable to find any correlation between RER and fibre type in young adult men during moderate-intensity exercise. It is possible that the variability in fibre type composition in these men was not sufficient to demonstrate a relationship between substrate use and fibre type. However, no studies are known

Abbreviations: IMTG, intramuscular triacylglycerols; NEFA, non-esterified fatty acids; PCr, phosphocreatinine; Ra, rate of appearance; Rd, rate of disappearance; TG, triacylglycerols; VO_2max, maximal O_2 consumption.

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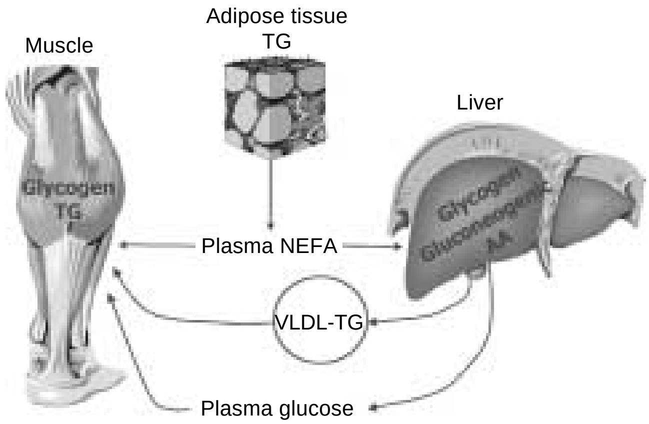

Fig. 1. Fuel sources for exercising muscle. TG, triacylglycerol; AA, amino acids; NEFA, non-esterified fatty acids.

that compared fibre type composition and substrate oxidation in a larger and more diverse group of subjects.

In the present paper, the regulation of substrate use during exercise in human subjects is reviewed, particularly the role of exercise-independent factors.

Exercise intensity and duration

Immediately after the onset of exercise (0–30 s) energy is derived predominantly from anaerobic metabolism (Grassi *et al*. 1996). The switch from aerobic to anaerobic energy metabolism at the onset of exercise is due to some yet unknown mechanism because O_2 availability (Bangsbo *et al*. 2000; Savasi *et al*. 2002) or delivery of substrate to skeletal muscle (Howlett *et al*. 1999*a*,*b*; Savasi *et al*. 2002; Watt *et al*. 2002*b*) are not limiting. Following this initial phase of anaerobic metabolism, both exercise intensity and duration determine the fuel used for oxidation during prolonged exercise. The total amount of energy needed during exercise is determined by the absolute exercise intensity, whereas the proportional contribution of fat and carbohydrate oxidation is determined by relative exercise intensity. The contribution of fat oxidation to total energy requirements ranges from 40–80 % during prolonged exercise at low and moderate intensities (< 75 % of VO_2max), whereas strenuous exercise (> 75 % of VO_2max) relies predominantly on carbohydrate sources for energy (Holloszy *et al*. 1998).

Fatty acid and glucose metabolism

Most of the fatty acids provided to skeletal muscle during exercise are derived from lipolysis of adipose tissue triacylglycerols (TG), and delivered to muscle via the bloodstream. Adipose tissue lipolytic rate increases 2- to 3-fold during endurance exercise (Romijn *et al*. 1993; Klein *et al*. 1994; Horowitz & Klein, 2000*b*; Schrauwen *et al*. 2000; van Hall *et al*. 2002) and is mediated by increased β-adrenergic stimulation (Hall *et al*. 1987; Arner *et al*. 1990). In addition, exercise stimulates lipolysis of intramuscular TG (IMTG) (Carlson *et al*. 1971; Essen *et al*. 1977; Hurley *et al*. 1986), which releases fatty acids that are directly oxidized by local mitochondria. Table 1 summarizes the body energy stores for a lean individual.

The exact contribution of IMTG to total fat oxidation during exercise is not known because it is difficult to directly measure IMTG oxidation (Wendling *et al*. 1996; Watt *et al*. 2002*a*). Several studies, in which muscle biopsies were taken before and after exercise, found that IMTG concentration declines by 25–40 % after 1–2 h of moderate-intensity cycle ergometer exercise, which could account for 60–75 % of the total amount of fat oxidized (Carlson *et al*. 1971; Froberg & Mossfeldt, 1971; Essen *et al*. 1977; Hurley *et al*. 1986; Phillips *et al*. 1996*c*). In contrast, other investigators found that IMTG concentration decreases minimally or not at all after prolonged exercise and therefore does not contribute significantly to total energy production (Kiens *et al*. 1993; Wendling *et al*. 1996; Starling *et al*. 1997; Kiens & Richter, 1998; Bergman *et al*. 1999). When exercise is performed for more than 4 h, IMTG generally decreased from resting conditions (Froberg & Mossfeldt, 1971; Costill *et al*. 1973). The reason for the discrepancies between studies is not clear but may be related to difficulties in measuring IMTG concentration in muscle biopsies. Due to the high energy density of fat, only about 2–5 mmol TG/kg dry muscle are required to provide fuel during 2 h of moderate-intensity exercise. This amount of TG represents about 10–15 % of total muscle TG stores, whereas the variability of measuring IMTG concentration is about 25 % (Wendling *et al*. 1996; Watt *et al*. 2002*a*). The poor reproducibility of measuring IMTG concentration makes detection of small changes in IMTG content during exercise nearly impossible. The differences between these studies might, however, also be due to differences in exercise protocols and/or study subject characteristics.

Estimates of IMTG use can also be calculated by using a combination of isotope tracer and indirect calorimetry tech-

Table 1. Body energy stores*

			Energy equivalent to running or walking at 70 % VO_2 max	
Tissue	Fuel	Energy (MJ)	Time (h)	Distance (km)
Adipose	Triacylglycerol	585·76	168	2000
Muscle	Triacylglycerol	13·45	4	50
	Glycogen	8·37	2·5	32
Liver	Triacylglycerol	2·09	0·6	8
	Glycogen	1·26	0·3	5
Blood	Triacylglycerol, NEFA, glucose	0·42	0·1	1·5

NEFA, non-esterified fatty acids.
* Values are estimates based on a lean individual.

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niques. This approach assumes that the difference between whole-body fat oxidation, determined by indirect calorimetry, and plasma fatty acid oxidation, determined by isotope tracers, is due to oxidation of non-plasma fatty acids, presumably derived from IMTG. Data from studies that used this approach suggest that IMTG provides > 50 % of the total fat oxidized during prolonged moderate-intensity exercise (Martin *et al*. 1993; Dyck & Bonen, 1998).

Recently, Guo *et al*. (2000) used a dual-tracer, pulse-chase technique to directly measure IMTG oxidation during 90 min of moderate-intensity cycling exercise in twelve healthy non-obese men and women and found that: (1) the contribution of IMTG to total fat oxidation was about 50%; (2) the sum of plasma non-esterified fatty acids (NEFA) and IMTG oxidation rates was not different from the total fatty acid oxidation rate measured by using indirect calorimetry; (3) IMTG oxidation rates calculated by using the dual-tracer approach were not different from IMTG calculated as the difference between total fatty acid oxidation (by indirect calorimetry) and plasma fatty acid oxidation. These data suggest that, if there is no other significant source of lipid fuel, this approach can provide a direct measure of IMTG use during exercise that might provide a potentially robust direct measure of IMTG use.

The regulation of IMTG use during exercise has not been carefully studied. However, IMTG use is probably linked to catecholamine release in response to β_2-receptor stimulation during exercise. Endurance exercise increases the activity of TG lipase in rat (Langfort *et al*. 2000) and human muscle (Kjaer *et al*. 2000); this response is absent in adrenalectomized subjects but can be restored via infusion of adrenalin (Kjaer *et al*. 2000). These findings are supported by a study that investigated the role of β-receptor stimulation on IMTG use during about 1 h exercise to exhaustion (Cleroux *et al*. 1989); IMTG use was completely blocked by pharmacological blockage of β_1+β_2-receptors whereas β_1-blockage alone had no effect on IMTG use. However, the exercise-induced activation of TG lipase in muscle might also be controlled by other factors, probably intrinsic in muscle. Langfort *et al*. (2000) found that electrical stimulation of rat soleus muscle increases TG lipase activity for several minutes but returns to baseline after 60 min of stimulation, even in muscles from animals in which sympathoadrenal organs were removed. Furthermore, addition of propanolol to the incubation medium did not impair the contraction-induced activation of TG lipase (Langfort *et al*. 2000).

Fatty acids derived from plasma TG (i.e. VLDL-TG) can also be taken up by muscle and oxidized as fuel. Few studies have evaluated the contribution of plasma TG to total energy production, but the available data suggest it is unlikely that VLDL-TG is an important source of fuel during exercise. During resting conditions, plasma TG may account for 5–10 % of total fat oxidation (Ryan & Schwartz, 1965; Wolfe *et al*. 1985). There is also indirect evidence that only a very small fraction of total energy production is derived from plasma TG during exercise (Mackie *et al*. 1980; Kiens & Lithell, 1989; Turcotte *et al*. 1992). For example, Guo *et al*. (2000) and Kiens & Lithell (1989) found that both total plasma TG and VLDL-TG uptake by skeletal muscle is negligible during exercise. In addition, the activation of muscle lipoprotein lipase, the enzyme that hydrolyses plasma TG, occurs about 8–20 h after an exercise bout is completed (Seip *et al*. 1995; Greiwe *et al*. 2000; Pilegaard *et al*. 2002). Therefore, it is probable that muscle uptake of VLDL-TG after exercise is important for replenishing IMTG stores consumed during exercise.

At rest, the oxidation of plasma NEFA (derived from lipolysis of adipose tissue TG) can entirely account for total fat oxidation (Sidossis *et al*. 1995). Studies in which stable-isotope tracer techniques were applied found that during low- and moderate-intensity exercise, plasma NEFA and IMTG contribute equally to total fat oxidation (Sidossis *et al*. 1997, 1998; van Loon *et al*. 2001); during high-intensity exercise, total fat oxidation decreases, in part, because of a decrease in plasma fatty acid availability (Romijn *et al*. 1993, 1995) and a decrease in the use of IMTG (van Loon *et al*. 2001). Raising plasma fatty acid concentrations to 1–2 mmol/l by intravenously infusing a lipid emulsion and heparin during the exercise bout increases fat oxidation by about 30 % (Romijn *et al*. 1995) but does not completely restore it to the rate observed during moderate-intensity exercise (Romijn *et al*. 1993). Thus, high-intensity exercise probably decreases the capacity of skeletal muscle to oxidize fatty acids. The suppression of fat oxidation during high-intensity exercise may be related to increased glycogen metabolism in muscle. The high rate of muscle glycogenolysis during high-intensity exercise increases the amount of acetyl-CoA derived from glycogen, which presumably increases malonyl-CoA concentrations in muscle (Elayan & Winder, 1991; Saddik *et al*. 1993). Malonyl-CoA inhibits carnitine *O*-palmitoyltransferase-I, the enzyme responsible for long-chain fatty acid entry into mitochondria (McGarry *et al*. 1977, 1983; Robinson & Zammit, 1982; Rasmussen & Wolfe, 1999). Therefore, high rates of glycogenolysis during high-intensity exercise can reduce fat oxidation by impairing long-chain fatty acid transport into the mitochondria by inhibiting carnitine *O*-palmitoyltransferase-I (Sidossis *et al*. 1997).

Glucose delivered by the bloodstream (derived from hepatic glycogenolysis and gluconeogenesis) or released locally by breakdown of intramuscular glycogen can be used by skeletal muscle as fuel. At rest and during low-intensity exercise, blood glucose is the predominant source of carbohydrate for oxidation; the oxidation of blood glucose increases with increasing exercise intensity and reaches values of approximately three times resting values during high-intensity exercise (van Loon *et al*. 2001). The contribution of muscle glycogen to total energy expenditure is negligible at rest, but increases with increasing exercise intensity and accounts for the majority (> 75 %) of total carbohydrate oxidation during high-intensity exercise (van Loon *et al*. 2001). The increase in plasma glucose use during exercise is mediated by increased translocation of glucose transporter-4 vesicles to the plasma membrane, an increase in the insulin sensitivity of glucose transporter-4-mediated glucose transport, and an increase in glucose transporter-4 protein (Holloszy *et al*. 1998). Hepatic glucose production increases, primarily by increased glucagon secretion during mild- and moderate-intensity exercise (Wasserman *et al*. 1989; Kjaer *et al*. 1993; Wasserman, 1995; Coker *et al*. 2001), to maintain plasma glucose con-

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centration when muscle glucose uptake is increased by exercise (Coggan *et al*. 1992*a*; Holloszy *et al*. 1998; van Loon *et al*. 2001; Helge *et al*. 2003). However, other factors such as a rise in catecholamine concentrations might also contribute to glucose production, particularly at higher exercise intensities (Coggan, 1991; Sigal *et al*. 1994, 1996, 2000; Wasserman, 1995; Coggan *et al*. 1997; Coker *et al*. 2001). The increase in muscle glycogen use is caused by several factors. Muscle contraction increases muscle cytosolic Ca concentration, which activates phosphorylase causing glycogen breakdown (Holloszy *et al*. 1998). However, the increase in cytosolic Ca is short-lived and is only responsible for glycogen breakdown during the onset of exercise. Glycogen breakdown is also mediated continuously during exercise by β-adrenergic stimulation and a cAMP-activated mechanism of phosphorylase activation (Holloszy *et al*. 1998), which can eventually lead to complete muscle glycogen depletion.

Exercise training

The effect of endurance training on substrate metabolism has been previously reviewed (Holloszy *et al*. 1998; Rasmussen & Wolfe, 1999; Horowitz & Klein, 2000*a*). Endurance exercise training increases the oxidation of fatty acids and spares muscle glycogen and blood glucose use during submaximal exercise (Holloszy & Coyle, 1984; Horowitz & Klein, 2000*a*). Several adaptations within skeletal muscle itself facilitate the increased oxidation of fatty acids: increased density of the mitochondria in the skeletal muscles, which increases the capacity for fat oxidation (Holloszy, 1967; Ingjer, 1979*b*); a proliferation of capillaries within skeletal muscle, which enhances plasma fatty acid delivery to muscle (Ingjer, 1979*b*; Saltin & Gollnick, 1983); an increase in carnitine transferase, which facilitates fatty acid transport across the mitochondria membrane (Mole *et al*. 1971); an increase in fatty acid-binding proteins, which regulate myocyte fatty acid transport (Turcotte *et al*. 1991, 1999); and changes in muscle fibre type that favour fat oxidation (Andersen & Henriksson, 1977; Henriksson, 1992; Mujika & Padilla, 2001).

The training-induced increase in total fat oxidation is not due to an increase in the mobilization and oxidation of adipose tissue TG. Both cross-sectional studies of trained and untrained subjects and longitudinal training studies have found that training either does not change or actually decreases the rate of appearance (Ra) of fatty acids into plasma during exercise performed at the same absolute intensity (Jansson & Kaijser, 1987; Martin *et al*. 1993; Klein *et al*. 1994; Horowitz & Klein, 2000*a*). Plasma catecholamine concentrations, which stimulate lipolysis of adipose tissue TG during exercise, are lower during exercise performed at the same absolute intensity before and after training (Wolfel *et al*. 1990; Phillips *et al*. 1996*b*; Friedlander *et al*. 1998*b*) despite a training-induced increase in the capacity to secrete adrenaline (Kjaer & Galbo, 1988). In addition, training does not alter lipolytic sensitivity to adrenaline. Although maximally stimulated lipolytic activity (at adrenaline concentrations between 10^{-6} and 10^{-4} mol/l) is greater in adipocytes obtained from endurance-trained subjects than in those from untrained subjects (Despres *et al*. 1984; Crampes *et al*. 1986, 1989; Riviere *et al*. 1989), lipolytic activity is the same or slightly lower in adipocytes from endurance-trained subjects at physiological adrenaline concentrations (between 10^{-10} and 10^{-8} mol/l; Crampes *et al*. 1986, 1989). Moreover, whole-body and regional adipose tissue lipolytic sensitivity to adrenaline infusion *in vivo* is the same before and after training (Stallknecht *et al*. 1995; Horowitz *et al*. 1999). During exercise performed at the same relative intensity, whole-body lipolytic rates are greater in endurance-trained than in untrained individuals (Klein *et al*. 1996), but the mechanism responsible for the increased lipolytic response is not known.

Most available data indicate that the training-induced increase in fat oxidation during exercise is due primarily to an increase in the oxidation of non-plasma fatty acids. The exact source of these non-plasma fatty acids is not entirely clear. It is possible that increased oxidation of VLDL-TG contributes to the training-induced increase in total fat oxidation during exercise. Herd *et al*. (2001) found greater leg VLDL-TG uptake in response to endurance training, which was probably mediated by exercise-induced activation of muscle lipoprotein lipase. However, other investigators have found plasma triacylglycerols are not an important fuel during exercise even after short-term training (Kiens & Lithell, 1989; Guo *et al*. 2000). It is probable that fatty acids derived from IMTG are an important contributor to the increase in fat oxidation in trained subjects. Data from studies that measured IMTG content in muscle biopsies, however, yield conflicting results. Some (Hurley *et al*. 1986; Phillips *et al*. 1996*c*) but not all (Kiens *et al*. 1993; Dyck & Bonen, 1998; Bergman *et al*. 1999) studies showed a greater depletion of IMTG during exercise performed after, rather than before, training. The technical difficulty in measuring IMTG concentration in muscle biopsies (Wendling *et al*. 1996; Watt *et al*. 2002*a*) may have contributed to the differences between studies. It is also unclear how endurance training might increase IMTG lipolysis during exercise because the catecholamine response during exercise is decreased (Galbo *et al*. 1977; Winder *et al*. 1979) and skeletal muscle β-adrenergic receptor density remains the same (Klein *et al*. 1996). Therefore, if endurance training increases reliance on IMTG it must affect muscle sympathetic nervous system activation or other, as yet unknown, factors that regulate IMTG lipolysis.

Diet

Almost a century ago, Krogh & Lindhard (1920) and Christensen & Hansen (1939) observed that fat oxidation during exercise is increased in response to short-term consumption of a high-fat diet. Similar results have been obtained more recently (Phinney *et al*. 1983; Helge *et al*. 1996; Schrauwen *et al*. 2000) in studies that investigated fat oxidation during exercise after long-term (> 7 d) adaptation to a high-fat diet. The mechanisms responsible for the increase in fat oxidation are not entirely clear. High-fat diets increase the rate of plasma NEFA appearance in plasma and fat oxidation at rest (Mittendorfer & Sidossis, 2001), and increase plasma NEFA availability (Phinney *et al*. 1983), and decrease muscle (Phinney *et al*. 1983) and

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liver (Hultman & Nilsson, 1971) glycogen stores during exercise. Although it has been proposed that increased plasma fatty acid availability is responsible for the increase in fat oxidation in response to high-fat diets, Schrauwen *et al*. (2000) found that the rate of plasma NEFA oxidation was not different after high-carbohydrate or high-fat diets. Therefore, the high-fat diet-induced increase in fat oxidation in response to high-fat diets is probably due to the use of plasma TG or IMTG. This notion is supported by findings from studies that show that longer-term adaptation to high-fat diets increases the capacity of muscle for plasma TG uptake by increasing lipoprotein lipase activity (Kiens *et al*. 1987; Helge & Kiens, 1997) and IMTG storage (Kiens *et al*. 1987; Helge *et al*. 1998) whereas high-carbohydrate diets increase muscle glycogen stores (Helge *et al*. 2001). Helge *et al*. (2001) found that increased uptake and oxidation of plasma NEFA and VLDL-TG during exercise accounted for the increase in leg plasma fatty acid oxidation after 7 weeks of training while consuming a high-fat diet. Use of IMTG (determined as the difference between total fat use and the measured oxidation of plasma NEFA and VLDL-TG uptake) also tended to be higher with a high-fat diet but the increase was not statistically significant, possibly because of inadequate statistical power. In summary, these findings demonstrate that diet composition causes changes in substrate use during exercise.

Body composition

Obese individuals have increased TG stores in both adipose tissue and skeletal muscle (Phillips *et al*. 1996*a*). Therefore, endurance exercise may be particularly beneficial for obese individuals because of mobilization from both adipose tissue and skeletal muscle TG depots. The rate of lipolysis, determined by measuring NEFA Ra, during moderate-intensity endurance exercise is similar in lean and obese subjects (Kanaley *et al*. 1993; Horowitz & Klein, 2000*b*). However, the effect of obesity on fat oxidation is less clear because of conflicting results from different studies that found higher rates of fat oxidation in obese women and no difference in fat oxidation between lean and obese women during exercise (Kanaley *et al*. 1993; Colberg *et al*. 1995; Ardevol *et al*. 1998). Differences in aerobic fitness and age could have contributed to the discrepant findings between these studies. By matching lean and obese women on fat-free mass, aerobic capacity, and age, it was recently found that obese women had greater total fat oxidation than lean women but plasma NEFA oxidation was the same in both groups while carbohydrate oxidation rates were lower in obese than lean women (Horowitz & Klein, 2000*b*). This indicates increased reliance on other fatty acid sources, presumably derived from IMTG and possibly VLDL-TG, and sparing of carbohydrates in obese compared with lean women. Little is known about the effects of obesity on substrate use during exercise in men. Recently, Goodpaster *et al*. (2002) found a tendency for higher rates of total fat oxidation in obese compared with non-obese men during moderate-intensity exercise; this was due to higher rates of non-plasma, presumably IMTG-derived, fatty acid oxidation. In a study conducted in lean, overweight and obese men, who were matched on age and aerobic fitness, it was found that NEFA Ra and plasma NEFA oxidation during moderate-intensity exercise was highest in the lean and lowest in the obese group, whereas the rate of whole-body fat oxidation was not different between groups (B Mittendorfer and S Klein, unpublished results). This indicates that lean and obese men oxidize the same amount of fat during exercise but obese men rely more on IMTG and less on plasma NEFA than lean men. Endurance exercise training has similar effects in lean and obese subjects, and results in an increase in total fat oxidation during exercise, due to an increase in non-plasma fatty acid oxidation in obese men (van Aggel-Leijssen *et al*. 2002) and women (van Aggel-Leijssen *et al*. 2001). In these studies, exercise was performed at the same absolute intensity before and after training, and NEFA Ra was not affected by training. The composite of these data indicates that obesity is associated with increased use of non-plasma fatty acids, presumably derived from IMTG, during exercise in both men and women. In addition, the effect of training on substrate metabolism is similar in lean and obese subjects.

Sex effects

Women usually have more body fat (Clarys *et al*. 1999; Mittendorfer *et al*. 2003) and are less fit (Davis *et al*. 2002) than men. These differences complicate the investigation of the effect of gender on substrate use during exercise, because both body composition and fitness, as discussed earlier (p. 101), independently influence the rate of lipolysis and fat oxidation during endurance exercise. Several studies found that the rate of fat oxidation was higher in both untrained and trained women than men (Costill *et al*. 1979; Powers *et al*. 1980; Froberg & Pedersen, 1984; Blatchford *et al*. 1985; Keim *et al*. 1996; Friedlander *et al*. 1998*b*; Burguera *et al*. 2000; Carter *et al*. 2001; Roepstorff *et al*. 2002; Steffensen *et al*. 2002) whereas others found that women use more fat and less carbohydrate than men (Froberg & Pedersen, 1984; Blatchford *et al*. 1985; Tarnopolsky *et al*. 1990; Horton *et al*. 1998; Carter *et al*. 2001). Furthermore, menstrual cycle phase can affect substrate kinetics during exercise. Fat oxidation is higher, carbohydrate oxidation is lower, and glucose Ra and rate of disappearance (Rd) are lower during high-intensity exercise performed during the luteal than the follicular phase of the menstrual cycle (Zderic *et al*. 2001). In contrast, fatty acid kinetics is the same during the follicular and luteal phases of the menstrual cycle at rest (Heiling & Jensen, 1992; Corssmit *et al*. 1994; Zderic *et al*. 2001) and during low- and moderate-intensity exercise (Zderic *et al*. 2001; Horton *et al*. 2002).

The independent effect of gender on lipid metabolism was recently examined during moderate-intensity endurance exercise, by studying young adult men and women who were matched on adiposity (percentage body fat: 24 (SE 2) and 25 (SE 1) % in men and women, respectively), aerobic fitness (49 (SE 2) and 47 (SE 1) ml/kg fat-free mass per min in men and women, respectively) and age (33 (SE 3) and 29 (SE 4) in men and women, respectively) (Mittendorfer *et al*. 2002). It was found that NEFA Ra and Rd during exercise were greater in women than in men, but the rate of total fatty acid oxidation was similar in both

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groups. Compared with men, women oxidized more plasma NEFA, derived primarily from adipose tissue TG, and less non-plasma NEFA, presumably derived primarily from IMTG and possibly VLDL-TG. The greater reliance on plasma NEFA as a fuel in women than men was probably a result of greater NEFA availability in women than in men. In contrast, studies performed at the August Krogh Institute in Copenhagen (Roepstorff *et al*. 2002; Steffensen *et al*. 2002) found that IMTG use during exercise, determined by evaluating fat content in muscle biopsies, was greater in women than men, who were matched on aerobic fitness but not body composition. Limitations in using IMTG content as a measure of IMTG oxidation during exercise and differences in matching men and women on body composition may be responsible for the discrepancy between studies.

The mechanism(s) responsible for the gender differences in lipolysis of adipose tissue TG observed in our subjects during exercise is not known. Most of the increase in lipolytic activity that occurs during exercise is mediated through catecholamine stimulation of adipose tissue β-adrenergic receptors (Arner *et al*. 1990; Hellstrom *et al*. 1996; Mora-Rodriguez *et al*. 2001). However, plasma catecholamine concentrations during exercise were similar in both male and female subjects. Moreover, it is unlikely that differences in lipolytic sensitivity to β-adrenergic stimulation were responsible for the gender differences in lipid kinetics. Studies performed *in vitro* in isolated human adipocytes exposed to physiological concentrations of catecholamines (Leibel & Hirsch, 1987; Crampes *et al*. 1989; Wahrenberg *et al*. 1991; Mauriege *et al*. 1999) and *in vivo* in human subjects during catecholamine infusion (Jensen *et al*. 1996; Millet *et al*. 1998) found that adipose tissue lipolytic sensitivity was similar in men and women. However, activation of α-adrenergic receptors, which inhibits lipolysis, may also be involved in determining the net lipolytic response to exercise (Hellstrom *et al*. 1996; Stich *et al*. 1999), so gender differences in α-adrenergic receptor activity might have influenced lipolytic rates during exercise. By using the microdialysis technique, it has been shown that local adipose tissue α-adrenergic receptor blockade during endurance exercise increased regional glycerol release from abdominal subcutaneous adipose tissue in men (Hellstrom *et al*. 1996) but not women (Hellstrom *et al*. 1996). These results suggest that α-adrenergic receptor activity inhibits lipolysis during exercise in men but is not involved in the regulation of lipolysis during exercise in women.

Several studies have evaluated the metabolic response to endurance exercise training in men and women (for example, Martin *et al*. 1993; Phillips *et al*. 1996*b*; Friedlander *et al*. 1998*b*; Horowitz *et al*. 2000). In one study, exercise training caused a greater increase in fat oxidation during exercise in women than in men (Friedlander *et al*. 1998*a*,*b*, 1999). However, these findings are confounded by the fact that the increase in aerobic fitness was also greater in women (25 %) than in men (9 %). It has been found that 12 weeks of endurance training in women increased total fat oxidation by about 25 % during exercise performed at the same absolute intensity (Horowitz *et al*. 2000). This response is the same as that reported in men after a similar training-induced increase in fitness (Martin *et al*. 1993; Phillips *et al*. 1996*b*). The difference between plasma NEFA oxidation, assessed by isotope tracer methods, and whole-body fat oxidation, assessed by indirect calorimetry, suggests that the training-induced increase in fat oxidation was due primarily to an increase in the oxidation of non-plasma fatty acids, presumably IMTG. In contrast, Steffensen *et al*. (2002) found no effect of training status on IMTG use, assessed by measuring IMTG content in muscle biopsies, during moderate-intensity exercise in men or women, when exercise was performed at the same relative intensity in a cross-sectional study of untrained, moderately and highly trained subjects. However, total fat oxidation was higher in highly trained than sedentary and moderately trained subjects. The reason for the discrepancy in the source of oxidized TG between studies is not clear but may be related to differences in study design (longitudinal training *v*. cross-sectional analysis) and the methods used to assess IMTG use (muscle biopsy *v*. isotope tracer and indirect calorimetry techniques).

Ageing

Most studies investigating the effect of ageing on substrate metabolism during exercise has focused on measuring the RER to determine whole-body fat and carbohydrate oxidation rates. During brief (3–8 min) stages of incremental exercise, RER at any given absolute exercise intensity is greater in old compared with young subjects (Robinson, 1938; Durnin & Mikulcic, 1956; Julius *et al*. 1967; Montoye, 1982). This suggests that old subjects rely more on carbohydrate than fat as a fuel during exercise performed at the same absolute intensity, which was supported by higher blood lactate levels during submaximal exercise in older subjects (Robinson, 1938; Astrand, 1958; Strandell, 1964; Silverman & Mazzeo, 1996). However, given the lower aerobic capacity and fitness (VO_2max) in old than young individuals (for example, Hagberg *et al*. 1988; Kohrt *et al*. 1991; Schwartz *et al*. 1991; Coggan *et al*. 1993; Rooyackers *et al*. 1996; Sial *et al*. 1996), a greater dependence on carbohydrate for energy in old individuals would be expected during exercise performed at the same absolute, but higher relative, intensity (Jones *et al*. 1980; Coggan, 1991; Romijn *et al*. 1993; van Loon *et al*. 2001). Studies that evaluated RER during exercise performed at the same relative intensity have reported conflicting results, and RER has been reported to be lower (Hagberg *et al*. 1988), the same (Tankersley *et al*. 1991), and higher (Silverman & Mazzeo, 1996) in elderly compared with young subjects. However, these studies did not carefully control for dietary intake or training status (Hagberg *et al*. 1988; Tankersley *et al*. 1991), which can affect RER. In a study conducted in sedentary, lean young (26 (SE 2) years) and old (73 (SE 2) years) subjects, matched on gender, BMI, and fat-free mass, it was found that RER was higher in old than in young subjects during 60 min of cycle ergometer exercise performed at either the same absolute or relative intensity (Sial *et al*. 1996). Therefore, most of the available data indicate that ageing is associated with significant alterations in substrate oxidation during endurance exercise, manifested by a shift from using fat to carbohydrate as a fuel.

Age-related changes in skeletal muscle itself favour the oxidation of carbohydrate over fat and may be responsible for the shift in substrate metabolism observed in elderly subjects. Muscle mitochondrial oxidative enzymes, which are needed for fat oxidation, decrease with increasing age (Meredith *et al*. 1989). Mitochondrial citrate synthase, succinate dehydrogenase, and β-hydroxyl-CoA-dehydrogenase activities are lower in old (age 57–74 years) than in young (age 20–38 years) individuals (Coggan *et al*. 1992*b*, 1993; McCully *et al*. 1993) because of both decreased mitochondrial density (Conley *et al*. 2000) and enzyme activity relative to muscle mitochondrial volume (Trounce *et al*. 1989; Rooyackers *et al*. 1996). In addition, compared with young adults, elderly subjects have a lower rate of phosphocreatinine (PCr) resynthesis after exercise, suggesting a decreased rate of O_2 consumption during exercise (McCully *et al*. 1993; Conley *et al*. 2000). Furthermore, the inorganic phosphate : PCr value at any given power output, which reflects the balance between ATP hydrolysis (energy use) and ATP resynthesis (energy production), is greater in old than in young men (Coggan *et al*. 1993). These observations indicate that muscle oxidative capacity is diminished in old individuals, and that glucose may be preferred over fatty acids as a fuel during exercise in old individuals.

Ageing is associated with decreased lipolytic sensitivity to β-adrenergic stimulation (Lonnqvist *et al*. 1990; Ford *et al*. 1995) and lower sympathoadrenal response to exercise (Kohrt *et al*. 1993), suggesting that diminished lipolysis of adipose tissue TG might contribute to the observed decrease in fat oxidation. However, it has been found that fatty acid Ra in plasma during exercise performed at the same absolute intensity (about 800 ml O_2 consumed/min) was about 35 % higher in old (73 (SE 2) years) than young (26 (SE 2) years) subjects (Sial *et al*. 1996). Despite greater NEFA release into plasma and plasma NEFA uptake during exercise performed at the same absolute intensity, whole-body fat oxidation was lower in old than in young subjects. Therefore, it is probable that an ageing-related decrease in the respiratory capacity of skeletal muscle itself was responsible for the lower rate of fat oxidation during exercise in older than younger subjects, because adipose tissue lipolysis and plasma NEFA availability were not rate-limiting.

The decrease in fat oxidation is associated with an increase in carbohydrate oxidation during exercise in elderly subjects. Increased plasma glucose availability is not responsible for the increase in glucose oxidation. It has been found that the glucose Ra into plasma and the Rd from plasma was not different in young and old subjects when exercise was performed at the same absolute intensity. These data suggest that muscle glycogen use was higher in older than younger subjects (Sial *et al*. 1996).

Endurance training in elderly individuals increases skeletal muscle mitochondrial enzymes and respiratory capacity (Suominen *et al*. 1977). In addition, the inorganic phosphate : PCr value in muscle at any given power output in trained older men was lower compared with older sedentary men but similar to the value observed in sedentary young men (Coggan *et al*. 1993). It was found that 16 weeks of supervised endurance training did not affect whole-body lipolytic rate (NEFA Ra or glycerol Ra), but decreased glucose Ra and caused an increase in fat oxidation and a decrease in carbohydrate oxidation during exercise to values observed in untrained young adults. (Sial *et al*. 1998). Therefore, the adaptation to training in old subjects is similar to that seen in young adult subjects. The shift in substrate oxidation was probably due to changes within skeletal muscle itself, possibly an increase in the fractional oxidation of plasma fatty acids taken up by muscle and/or an increase in the use of intramuscular triacylglycerols.

Summary and perspectives

Substrate use during exercise is influenced by factors that are directly related to the exercise bout itself, such as exercise intensity and duration, and a variety of other factors, that are independent of exercise, such as an individual's sex, body composition, age and diet. All of these variables have to be considered as possible confounding factors between groups when evaluating substrate metabolism during exercise. Future investigations should concentrate on defining the contribution of IMTG and plasma TG to fuel use during exercise; this will probably involve use and development of novel techniques. A better understanding of the regulation of the use of these lipid sources is particularly important because it is yet unknown how variations in the availability of these lipid sources affect their use as fuel during exercise. Currently available isotope tracer techniques do not allow the distinction of these TG sources to total energy consumption during exercise, and measurement of IMTG use by muscle biopsy techniques is particularly difficult in subjects with increased muscle fat stores. Therefore, the contribution of IMTG and plasma TG to total energy consumption in obese individuals and individuals with insulin resistance, who have increased IMTG stores and plasma TG concentrations, remains largely unknown.

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