Use of endogenous carbohydrate and fat as fuels during exercise

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Carbohydrate and fat are the major fuels used by working muscles during exercise. The use of these substrates requires the mobilization of endogenous reserves present in adipose tissue, liver, and skeletal muscle and delivery to muscle mitochondria for oxidation. The integration of these processes is complex and is affected by many factors. In the present article we will review the effect of exercise duration, exercise intensity, and aerobic fitness on carbohydrate and lipid metabolism during endurance exercise in human subjects.

Endogenous fuel stores

Glycogen present in liver and skeletal muscle represents the major storage form of carbohydrate. Most of the glycogen metabolized during exercise is derived from intramuscular stores. At rest, muscle glycogen concentration ranges between 10 and 30 g/kg muscle mass and represents approximately 10-4 MJ potential energy, while the liver contains approximately 80 g glycogen representing 1-25 MJ potential energy. In contrast to the limited total body stores of carbohydrate, the supply of fat is virtually inexhaustable. Two major sources of fat are oxidized during exercise: non-esterified fatty acids (NEFA) released from adipose-tissue triacylglycerols and transported by the bloodstream to skeletal muscle, and NEFA derived from triacylglycerol deposits located within skeletal muscle fibres. Adipose-tissue triacylglycerols comprise approximately 150-200 and 250-300 g/kg body mass in lean men and women respectively, which represents approximately 5420-6670 MJ potential energy. Skeletal muscle contains approximately 12 mmol triacylglycerol/kg tissue which represents 12-5 MJ potential energy (Newsholme & Leech, 1994).

Substrate metabolism during rest and exercise

In the post-absorptive state at rest, the brain, liver, heart and kidneys, which comprise only 50 g/kg body weight, are responsible for 60% of resting energy requirements (Table 1). Skeletal muscle constitutes approximately 400 g/kg total body mass but consumes only 20% of energy requirements. Approximately 60% of energy requirements are provided by the oxidation of plasma fatty acids derived from adipose-tissue triacylglycerols, 30% from the oxidation of plasma glucose produced by the liver, and the remainder from the oxidation of protein (Klein et al. 1989). The rate at which energy substrates are released into the bloodstream from endogenous stores is much greater than their rate of oxidation. The rate of appearance (Ra) of NEFA in plasma from adipose tissue is normally twice the rate of fatty acid oxidation (Klein et al. 1993). Therefore, half the NEFA liberated by lipolysis of adipose-tissue triacylglycerols are re-esterified back into triacylglycerols, presumably by the liver. Hepatic glucose output is also approximately twice the rate of glucose oxidation (Klein et al. 1993). During resting conditions, fatty acids are the major fuel used by resting skeletal muscle, which consumes only 10% of total glucose production (Andres et al. 1956).

During exercise there is a dramatic increase in energy requirements because of the metabolic needs of working muscles. The rates of fat and glucose oxidation increase 5-10-fold during prolonged mild or moderate-intensity exercise (25-65% maximum O2 uptake (VO2 max; Klein et al. 1994; Mendenhall et al. 1994). The large consumption of oxidative fuels by skeletal muscle is supplied by increased mobilization of endogenous triacylglycerols and glycogen, located within adipose tissue, liver, and skeletal muscle itself (Fig. 1).

Whole-body lipolytic activity and the uptake of plasma NEFA increase progressively throughout exercise (Fig. 2). The increase in lipolysis is mediated by an increase in

Table 1. Post-absorptive energy requirements of human tissues

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Mass (g)</th>
<th>Energy expenditure (MJ/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/kg total body mass</td>
<td>% total</td>
</tr>
<tr>
<td>Brain</td>
<td>1400</td>
<td>20</td>
</tr>
<tr>
<td>Liver</td>
<td>1800</td>
<td>25</td>
</tr>
<tr>
<td>Heart</td>
<td>300</td>
<td>5</td>
</tr>
<tr>
<td>Kidneys</td>
<td>300</td>
<td>5</td>
</tr>
<tr>
<td>Anaerobic tissues</td>
<td>5000</td>
<td>70</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>14 000</td>
<td>200</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>28 000</td>
<td>400</td>
</tr>
</tbody>
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Abbreviations: NEFA, non-esterified fatty acids; Ra, rate of appearance; Rd, rate of disappearance; VO2 max, maximum O2 uptake.
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Fig. 1. Interrelationships between carbohydrate and lipid metabolism during exercise. Exercise increases (1) the release of fatty acids (from lipolysis of adipose-tissue triacylglycerols (TAG)) into the bloodstream, (2) the rate at which glucose is produced by the liver (hepatic glycogenolysis and gluconeogenesis), and (3) intramuscular TAG and glycogen breakdown. Peripheral and local fuels, therefore, are used to provide energy to working muscles. NEFA, non-esterified fatty acids; glycerol-3-P, glycerol-3-phosphate; AcCoA, acetyl-CoA.

circulating catecholamines and sympathetic nervous system stimulation, a decrease in plasma insulin, and an increase in adipose-tissue blood flow (Bulow & Madsen, 1981; Coppack et al. 1994). During mild and moderate-intensity exercise (25–65% \(V_{O_{max}}\)), lipolysis of adipose-tissue triacylglycerols increases up to 5-fold (Wolfe et al. 1990; Klein et al. 1994) and the percentage of released fatty acids re-esterified decreases by half (Wolfe et al. 1990). The decrease in the relative rate of re-esterification reflects the enhanced delivery of fatty acids from adipose-tissue to muscle for oxidation, making less plasma NEFA available for hepatic re-esterification.

Moderate-intensity exercise causes a 2-fold increase in adipose-tissue blood flow (Bulow & Madsen, 1976, 1981) and as much as a 25-fold increase in skeletal-muscle blood flow (Mackie & Terjung, 1983). An increase in adipose-tissue blood flow is essential to remove the large amount of NEFA released during exercise. In fact, Hodgetts et al. (1991) found the molar ratio NEFA : albumin in venous blood draining abdominal subcutaneous fat increased from

Fig. 2. Rates of whole-body lipolysis (3 x rate of appearance of glycerol; △), plasma fatty acid uptake (rate of disappearance of non-esterified fatty acids; ○), and fatty acid oxidation (○) at rest and during 4 h of treadmill exercise performed at 45% maximum oxygen uptake in untrained subjects. Values are means with their standard errors represented by vertical bars. (Data adapted from Klein et al. 1994.)
2:1 at rest to approximately 6:1 at the end of exercise. Higher ratios, resulting in a local increase in potentially-toxic unbound NEFA (Spector, 1975), could be reached during exercise if released NEFA were not removed by the circulation.

The rate of release of NEFA from adipose tissue may differ among adipose-tissue depots. Up to 10-fold differences in the lipolytic effect of catecholamines in vitro has been demonstrated in adipocytes isolated from visceral, subcutaneous abdominal, and subcutaneous lower extremity sites (Rebuffe-Scrive et al. 1989; Wahrenberg et al. 1989). An assessment of regional lipolytic activity in vivo, by using microdialysis probes, found that exercise caused a greater increase in abdominal- than in subcutaneous-fat glycerol concentrations (Arner et al. 1990).

During the first 120 min of moderate-intensity exercise (50–65% \( V_{o,max} \)), the uptake of fatty acids from plasma (rate of disappearance \( R_d \) of NEFA) is often lower than the rate of fatty acid oxidation (Kanaley et al. 1993; Romijn et al. 1993). This observation suggests that another fat source(s) is being oxidized in addition to plasma NEFA derived from adipose tissue. It is likely that intramuscular triacylglycerols represent a portion of total fat oxidized during endurance exercise (Froberg & Mossfeldt, 1971; Essen, 1977; Hurley et al. 1986; Martin et al. 1993). However, it is likely that the relative contribution of intramuscular triacylglycerols to total fat oxidation declines while the contribution from plasma NEFA rises during prolonged exercise. Intramuscular triacylglycerol concentration decreases 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 (Froberg & Mossfeldt, 1971; Essen, 1977). Moreover, the difference between the rate of plasma fatty acid oxidation, measured by isotope-tracer methodology, and the rate of whole-body fatty acid oxidation, measured by indirect calorimetry, suggests that intramuscular triacylglycerols may provide more than 50% of the total fat oxidized during cycle ergometer or treadmill exercise (Romijn et al. 1993; Martin et al. 1993). In contrast, Kiens et al. (1993) found that intramuscular triacylglycerol concentration did not change after 2 h of one-leg knee-extension exercise. Differences in catecholamine response between one- and two-leg exercise may explain the discrepancy between these studies; plasma catecholamines during one-leg exercise are only slightly above resting values (Turcotte et al. 1992), while plasma catecholamines increase 5–20-fold during two-leg exercise (Galbo, 1983). Therefore, the modest level of sympathetic activity during one-leg exercise may not be sufficient to stimulate intramuscular triacylglycerol lipolysis.

Studies performed in animals demonstrate heterogeneity among different fibre types in intramuscular triacylglycerol metabolism. In rats performing prolonged exhausting exercise (several hours of swimming), there was a 70% depletion of intramuscular triacylglycerols in fast-twitch red (oxidative) fibres of the deep quadriceps muscle compared with only a 25% decrease in slow-twitch fibres of the soleus, and minimal depletion in the superficial quadriceps muscle (Reitman et al. 1973). Similar qualitative differences in intramuscular triacylglycerol metabolism among fibre types may also exist in human subjects, but this issue has not been carefully evaluated.

The contribution of circulating plasma triacylglycerols as an oxidative fuel during exercise is not clear. During resting conditions plasma triacylglycerols may account for 5–10% of total fat oxidation (Ryan & Schwartz, 1965; Wolfe et al. 1985). The available data suggest that plasma triacylglycerols are not an important fuel during exercise (Issekutz et al. 1964; Mackie et al. 1980; Kiens & Lithell, 1989); for example, Kiens & Lithell (1989) found that VLDL-triacylglycerol arterio-venous balance across skeletal muscle was negligible during exercise. However, small but physiologically important differences in arterio-venous VLDL-triacylglycerol concentrations may be difficult to detect. Direct measurement of plasma triacylglycerol oxidation during exercise has not been reported.

At the onset of exercise there is a marked increase in both the absolute and relative oxidation of glucose as a fuel. Glucose is made available to skeletal muscle by increased delivery from plasma (hepatic glycogenolysis and gluconeogenesis from plasma glycerol, lactate, and alanine precursors) and increased breakdown of intramuscular glycogen (Fig. 3). During the early part of moderate-intensity exercise, plasma glucose provides approximately one-third and muscle glycogen approximately two-thirds of the carbohydrate oxidized (Coggan, 1991). However, as exercise continues the relative contribution from plasma glucose increases and that from muscle glycogen decreases (Coyle et al. 1986; Romijn et al. 1993). Thus, after prolonged exercise virtually all carbohydrate oxidized is derived from plasma glucose. The decline in plasma glucose and muscle glycogen content that occurs with continued exercise contributes to the onset of fatigue. Carbohydrate feeding during exercise can delay fatigue and permit continued exercise by preventing hypoglycaemia (Coyle et al. 1986).
As exercise intensity increases there is a progressive increase in the relative oxidation of carbohydrate and a corresponding decrease in the relative oxidation of fat. This relationship is consistent across mammalian species and is independent of aerobic capacity (Roberts et al. 1996). In addition, studies performed in human subjects demonstrate that the absolute rates of hepatic glucose production, skeletal-muscle glycogenolysis, and whole-body glucose oxidation increase with increasing exercise intensity (Coggan, 1991). In contrast, the absolute rate of fat oxidation declines at high-intensity exercise compared with moderate-intensity exercise (Jones et al. 1980).

The effect of exercise intensity on lipid metabolism has been carefully studied by Romijn et al. (1993) who evaluated trained human subjects exercising at 25, 65, and 85 % $V_{O_{2}\text{max}}$. As the intensity of exercise increased, the absolute fatty acid $R_a$ decreased. The decrease in NEFA $R_a$ at high-intensity exercise was not caused by a decrease in lipolysis because glycerol $R_a$, an index of lipolysis, was the same during exercise performed at both 85 and 65 % $V_{O_{2}\text{max}}$. The decrease in NEFA $R_a$ may be due to trapping of NEFA within adipose tissue because of decreased adipose-tissue blood flow and inadequate NEFA removal by the bloodstream (Jones et al. 1980; Bulow & Madsen, 1981; Hodggets et al. 1991; Romijn et al. 1993). The rate of fat oxidation rose as exercise intensity increased from 25 to 65 % $V_{O_{2\text{max}}}$ but declined at high-intensity exercise (85 % $V_{O_{2\text{max}}}$). During low-intensity exercise most of the energy consumed was derived from plasma NEFA. As the intensity of exercise increased, the relative contribution of intramuscular triacylglycerols increased to nearly half all fat oxidized.

The decrease in fat oxidation during high-intensity exercise can be partly explained by a decrease in plasma NEFA availability. However, raising plasma NEFA concentrations by infusing a lipid emulsion plus heparin increases but does not completely restore the rate of fat oxidation to that observed during moderate intensity exercise (Romijn et al. 1995). Furthermore, Sidosissis et al. (1997) found that the oxidation of long-chain fatty acids (oleate) but not medium-chain fatty acids (octanoate) is inhibited at high-intensity exercise (80 % $V_{O_{2\text{max}}}$) compared with exercise performed at a lower intensity (40 % $V_{O_{2\text{max}}}$). The suppression of fat oxidation, therefore, is related to alterations in fatty acid metabolism within skeletal muscle itself. It is likely that the decrease in fat oxidation is related to an increase in muscle glycogenolysis. One hypothesis is that the high rate of muscle glycogenolysis during high-intensity exercise increases the amount of acetyl-CoA derived from glycogen which can increase malonyl-CoA concentration (Elayan & Winder, 1991; Saddik et al. 1993) and inhibit carnitine palmitoyltransferase-1 (EC 2.3.1.21), the enzyme responsible for long-chain fatty acid entry into mitochondria (Robinson & Zammit, 1982; McGarry et al. 1983). An alternative explanation is that pyruvate-derived acetyl-CoA effectively competes with fatty acid-derived acetyl-CoA for entry into the tricarboxylic acid cycle.

Endurance exercise training increases the oxidation of fat and decreases the oxidation of glucose during exercise performed at the same absolute intensity (Holloszy & Booth, 1976; Henriksson, 1977). Endurance training decreases the reliance on carbohydrate as a fuel by sparing the use of muscle glycogen and decreasing the rate of hepatic glucose production and plasma glucose utilization (Holloszy & Coyle, 1984; Mendenhall et al. 1994). The increase in fat oxidation is not the result of an increase in adipose-tissue lipolysis. Glycerol $R_a$, an index of whole-body lipolysis, measured during exercise performed at the same absolute intensity was similar in endurance-trained and untrained young adult men (Klein et al. 1994). Furthermore, two longitudinal training studies have shown that 4–12 weeks of endurance training increased fat oxidation but decreased plasma NEFA $R_d$ by approximately 30 % during moderate-intensity exercise performed at the same pretraining peak $O_2$ consumption (Martin et al. 1993; Phillips et al. 1996).

Although it is possible that training may increase skeletal muscle NEFA uptake from plasma (Jansson & Kajser, 1987; Turcotte et al. 1992), it is likely that the mobilization of another source of endogenous triacylglycerols, presumably intramuscular triacylglycerols (Martin et al. 1993), is responsible for most of the increase in total fat oxidation. However, direct measurement of intramuscular fat content by percutaneous skeletal-muscle biopsies performed before and after exercise has generated conflicting results. Hurley et al. (1986) found that 12 weeks of endurance cycling training doubled the use of intramuscular triacylglycerols during 2 h of cycle ergometer exercise. In contrast, Kiens et al. (1993) reported that intramuscular triacylglycerol use during 2 h of one-leg knee extension exercise did not change after 8 weeks of endurance training. These discrepant results suggest that lipolysis of intramuscular triacylglycerols is regulated differently during exercise of large and small muscle groups and may be related to the magnitude of the sympatho-adrenal response to exercise. Further studies are needed to delineate the precise relationship between aerobic fitness and the use of intramuscular triacylglycerol during exercise.
Ageing is associated with a decline in aerobic fitness. We have recently found that during exercise performed at the same absolute intensity (same \( VO_2 \)), sedentary elderly persons oxidize less fat than do sedentary young adults (Sial et al. 1996). The shift in substrate oxidation was probably caused by age-related changes in skeletal muscle mass and respiratory capacity because lipolytic rates (glycerol Ra) and NEFA availability (NEFA Ra) were similar in both groups. However, the proportion of energy derived from fat oxidation was similar in both the elderly and young adults during exercise performed at the same relative intensity (same \( % VO_2\text{max} \)). Thus, although elderly persons oxidize less fat than young adults during exercise, the mixture of fuels oxidized may be appropriate for their level of aerobic fitness. In fact, vigorous endurance training for 16 weeks increased the rate of fat oxidation during exercise performed at the same pretraining \( VO_2 \) to values similar to those observed in sedentary young adults (S Sial, A Coggan, R Hickner and S Klein, unpublished results). Moreover, the increase in fat oxidation was not caused by an increase in plasma NEFA availability because glycerol Ra and NEFA Ra during exercise performed after training were similar to values observed beforehand. These data demonstrate that exercise training can either correct or compensate for the alterations in skeletal muscle metabolism during exercise in sedentary elderly persons.

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References


