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Nutritional strategies for promoting fat utilization and delaying the onset of fatigue during prolonged exercise

E.V. LAMBERT,* J.A. HAWLEY, J. GOEDECKE, T.D. NOAKES and S.C. DENNIS

MRC/UCT Bioenergetics of Exercise Research Unit, University of Cape Town Medical School, Sports Science Institute of South Africa, PO Box 115, Newlands 7725, South Africa

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Carbohydrate ingestion before and during endurance exercise delays the onset of fatigue (reduced power output). Therefore, endurance athletes are recommended to ingest diets high in carbohydrate (70% of total energy) during competition and training. However, increasing the availability of plasma free fatty acids has been shown to slow the rate of muscle and liver glycogen depletion by promoting the utilization of fat. Ingested fat, in the form of long-chain (C_{16-22}) triacylglycerols, is largely unavailable during acute exercise, but medium-chain (C_{8-10}) triacylglycerols are rapidly absorbed and oxidized. We have shown that the ingestion of medium-chain triacylglycerols in combination with carbohydrate spares muscle carbohydrate stores during 2 h of submaximal (< 70% $\dot{V}O_2$ peak) cycling exercise, and improves 40 km time-trial performance. These data suggest that by combining carbohydrate and medium-chain triacylglycerols as a pre-exercise supplement and as a nutritional supplement during exercise, fat oxidation will be enhanced, and endogenous carbohydrate will be spared. We have also examined the chronic metabolic adaptations and effects on substrate utilization and endurance performance when athletes ingest a diet that is high in fat (> 70% by energy). Dietary fat adaptation for a period of at least 2–4 weeks has resulted in a nearly two-fold increase in resistance to fatigue during prolonged, low- to moderate-intensity cycling (< 70% $\dot{V}O_2$ peak). Moreover, preliminary studies suggest that mean cycling 20 km time-trial performance following prolonged submaximal exercise is enhanced by 80 s after dietary fat adaptation and 3 days of carbohydrate loading. Thus the relative contribution of fuel substrate to prolonged endurance activity may be modified by training, pre-exercise feeding, habitual diet, or by artificially altering the hormonal milieu or the availability of circulating fuels. The time course and dose–response of these effects on maximizing the oxidative contribution of fat for exercise metabolism and in exercise performance have not been systematically studied during moderate- to high-intensity exercise in humans.

Keywords: Exercise, fat metabolism, fatty acids, high-fat diet, medium-chain triacylglycerols.

Introduction

Carbohydrate ingestion before and during endurance cycling exercise has been shown to delay the onset of fatigue associated with hypoglycaemia in subjects fasted overnight (Coyle *et al.*, 1983, 1986) or low muscle glycogen contents in previously fed subjects (Bergstrom *et al.*, 1967; Bosch *et al.*, 1993). In studies of running, Callow *et al.* (1986) and O'Brien *et al.* (1993) also found a direct relationship between increased rates of carbohydrate oxidation and improved marathon running speed. Callow *et al.* (1986) proposed that for the optimal marathon race strategy, runners should 'train, eat and run at a pace' such that muscle glycogen stores are depleted as the finish line is crossed. The inherent risk in this strategy is that even when carbohydrate stores are depleted, carbohydrate oxidation is still occurring at a rate that is ten-fold higher than that at rest. Hence, athletes undergoing prolonged strenuous training are recommended to ingest diets containing a high carbohydrate content (60–70% by energy) before, during and after endurance exercise.

*Author to whom all correspondence should be addressed.

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The importance of athletes ingesting a high carbohydrate diet is that fatigue is associated with critically low (~20 mmol kg^{-1}) muscle glycogen contents, irrespective of whether or not carbohydrate is ingested during exercise (Bosch *et al.*, 1993, 1996). While carbohydrate ingestion during exercise decreases the conversion of liver glycogen to plasma glucose (Bosch *et al.*, 1994), and attenuates the rise in fat oxidation at lower (55 *vs* 70% $\dot{V}O_2$ peak) exercise intensities (Rauch *et al.*, 1995a), it does not measurably slow the rates of glycogen utilization in working muscle (Coyle *et al.*, 1986; Bosch *et al.*, 1994) until muscle glycogen contents fall below 70 mmol kg^{-1} (Bosch *et al.*, 1996).

Because carbohydrate ingestion has no significant effect on rates of glycogen utilization in working muscle, research has focused on increasing the availability of free fatty acids (FFA) and increasing the reliance on fat for oxidation during exercise to slow the rate of muscle and liver glycogen depletion. The question remains, however, as to why muscle and adipocyte triacylglycerol cannot sustain the same power output as carbohydrate. The aim of this review is to provide new insights into the role of fat metabolism and fatigue resistance at different exercise intensities, and to examine nutritional strategies that can maximize the oxidative contribution of stored fat and ingested fat to energy production during prolonged moderate- to high-intensity endurance exercise.

Limits to fat oxidation during exercise

Hawley and Hopkins (1995) have recently suggested that aerobic glycolysis and aerobic lipolysis are functionally distinct systems for the provision of energy in moderate- to high-intensity exercise. They argued that, while aerobic glycolysis may be crucial in exercise lasting less than 4 h at $\geqslant$70% of peak oxygen consumption ($\dot{V}O_2$ peak), aerobic lipolysis could become increasingly important in ultra-endurance events. These authors recommended that training for ultra-endurance events should consist predominantly of prolonged, continuous, low- to moderate-intensity workouts, and that the athlete should be adapted to a high-fat, low-carbohydrate diet before exercise, and ingest some easily digested fat during exercise. Both perturbations would, theoretically, increase the contribution of aerobic lipolysis to energy production.

Newsholme and Leech (1983) have calculated that the body triacylglycerol stores have the potential to supply 30- to 40-fold more energy than the carbohydrate stores (Table 1). However, the rates of triacylglycerol breakdown and fatty acid oxidation appear to be highly regulated. Free fatty acid mobilization from adipose tissue depends on an adrenaline-stimulated activation of hormone-sensitive lipase and is subject to feedback inhibition at high (1 mmol l^{-1}) circulating FFA concentrations (Hodgetts *et al.*, 1991). This feedback inhibition seems to result from a limited, 3 FFA:1 albumin, plasma transport capacity and/or saturable FFA uptake across the plasmalemma (Turcotte *et al.*, 1991, 1992; Sherman and Leenders, 1995).

It is well accepted that endurance training increases the contribution to energy production from fat oxidation (Holloszy and Coyle, 1984; MacRae *et al.*, 1995). Higher rates of fat oxidation after endurance training have been attributed to a tighter metabolic control of respiration associated with an increased mitochondrial density (Holloszy and Coyle, 1984) and a greater storage and utilization of intramuscular triacylglycerol (Hurley *et al.*, 1986; Martin *et al.*, 1993), as well as a slower rate of muscle glycogenolysis and plasma glucose uptake, even during high-intensity exercise (Coggan *et al.*, 1995).

Martin *et al.* (1993) have shown that, while plasma FFA concentrations and turnover were lower in subjects cycling for 2 h at the same absolute work rates after training, overall fat oxidation was increased (Fig. 1). Conversely, Turcotte *et al.* (1992) found that the fractional extraction of plasma FFA by muscles performing knee extensions for 3 h was increased at the

Table 1 Endogenous fuel stores in man (adapted from Newsholme and Leech, 1983)

	Approximate fuel reserve		Estimated days for which store would provide energy (*n*)		
Tissue fuel store	g	kJ	Starving	Walking	Running
Adipose tissue	9000	337 000	34.00	10.80	3.85
Glycogen (liver)	90	1 500	0.15	0.05	0.02
Glycogen (muscle)	350	6 000	0.60	0.20	0.07
Triacylglycerol (muscle)	400	15 048	1.50	0.48	0.17
Glucose (blood)	20	320	0.03	0.01	> 0.01
Protein	8800	150 000	15.00	4.80	1.29

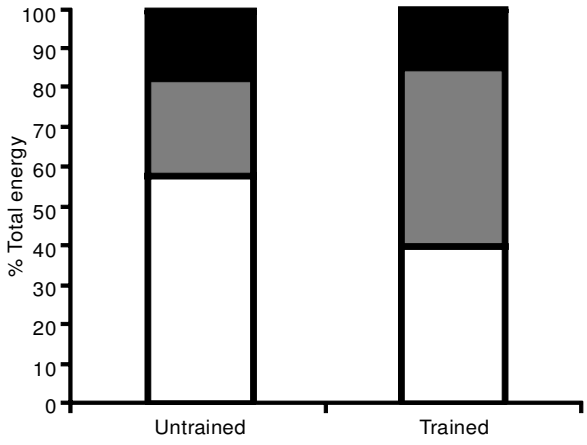

Figure 1 Training is associated with a greater reliance on the oxidation of non-plasma-derived FFA (adapted from Martin *et al.*, 1993). Mean % contribution of various substrates to exercise metabolism during 2 h of cycling at the same absolute work rate, before and after training ($P < 0.05$). ■, Plasma FFA; ▨,non-plasma FFA; □, carbohydrate.

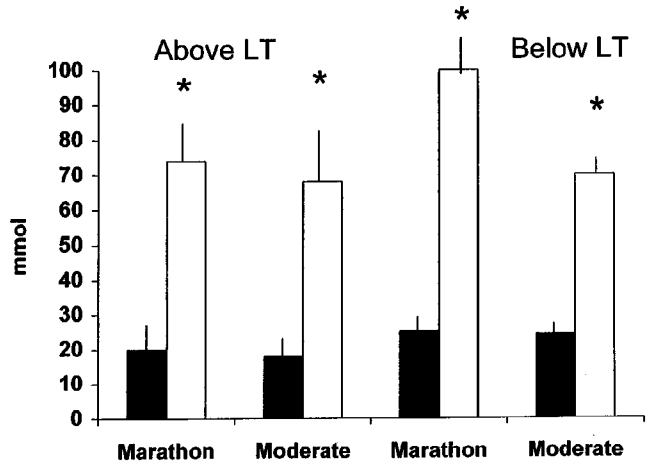

Figure 2 Total fat oxidation exceeds FFA availability, measured as the total area under the curve for FFA (mmol) released from adipose tissue during 1 h cycling exercise, above and below the 'lactate threshold' ($P < 0.05$) in highly trained marathon runners (Kanaley *et al.*, 1995). ■, FFA availability; □, total fat oxidation.

same relative (% $\dot{V}O_2$ peak) work rate after endurance training. Whereas FFA uptake levelled off at ~130 μmol min^{-1} kg^{-1} before training, it increased linearly over time from ~100 to 200 μmol min^{-1} kg^{-1} after training.

Although the effects of endurance training on lipid utilization have been well studied (Holloszy and Coyle, 1984; Hurley *et al.*, 1986; Turcotte *et al.*, 1992; Martin *et al.*, 1993; MacRae *et al.*, 1995), a limitation with some of these investigations is that training consisted of a combination of high- and low-intensity workouts, which would provide training stimuli to both the aerobic glycolytic and lipolytic systems (Hawley and Hopkins, 1995). The observed 'increase' in lipid oxidation, therefore, could represent a change in the maximal power of the aerobic lipolytic system, or could simply be the consequence of the fact that the same absolute exercise intensity represents a lower relative intensity following training, which would favour lipid oxidation (Brooks and Mercier, 1994).

Fatty acid availability

Even with training, however, there appears to be a limit to the rates of plasma FFA oxidation. Kanaley *et al.* (1995) showed that the rate of oxidation of FFA is three- to four-fold greater than total mmol of FFA released into the plasma during a 1 h exercise bout in highly trained and moderately trained individuals running for 60 min above and below the lactate threshold (Fig. 2). The release of FFA from adipocytes appears to depend on regional blood flow (Burlow, 1987) and may be reduced at higher exercise intensities (Hodgetts *et al.*, 1991; Kanaley *et al.*, 1995). Perfusion of adipose tissue during high-intensity exercise may be limited in part by increased sympathetic tone and a high FFA: albumin ratio (Hodgetts *et al.*, 1991). Romijn *et al.* (1993, 1995) showed that the rate of appearance of FFA in the blood was lower during exercise at 85% $\dot{V}O_2$ peak than during exercise at 25% or 65% $\dot{V}O_2$ peak, where adipocyte perfusion would be expected to be maintained better. In the post-exercise recovery period, there was a marked increase in the rate of appearance of plasma FFA, suggesting that FFA mobilization may be limited during high-intensity exercise, and that FFA could be trapped in adipose tissue and, therefore, be unavailable for oxidation.

FFA uptake

There also seems to be a limited uptake and/or oxidation of plasma FFA by the muscle. Havel *et al.* (1963) found that, while the delivery of plasma FFA to the leg increased during prolonged moderate- to high-intensity exercise, the fractional extraction of FFA decreased. Romijn *et al.* (1995) also showed that rates of plasma FFA oxidation may be regulated by physiological concentrations of circulating FFA. When they increased plasma FFA concentrations by 1–2 mmol l^{-1} with intravenous infusions of long-chain triacylglycerols and heparin during high-intensity (85% $\dot{V}O_2$ peak) exercise, fat

oxidation increased by 27% and carbohydrate oxidation decreased by 11%.

Muscle work rate

In the studies by Romijn *et al.* (1993, 1995), even when the availability of plasma FFA was increased by intravenous infusions of long-chain triacylglycerols and heparin, the increase in the rate of fat oxidation during exercise at 85% $\dot{V}O_2$ peak did not equal the rate at which physiological concentrations of plasma FFA were oxidized at 65% $\dot{V}O_2$ peak. These data suggest that factors other than decreased FFA availability are likely to limit plasma FFA oxidation during high-intensity exercise.

Promoting FFA availability

The seminal studies of Randle *et al.* (1963) demonstrated that increased FFA availability, typically associated with starvation, a high-fat diet or uncompensated diabetes, resulted in impaired muscle glucose uptake and decreased glycolytic flux, probably as a result of inhibition of phosphofructokinase. In exercise studies in which rats were fed long-chain triacylglycerols and later infused with heparin, elevated circulating FFA concentrations were found to be associated with a decrease in muscle glycogen utilization (Rennie *et al.*, 1976; Hickson *et al.*, 1977) and an increase in submaximal endurance (Hickson *et al.*, 1977). Similar heparin-induced increases in serum FFA concentrations have also been shown to reduce muscle glycogen utilization (Costill *et al.*, 1977; Dyck *et al.*, 1993; Vukovich *et al.*, 1993) and leg glucose uptake (Hargreaves *et al.*, 1991) in humans during exercise and at rest (Wolfe *et al.*, 1988). Furthermore, increasing FFA availability in athletes who have fasted overnight, by caffeine ingestion, has been shown to delay the onset of fatigue during steady-state exercise (Costill *et al.*, 1978).

Interactions with carbohydrate metabolism

Brooks and Mercier (1994) proposed the 'crossover' concept to explain the interaction between exercise-intensity-induced responses that promote carbohydrate oxidation and exercise-training-induced responses that promote fat oxidation. The 'crossover' point is the exercise intensity at which there is a change in the predominant oxidative fuel from fat to carbohydrate. However, the 'crossover' point is perhaps oversimplified, in that it can be affected by chronic adaptations to factors such as training and habitual diet, sympathetic nervous system activity (in relation to β-blockade or sympathomimetic drugs), carbohydrate 'stress', insulin insufficiency or insulin resistance. In addition, it may be modified acutely by carbohydrate ingestion before or during exercise, by altering FFA availability, or by providing a readily accessible source of dietary fat such as medium-chain triacylglycerols.

There are numerous examples of the important role of the 'prevailing' oxidative substrate for influencing endogenous substrate utilization during exercise. Carbohydrate 'loading' trials (in excess of 500 g day^{-1} or more than 10 g kg^{-1} day^{-1}) for maximizing muscle glycogen stores several days before performance resulted in a greater reliance on muscle glycogen as an oxidative substrate during exercise at a given intensity (Sherman *et al.*, 1993; Rauch *et al.*, 1995b). To the best of our knowledge, Rauch *et al.* (1995b) have conducted the only study that has shown that glycogen supercompensation results in a 'performance' advantage, as opposed to greater resistance to fatigue.

Carbohydrate ingestion before (Pirnay *et al.*, 1982) and during exercise (Rauch *et al.*, 1995a) results in an overall greater reliance on carbohydrate oxidation, even during exercise at low to moderate intensities (50–55% $\dot{V}O_2$ peak). These studies suggest that relative exercise intensity may *only* influence the pattern of substrate utilization when dietary carbohydrate is not ingested before or during exercise.

Carbohydrate loading and a pre-exercise carbohydrate meal also attenuate the effects of increasing FFA availability on substrate utilization during exercise at a given intensity, by altering plasma insulin, cortisol and adrenaline concentrations. Weir *et al.* (1987) found that caffeine ingestion did not result in an increased FFA availability during submaximal exercise, as had been found in subjects who were fasted overnight, when subjects were carbohydrate-replete or had ingested a carbohydrate meal (Costill *et al.*, 1978).

Dietary fat ingestion: Availability of long-chain and medium-chain triacylglycerols during exercise

Because the 're-assembly' and 'packaging' of naturally occurring long-chain (C_{16-22}) triacylglycerols (LCTs) into chylomicrons for absorption via the lymph is too slow to be of any advantage to the athlete during exercise, an alternative source of fat is required. Typically, lipaemia only develops several hours after a conventional meal containing fat and, when it does occur, the triacylglycerols in chylomicrons are mainly stored rather than directly oxidized. In contrast, medium-chain (C_{8-10}) triacylglycerols (MCTs) ingested 1 h prior to exercise are metabolized as rapidly as glucose (Decombaz *et al.*, 1983). In this case, medium-chain fatty acids diffuse across the enterocytes and enter the

systemic blood supply via the hepatic portal system. Once in the systemic blood supply, medium-chain fatty acids can diffuse into muscle mitochondria independently of the transport mechanisms that are thought to limit the rates of long-chain fatty acid oxidation (Dennis *et al.*, 1979) and are oxidized relatively rapidly (Decombaz *et al.*, 1983).

While there is substantial evidence that exercise training is associated with increased post-prandial triacylglycerol clearance rate and enhanced triacylglycerol uptake in the post-exercise period (over 3 days; Thompson *et al.*, 1980; Anuzzi *et al.*, 1987), there is little evidence of a significant role for plasma triacylglycerols as a fuel for skeletal muscle during exercise lasting less than 4 h. This is supported by the failure to show changes in plasma triacylglycerol concentrations (Thompson *et al.*, 1980; Anuzzi *et al.*, 1987), or plasma lipoprotein lipase activity, during moderate- to high-intensity exercise lasting up to 3 h.

The effects of the ingestion of medium-chain triacylglycerols on substrate utilization during exercise have been studied in subjects fasted overnight who ingested test meals 1 h before exercise. Ivy *et al.* (1980) showed that adding 30 g of medium-chain triacylglycerols to a breakfast cereal had no effect on rates of carbohydrate oxidation during 1 h of cycling at 70% $\dot{V}O_2$ peak. Others have also reported that replacing ingested carbohydrate with 25 g of medium-chain triacylglycerols did not decrease carbohydrate oxidation significantly during subsequent cycling for 1 and 2 h at 60 and 65% $\dot{V}O_2$ peak, respectively (Decombaz *et al.*, 1983; Massicotte *et al.*, 1992). However, Satabin *et al.* (1987) showed that ingesting a relatively greater (~45 g) quantity of medium-chain triacylglycerols and an isocaloric amount of long-chain triacylglycerols slowed the rates of carbohydrate oxidation after 90 min of cycling at 60% $\dot{V}O_2$ peak. Despite similarities between plasma FFA availability in the MCT and LCT trials, and in overall fat oxidation, only 9% of the ingested long-chain triacylglycerols (by energy) was oxidized versus 45% of ingested medium-chain triacylglycerols. This study, using stable isotopic tracers, provides some indication as to the extent that exogenous long-chain triacylglycerols are oxidized during moderate- to high-intensity exercise. In summary, fatty acids derived from long-chain triacylglycerols, even in the post-prandial state, make a minimal contribution to oxidative metabolism during exercise lasting less than 4 h.

In our recent investigations into the effects of the ingestion of medium-chain triacylglycerols on endurance performance during moderate- to high-intensity exercise, six male endurance cyclists rode for 2 h at 60% $\dot{V}O_2$ peak and then immediately performed a simulated 40 km time-trial on three occasions (van Zyl *et al.*, 1996). During the rides, the subjects ingested a random order of either 1 g min^{-1} of U-^{14}C glucose (10 g 100 ml^{-1} carbohydrate), or carbohydrate (CHO) plus an isocaloric quantity of 0.43 g min^{-1} of medium-chain triacylglycerols (10 g 100 ml^{-1} CHO + 4.3 g 100 ml^{-1} MCT), or just medium-chain triacylglycerols labelled with trace amounts of U-^{14}C glucose (4.3 g 100 ml^{-1} MCT). While ingesting 4.3 g 100 ml^{-1} MCT slowed the time-trials by almost 5 min, adding 4.3 g 100 ml^{-1} MCT to a 10 g 100 ml^{-1} CHO solution improved the time-trials by ~2 min (Fig. 3). Time-trials in the MCT-only trial were slower than in the CHO-only trial, probably as a result of lower rates of ATP production from ingested MCT oxidation than from ingested carbohydrate oxidation. Whereas the estimated contribution to energy production from ingested MCT oxidation rose to ~10% after 2 h in the CHO + MCT trial, the corresponding contribution to energy production from ingested carbohydrate oxidation increased to ~24%. Hence, the additional energy from ingested MCT oxidation may not have compensated for the observed 51% to 36% decline in energy production from carbohydrate oxidation in the MCT 40 km time-trial.

In contrast, the superior athletic performances in the CHO + MCT 40 km time-trial compared to the CHO-only 40 km time-trial are less readily explained. Although adding medium-chain triacylglycerols to ingested carbohydrate decreased the direct and/or indirect (via lactate) oxidation of muscle glycogen towards the end of the 2 h submaximal ride, it did not lead to an increased utilization of glycogen in the subsequent 40 km time-trial as we had expected. Despite an increase in exercise intensity from 60% to nearly 80% $\dot{V}O_2$ peak, there was no significant rise in the relative

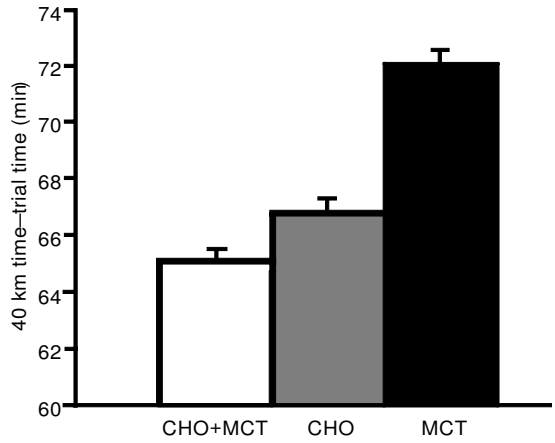

Figure 3 Simulated time-trial performance (km h^{-1}) for a 40 km cycle after 150 min of steady-state exercise at 60% $\dot{V}O_2$ peak is fastest when cyclists ingest a MCT + CHO solution, compared to either CHO alone or MCT alone ($P < 0.05$) (van Zyl *et al.*, 1996).

contribution of energy from carbohydrate oxidation in the 40 km time-trials. In the CHO-only 40 km time-trials, energy production from carbohydrate oxidation remained at ~65% and, in the CHO + MCT 40 km time-trials, it remained at ~55%. Faster cycling performances in the CHO + MCT 40 km time-trials than in the CHO-only 40 km time-trials were therefore analogous to the association between the improvements in peak work rates and the decreased reliance on carbohydrate oxidation after endurance training (MacRae *et al.*, 1995).

Less energy from carbohydrate oxidation at comparable $\dot{V}O_2$ values in the CHO + MCT 40 km time-trials than in the CHO-only 40 km time-trials was associated with lower circulating lactate concentrations, and a consequent reduction in circulating H^+. A reduced accumulation of H^+ could have decreased the inhibition of force development by H^+ buffering. Displacements of the intracellular $H^+ + HPO_4^{2-} \leftrightarrow H_2PO_4^-$ equilibrium towards $H_2PO_4^-$ formation inhibit the release of $H_2PO_4^-$ from the myosin heads via feedback (Wilkie, 1986). Whether this is the reason for improved exercise performance remains to be determined.

The simultaneous ingestion of medium-chain triacylglycerols and carbohydrate during exercise has been shown to result in maximal rates of oxidation of medium-chain triacylglycerols within 90 min of the onset of exercise (Jeukendrup *et al.*, 1995). When medium-chain triacylglycerols are ingested with carbohydrate during exercise, the overall rate of oxidation of medium-chain triacylglycerols is two-fold higher (72% of ingested) than when they are ingested in the absence of carbohydrate (33% of ingested). Jeukendrup *et al.* (1995) showed that the maximum rate of uptake and oxidation of ingested medium-chain triacylglycerols during exercise was ~0.12 g min^{-1}, when the rate of ingestion was ~0.15 g min^{-1}. This is in contrast to the estimated rate of oxidation of medium-chain triacylglycerols in our study of ~0.2 g min^{-1}, when subjects ingested medium-chain triacylglycerols at a rate of 0.43 g min^{-1} (van Zyl *et al.*, 1996). These studies show that medium-chain triacylglycerols provide a limited, rapidly oxidized fuel for exercise. The ingestion of small amounts of medium-chain triacylglycerols in combination with carbohydrate during exercise results in increased concentrations of plasma FFA and ketone bodies, without a concomitant reduction in carbohydrate oxidation (Jeukendrup *et al.*, 1996). Conversely, larger amounts of medium-chain triacylglycerols ingested during exercise may result in a significant 'sparing' of muscle glycogen, and a greater reliance on fat oxidation, even during high-intensity exercise.

Adaptations to a low-carbohydrate, high-fat diet

Another procedure that has been used to decrease the reliance on endogenous carbohydrate stores during prolonged moderate- to high-intensity exercise is chronic exposure to a low-carbohydrate, high-fat diet. Figure 4 presents a likely time course of the metabolic adaptations to a high-fat diet and the possible mechanisms to explain the effects of 'fat loading' on substrate metabolism during exercise. Early adaptations include insulin resistance in the liver, which would result in a

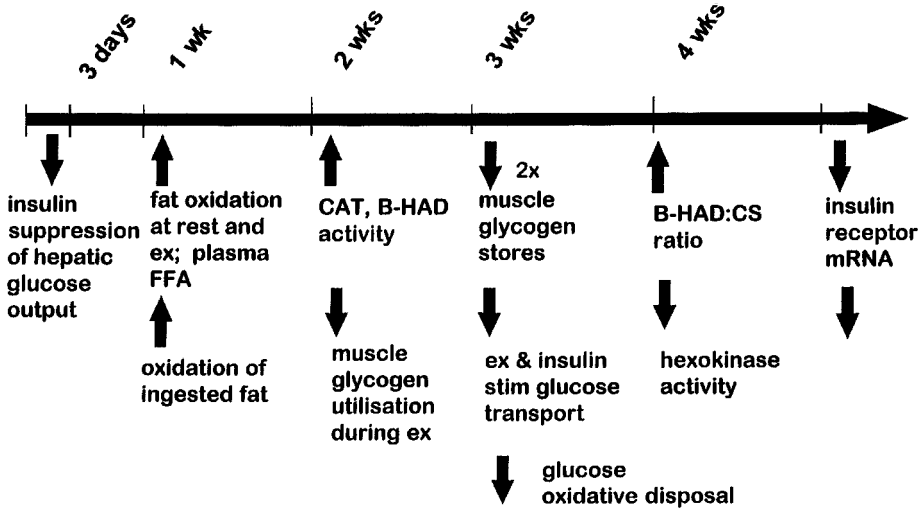

Figure 4 Schema representing the likely time course of the metabolic adaptations to a high-fat, low-carbohydrate diet in endurance-trained athletes. CAT = carnitine acyl transferase; B-HAD = 3-hydroxy-acyl CoA-dehydrogenase; CS = citrate synthase; ex = exercise; insulin stim = insulin-stimulated; Glut-4 = Glut 4 glucose transporter.

failure of the liver to suppress hepatic glucose output, and an attenuation of liver glycogen synthesis. (Kraegen *et al.*, 1991). Thus it should not be surprising that exercise performance is impaired after short-term exposure to a low-carbohydrate, high-fat diet.

On the other hand, skeletal muscle adaptations in favour of fat oxidation, such as increased activity of carnitine acyl transferase and 3-hydroxy-acyl CoA-dehydrogenase, have been demonstrated as early as 2 weeks after the initiation of high-fat feeding (Fig. 5; Cheng *et al.*, 1994). At this stage, maximal insulin-stimulated muscle glucose uptake and oxidative glucose disposal are decreased (Kraegen *et al.*, 1991; Cutler *et al.*, 1995), and there is a two-fold decrease in muscle glycogen concentrations (Conlee *et al.*, 1990). Several weeks after high-fat feeding is introduced in training rats, there is an increase in the activities of carnitine-acyl transferase (Fisher *et al.*, 1983) and 3-hydroxy-acyl CoA-dehydrogenase relative to the activity of citrate synthase in skeletal muscle mitochondria (Miller *et al.*, 1984; Simi *et al.*, 1991; Cheng *et al.*, 1994). Finally, studies of prolonged exposure to high-fat feeding have demonstrated a decrease in both insulin receptor and Glut-4 glucose transporter mRNA, reflecting marked insulin resistance (Kim *et al.*, 1994; Rosholt *et al.*, 1994).

Adaptations to a low-carbohydrate, high-fat diet appear to be 'dose-dependent'. Cheng *et al.* (1994) found earlier and more significant increases in muscle 3-hydroxy-acyl CoA-dehydrogenase activity and a greater resistance to fatigue during submaximal exercise in treadmill-trained rats when they ingested a 70% fat diet (by energy) than when they ingested a 40% fat diet or a standard chow diet. Muoio *et al.* (1994) also found that $\dot{V}O_2$ peak and submaximal running time to exhaustion at 70–85% $\dot{V}O_2$ peak were improved when athletes ingested an ~40% fat diet (by energy) for 7 days compared to their habitual diet (24% fat by energy) or a high-carbohydrate diet (15% fat by energy). These studies question the efficacy of habitual high carbohydrate diets (> 7 g CHO kg^{-1}), which are routinely recommended by exercise scientists and sports nutritionists. Indeed, a review of eating patterns of top runners from the past century reveals that athletes self-select a diet that contains only a moderate amount of carbohydrate (Hawley *et al.*, 1995).

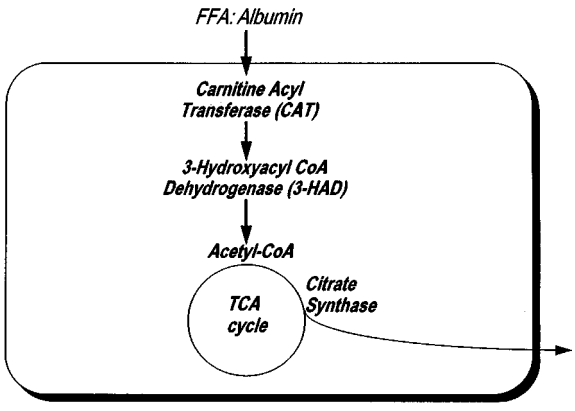

Figure 5 Key steps in FFA oxidation. The FFA:albumin ratio or plasma transport capacity of FFA may be limiting. Also, the uptake of FFA into the plasmalemma displays saturation kinetics and is dependent on fatty acid binding proteins. Uptake into the mitochondria is dependent on the acyl-carnitine transferase mechanism. Finally, the rate of β-oxidation may be influenced by training, diet and prevailing substrate oxidation.

Improvements in the capacity to oxidize fat after a low-carbohydrate diet have been associated with marked improvements in endurance during exercise lasting 60–120 min in sled dogs (Hammel *et al.*, 1977) and rats (Miller *et al.*, 1984; Conlee *et al.*, 1990; Simi *et al.*, 1991; Cheng *et al.*, 1994). In contrast, there was no effect of a 2 week high-fat (60% by energy) diet on endurance during exercise lasting 150–180 min in humans, but rates of carbohydrate oxidation were decreased (Phinney *et al.*, 1983).

We also compared the effects of a 2 week high-fat (70% fat, 7% CHO, by energy) diet or a high-carbohydrate (74% CHO, 12% fat) diet on exercise performance in trained cyclists (Lambert *et al.*, 1994). Cyclists performed five 5 s supramaximal work bouts, followed by a 30 s Wingate test. After these tests, subjects rode to exhaustion at 90% $\dot{V}O_2$ peak and, after a 20 min rest, again rode to exhaustion at 60% $\dot{V}O_2$ peak. Despite a lower muscle glycogen content at the onset of the submaximal ride at 60% $\dot{V}O_2$ peak after the high fat diet (~30 *vs* ~70 mmol kg^{-1} wet wt, $P < 0.01$), mean exercise time to exhaustion was nearly two-fold longer (~80 *vs* ~40 min, $P < 0.01$). This increase in endurance was associated with a marked decrease in the rate of carbohydrate oxidation (~2 *vs* 1.5 g min^{-1}).

In a more recent study, we fed five endurance-trained cyclists a random order of either a high-fat diet for 10 days or habitual diet for 10 days, followed by 3 days of carbohydrate loading (van Zyl *et al.*, 1994). The cyclists then performed a 150 min ride at 70% $\dot{V}O_2$ peak followed by a simulated 20 km time-trial. During the trials, subjects ingested 10 g 100 ml^{-1} CHO + 0.43 g 100 ml^{-1} MCT suspension. Adaptation to a high-fat diet, together with the ingestion of CHO + MCT, significantly decreased the direct and/or indirect (via lactate) oxidation of muscle glycogen and improved the 20 km time-trial performances by an average of 80 s.

It is important for athletes and sports scientists to recognize that the conventional paradigm of fuel substrate utilization is linked to maximizing carbohydrate

stores to prolong resistance to fatigue. We have provided substantial evidence, however, that nutritional strategies may be used alone or in combination with training interventions to maximize the rate of fat utilization during prolonged exercise, thereby enhancing resistance to fatigue even during high-intensity exercise. It is of particular interest that despite evidence for 'sparing' of muscle glycogen with dietary fat adaptation and ingestion of medium-chain triacylglycerols with carbohydrate during prolonged steady-state cycle exercise, there was not a greater reliance on carbohydrate during subsequent, high-intensity exercise.

Practical implications and recommendations to athletes

Based on the current review, a diet that is habitually high in carbohydrate (>7 g CHO kg^{-1}) may not enhance training capacity, nor subsequent endurance performance. There is evidence that relatively short-term exposure to a high-fat diet results in specific adaptations that can enhance the maximal rate of fat oxidation during exercise from 60 to 80% $\dot{V}O_2$ peak. This response appears to be dose-dependent. Because the simultaneous ingestion of medium-chain triacylglycerols and carbohydrate results in a greater overall oxidation of fat and slows the depletion of muscle glycogen, it might be advisable for athletes to consume a solution containing CHO + MCT during prolonged, moderate- to high-intensity exercise. Since the calculated maximum rates of MCT oxidation are ~0.1–0.2 g min^{-1} (Jeukendrup *et al.*, 1995; van Zyl *et al.*, 1996), we recommend that athletes begin ingesting 100 ml every 10 min of an ~2 g 100 ml^{-1} solution of medium-chain triacylglycerols 60–90 min before exercise, and thereafter add the same amount of medium-chain triacylglycerols to the 10 g 100 ml^{-1} CHO solutions ingested during exercise. With this drinking pattern, the products of MCT digestion would be available from the start of exercise and the early utilization of muscle glycogen may be decreased. One important caveat to the use of medium-chain triacylglycerols for endurance performance is that, in some individuals, ingested in large quantities medium-chain triacylglycerols have been reported to cause hyperosmolar diarrhoea. Thus it is very important to 'rehearse' all nutritional strategies during training and before a major competition.

References

Anuzzi, G., Jansson, E., Kaijser, L., Holmquist, L. and Carlson, L.A. (1987). Increased removal rate of exogenous triglycerides after prolonged exercise in man: Time course and effect of exercise duration. *Metabolism*, **36**, 438–443.

Bergstrom, J., Hermanssen, J., Hultman, E. and Saltin, B. (1967). Diet, muscle glycogen and physical performance. *Acta Physiologica Scandinavica*, **71**, 140–150.

Bosch, A.N., Dennis, S.C. and Noakes, T.D. (1993). Influence of carbohydrate loading on fuel substrate turnover and oxidation during prolonged exercise. *Journal of Applied Physiology*, **74**, 1921–1927.

Bosch, A.N., Dennis, S.C. and Noakes, T.D. (1994). Influence of carbohydrate ingestion on fuel substrate turnover and oxidation during prolonged exercise. *Journal of Applied Physiology*, **76**, 2364–2374.

Bosch, A.N., Weltan, S.M., Dennis, S.C. and Noakes, T.D. (1996). Comparison of effects of carbohydrate loading *vs* carbohydrate ingestion on fuel substrate turnover and oxidation during prolonged exercise. *Metabolism*, **45**, 415–423.

Brooks, G.A. and Mercier, M. (1994). The balance of carbohydrate and lipid utilization during exercise: The 'crossover' concept. *Journal of Applied Physiology*, **76**, 2253–2261.

Bulow, J. (1987). Regulation of lipid mobilization in exercise. *Canadian Journal of Sports Science*, **12** (suppl. 1): S117–S119.

Callow, M., Morton, A. and Guppy, M. (1986). Marathon fatigue: The role of plasma fatty acids, muscle glycogen and blood glucose. *European Journal of Applied Physiology*, **55**, 654-661.

Cheng, B., Karamizerak, O., Noakes, T.D., Dennis, S.C. and Lambert, E.V. (1994). Time course of changes in rat muscle enzymes involved in fat oxidation following exercise training and a high fat diet. *Clinical Science*, **87** (suppl.), 17.

Coggan, A.R., Comasia, A.R., Williams, B.D., Sidossis, L.S. and Gastaldelli, A. (1995). Glucose kinetics during high-intensity exercise in endurance-trained and untrained humans. *Journal of Applied Physiology*, **78**, 1203–1207.

Conlee, R.K., Hammer, R.L., Winder, W.W., Bracken, M.L., Neelson, A.G. and Barnett, D.W. (1990). Glycogen repletion and exercise endurance in rats adapted to a high-fat diet. *Metabolism*, **39**, 289-294.

Costill, D.L., Coyle, E., Dalsky, G., Evans, W., Fink, W. and Hoopes, D. (1977). Effects of elevated plasma FFA and insulin on muscle glycogen usage during exercise. *Journal of Applied Physiology*, **4**, 695-699.

Costill, D.L., Dalsky, G.P. and Fink, W.J. (1978). Effects of caffeine ingestion on metabolism and exercise performance. *Medicine and Science in Sports*, **10**, 155–158.

Coyle, E.F., Hagberg, J.M., Hurley, B.F., Martin, W.H., Ehsani, A.A. and Holloszy, J.O. (1983). Carbohydrate feeding during prolonged, strenuous exercise can delay the onset of fatigue. *Journal of Applied Physiology*, **55**, 230-235.

Coyle, E.F., Coggan, E.R., Hemmert, M.K. and Ivy, J.L. (1986). Muscle glycogen utilization during prolonged strenuous exercise when fed carbohydrate. *Journal of Applied Physiology*, **61**, 163–172.

Cutler, D.L., Gray, C.G., Park, S.W., Hickman, M.G., Bell, J.M. and Kolterman, O.G. (1995). Low carbohydrate diet

alters intracellular glucose metabolism but not overall glucose disposal in exercise-trained subjects. *Metabolism*, **44**, 1264–1270.

Decombaz, J., Arnaud, M.J., Milon, H., Moesch, H., Phillipossian, G., Thelin, A.L. and Howald, H. (1983). Energy metabolism of medium-chain triacylglycerols versus carbohydrates during exercise. *European Journal of Applied Physiology*, **52**, 9–14.

Dennis, S.C., Padma, A., Debuysere, M. and Olson, M.S. (1979). Studies on the regulation of pyruvate dehydrogenase in the isolated perfused rat heart. *Journal of Biological Chemistry*, **254**, 1252–1258.

Dyck, D.J., Putman, C.T., Heigenhauser, G.J.F., Hultman, E. and Spriet, L.L. (1993). Regulation of fat-carbohydrate interaction in skeletal muscle during intense aerobic cycling. *American Journal of Physiology*, **28**, E852–E859.

Fisher, E.C., Evans, W.J., Phinney, S.D., Blackburn, G.L., Bistrian, B.R. and Young, V.R. (1983). Changes in skeletal muscle metabolism induced by a eucaloric ketogenic diet. In *Biochemistry of Exercise XIII* (edited by H.G. Knuttgen, J.A. Vogel and J. Poortmans), pp. 497–501. Champaign, IL: Human Kinetics.

Hammel, E.P., Kronfeld, D.S., Ganjam, V.K. and Dunlap, H.L. (1977). Metabolic responses to exhaustive exercise in racing sled dogs fed diets containing medium, low or zero carbohydrate. *American Journal of Clinical Nutrition*, **30**, 409–418.

Hargreaves, M., Kiens, B. and Richter, E.A. (1991). Effect of increased plasma free fatty acid concentrations on muscle metabolism in exercising men. *Journal of Applied Physiology*, **70**, 194–201.

Havel, R.J., Naimark, A. and Borchgrevink, C.F. (1963). Turnover rate and oxidation of free fatty acids of blood plasma in man during exercise: Studies during continuous infusion of palmitate 1-C^{14}. *Journal of Clinical Investigation*, **42**, 1054–1059.

Hawley, J.A. and Hopkins, W.G. (1995). Aerobic glycolytic and aerobic lipolytic power systems. *Sports Medicine*, **19**, 240–250.

Hawley, J.A., Dennis, S.C., Lindsay, F.H. and Noakes, T.D. (1995). Nutritional practices of athletes: Are they suboptimal? *Journal of Sports Sciences*, **13**, S75–S81.

Hickson, R.C., Rennie, M.J., Conlee, R.K., Winder, W.W. and Holloszy, J.O. (1977). Effects of increased plasma free fatty acids on muscle glycogen utilization and endurance. *Journal of Applied Physiology*, **43**, 829–833.

Hodgetts, V., Coppack, S.W., Frayn, K.N. and Hockaday, T.D.R. (1991). Factors controlling fat mobilization from human subcutaneous adipose tissue during exercise. *Journal of Applied Physiology*, **71**, 445–451.

Holloszy, J.O. and Coyle, E.F. (1984). Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *Journal of Applied Physiology*, **56**, 831–838.

Hurley, B.F., Nemeth, P.M., Martin III, W.H., Hagberg, J.M., Dalsky, G.P. and Holloszy, J.O. (1986). Muscle triacylglycerol utilization during exercise: Effect of training. *Journal of Applied Physiology*, **60**, 562–567.

Ivy, J.L., Costill, D.L., Fink, W.J. and Maglischo, E. (1980). Contribution of medium and long chain triacylglycerol intake to energy metabolism during prolonged exercise. *International Journal of Sports Medicine*, **1**, 15–20.

Jeukendrup, A.E., Saris, W.H.M., Schrauwen, P., Brouns, F. and Wagenmakers, A.J.M. (1995). Metabolic availability of medium-chain triacylglycerols coingested with carbohydrates during prolonged exercise. *Journal of Applied Physiology*, **79**, 756–762.

Jeukendrup, A.E., Saris, W.H., Brouns, F., Halliday, D and Wagenmakers, A.J.M. (1996). Effects of carbohydrate and fat supplementation on CHO metabolism during prolonged exercise. *Metabolism*, **46**, 915–921.

Kanaley, J.A., Mottram, C.D., Scanlon, P.D. and Jensen, M.D. (1995). Fatty acid kinetic responses to running above or below lactate threshold. *Journal of Applied Physiology*, **79**, 439–447.

Kim, Y., Tamura, T., Iwashita, S., Tokuyama, K. and Suzuki, M. (1994). Effect of high-fat diet on gene expression of Glut4 and insulin receptor in soleus muscle. *Biochemical and Biophysical Research Communications*, **202**, 519–526.

Kraegen, E.W., Clark, P.W., Jenkins, A.B., Daley, E.A., Chisholm, D.J. and Storlien, L.H. (1991). Development of muscle insulin resistance after liver insulin resistance in high-fat-fed rats. *Diabetes*, **40**, 1397–1403.

Lambert, E.V., Speechly, D.S., Dennis, S.C. and Noakes, T.D. (1994). Enhanced endurance performance during moderate intensity exercise following 2 weeks adaptation to a high-fat diet in trained cyclists. *European Journal of Applied Physiology*, **69**, 287–293.

MacRae, H.S., Noakes, T.D. and Dennis, S.C. (1995). Role of decreased carbohydrate oxidation on slower rises in ventilation with increasing exercise intensity after training. *European Journal of Applied Physiology*, **71**, 523–529.

Martin III, W.H., Dalsky, G.P., Hurley, B.F., Matthews, E., Bier, D.M., Hagberg, J.M., Rogers, M.A., King, D.S. and Holloszy, J.O. (1993). Effect of endurance training on plasma free fatty acid turnover and oxidation during exercise. *American Journal of Physiology*, **265**, E708–E714.

Massicotte, D., Peronnet, F., Brisson, G.R. and Hillaire-Marcel, C. (1992). Oxidation of exogenous medium-chain fatty acids during prolonged exercise: Comparison with glucose. *Journal of Applied Physiology*, **73**, 1334–1339.

Miller, W.C., Bryce, G.R. and Conlee, R.K. (1984). Adaptations to a high-fat diet that increase exercise endurance in male rats. *Journal of Applied Physiology*, **56**, 78–83.

Muoio, D.M., Leddy, J.L., Horvath, P.J., Awad, A.B. and Pendergast, D.R. (1994). Effect of dietary fat on metabolic adjustments to maximal $\dot{V}O_2$ and endurance in runners. *Medicine and Science in Sports and Exercise*, **26**, 81–88.

Newsholme, E.A. and Leech, A.R. (1983). *Biochemistry for the Medical Sciences*. Chichester: John Wiley.

O'Brien, M.J., Viguie, C.A., Mazzeo, R.S. and Brooks, G.A. (1993). Carbohydrate dependence during marathon running. *Medicine and Science in Sports and Exercise*, **25**, 1009–1017.

Phinney, S.D., Bistrian, B.R., Evans, W.F., Gervino, E. and Blackburn, G.L. (1983). The human metabolic response to chronic ketosis without caloric restriction: Preservation of submaximal exercise capacity with reduced carbohydrate oxidation. *Metabolism*, **32**, 769–776.

Pirnay, F., Crielaard, J.M., Pallikarakis, N., Lacroix, M., Mosora, F., Krzentowski, G., Luyckx, A.S. and Lefebvre, P.J. (1982). Fate of exogenous glucose during exercise of different intensities in humans. *Journal of Applied Physiology*, **53**, 1620–1624.

Randle, P.J., Garland, P.B., Hales, C.N. and Newsholme, E.A. (1963). The glucose fatty acid cycle: Its role in insulin sensitivity and metabolic disturbances of diabetes mellitus. *Lancet*, **1**, 785–789.

Rauch, L.H.G., Bosch, A.N., Noakes, T.D., Dennis, S.D. and Hawley, J.A. (1995a). Fuel utilisation during prolonged low-to-moderate intensity exercise when ingesting water or carbohydrate. *Pflügers Archiv*, **430**, 971–977.

Rauch, L.H.G., Roger, I., Wilson, G.R., Belonje, J., Dennis, S.C., Noakes, T.D. and Hawley, J.A. (1995b). The effects of starting leg muscle glycogen content on cycling performance. *International Journal of Sport Nutrition*, **5**, 25–36.

Rennie, M.J., Winder, W.W. and Holloszy, J.O. (1976). A sparing effect of increased plasma fatty acids on muscle and liver glycogen content in the exercising rat. *Biochemistry Journal*, **156**, 647-655.

Romijn, J.A., Coyle, E.F., Sidossis, L.S., Gastaldelli, A., Horowitz, J.F. and Wolfe, R.R. (1993). Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. *American Journal of Physiology*, **265**, E380–E391.

Romijn, J.A., Coyle, E.F., Sidossis, L.S., Zhang, X.J. and Wolfe, R.R. (1995). Relationship between fatty acid delivery and fatty acid oxidation during strenuous exercise. *Journal of Applied Physiology*, **79**, 1939–1949.

Rosholt, M.N., King, P.A. and Horton, E.S. (1994). High-fat diet reduces glucose transporter responses to both insulin and exercise. *American Journal of Physiology*, **35**, R95–R101.

Satabin, P., Portero, P., Defer, G., Bricouti, J. and Guezennec, C.Y. (1987). Metabolic and hormonal responses to lipid and carbohydrate diets during exercise in man. *Medicine and Science in Sports and Exercise*, **19**, 218-223.

Sherman, W.M. and Leenders, N. (1995). Fat loading: The next magic bullet? *International Journal of Sport Nutrition*, **5**, S1-S12.

Sherman, W.M., Doyle, J.A., Lamb, D.R. and Strauss, R.H. (1993). Dietary carbohydrate, muscle glycogen, and exercise performance during 7 days of training. *American Journal of Clinical Nutrition*, **57**, 27–31.

Simi, B., Sempore, B., Mayet, M.H. and Faiver, J.R. (1991). Additive effects of training and high-fat diet on energy metabolism and exercise. *Journal of Applied Physiology*, **71**, 197-203.

Thompson, P.D., Cullinane, E., Henderson, L.O. and Herbert, P.N. (1980). Acute effects of prolonged exercise on serum lipids. *Metabolism*, **29**, 662-665.

Turcotte, L.P., Kiens, B. and Richter, E.A. (1991). Saturation kinetics of palmitate uptake in perfused skeletal muscle. *FEBS Letters*, **279**, 327-329.

Turcotte, L.P., Richter, E.A. and Kiens, B. (1992). Increased plasma FFA uptake and oxidation during prolonged exercise in trained *vs* untrained humans. *American Journal of Physiology*, **262**, E791–E799.

van Zyl, C., Murphy, K., Lambert, E.V., Noakes, T.D. and Dennis, S.C. (1994). Effects of a low carbohydrate, high fat diet prior to carbohydrate loading on endurance cycling performance. *Clinical Science*, **87**(suppl.), 32–33.

van Zyl, C., Lambert, E.V., Noakes, T.D., Hawley, J.A., Bosch, A.B. and Dennis, S.C. (1996). Effects of medium-chain triacylglycerol ingestion on carbohydrate metabolism and cycling performance. *Journal of Applied Physiology*, **80**, 2217–2225.

Vukovich, M.D., Costill, D.L., Hickey, M.S., Trappe, S.W., Cole, K.J. and Fink, W.J. (1993). Effect of fat emulsion infusion and fat feeding on muscle glycogen utilization during cycle exercise. *Journal of Applied Physiology*, **75**, 1513–1518.

Weir, J., Noakes, T.D., Myburgh, K.H. and Adams, B. (1987). A high carbohydrate diet negates the metabolic effects of caffeine during exercise. *Medicine and Science in Sports and Exercise*, **19**, 100–105.

Wilkie, D.R. (1986). Muscular fatigue: Effects of hydrogen ions and inorganic phosphate. *Federation Proceedings*, **45**, 2921–2923.

Wolfe, B.M., Klein, S., Peters, E.J., Schmidt, B.F. and Wolfe, R.R. (1988). Effect of elevated free fatty acids on glucose oxidation in normal humans. *Metabolism*, **37**, 323–329.