Effect of increased fat availability on metabolism and exercise capacity

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ABSTRACT

HAWLEY, J. A. Effect of increased fat availability on metabolism and exercise capacity. *Med. Sci. Sports Exerc.*, Vol. 34, No. 9, pp. 1485–1491, 2002. Several procedures have been utilized to elevate plasma free fatty acid (FFA) concentration and increase fatty acid (FA) delivery to skeletal muscle during exercise. These include fasting, caffeine ingestion, L-carnitine supplementation, ingestion of medium-chain and long-chain triglyceride (LCT) solutions, and intravenous infusion of intralipid emulsions. Studies in which both untrained and well-trained subjects have ingested LCT solutions or received an infusion of intralipid (in combination with an injection of heparin) before exercise have reported significant reductions in whole-body carbohydrate oxidation and decreased muscle glycogen utilization during both moderate and intense dynamic exercise lasting 15–60 min. The effects of increased FA provision on rates of muscle glucose uptake during exercise are, however, equivocal. Despite substantial muscle glycogen sparing (15–48% compared with control), exercise capacity is not systematically improved in the face of increased FA availability. **Key Words:** CARBOHYDRATE OXIDATION, CROSS-OVER CONCEPT, FAT OXIDATION, GLYCOGENOLYSIS, INTRALIPID, MEDIUM-CHAIN TRIGLYCERIDE, LONG-CHAIN TRIGLYCERIDE

Unlike carbohydrate (CHO) metabolism, which is closely geared to the energy requirements of the working muscle, fat utilization is not as tightly regulated: there are no mechanisms for matching the availability and metabolism of fatty acids (FA) to the prevailing rate of energy expenditure (25). Accordingly, the rate of fat oxidation during exercise is principally determined by the rate of carbohydrate utilization and the availability of circulating FA (25). The importance of energy flux as a major factor determining the balance of substrate utilization during exercise is shown in Figure 1 and has recently been highlighted by Brooks and coworkers (2–4).

As the relative exercise intensity increases, there is a shift from fat-based to CHO-based fuels (41,42), the "crossover" point (3), so that at the power outputs/speeds sustained by athletes during training (46) and competition (7), CHO-based fuels are the primary energy source for the working muscles. In all cases, the longer an exercise bout is sustained, the greater the contribution from fat to total energy metabolism. This finding was first reported in 1934 by Edwards and coworkers (15), who observed that during the latter stages of prolonged (6 h) low-intensity exercise ($\dot{V}O_2$ ~2.3 $L \cdot min^{-1}$) almost 90% of total energy was derived from fat oxidation.

The shift from fat to CHO as the intensity of exercise is increased is due to a failure of FA mobilization to increase above levels seen at lower exercise intensities (32,42) and a subsequent suppression of the rate of appearance (Ra) of FA into the plasma (42,45), a reduction in net contracting leg FA uptake (33), and insufficient blood flow and albumin delivery to carry FA from peripheral adipocytes into the systemic circulation (24). The relatively greater abundance of glycolytic versus lipolytic enzymes in muscle along with altered recruitment patterns (from slow-twitch oxidative [Type I] to fast-twitch glycolytic [Type II]) fibers and the resultant production of lactate, a strong inhibitor of lipolysis (17), all favor the biochemical pathways for glycogenolysis and glycolysis. Taken collectively, these perturbations exert well-coordinated effects to minimize the appearance of FA that cannot be oxidized by skeletal muscle (10,11).

Accordingly, any intervention that increases the Ra of FA into the systemic circulation has the potential to enhance fat oxidation and slow the rate of muscle glycogen utilization. As preexercise muscle glycogen content is strongly correlated to subsequent endurance capacity (6), it is not surprising that a number of nutritional and other practices have been tested in an attempt to increase FA availability and promote fat metabolism (5,19–21). This article provides a synopsis of several techniques used to increase FA availability during exercise and examines the impact of such perturbations on substrate oxidation and exercise capacity.

INTERVENTIONS TO INCREASE FATTY ACID AVAILABILITY DURING AEROBIC EXERCISE

A number of interventions have been used to increase FA availability before/during exercise including fasting, caffeine ingestion, L-carnitine supplementation, ingestion of medium-chain triglyceride (MCT) solutions, ingestion of long-chain triglyceride (LCT) solutions, and infusion of intralipid emul-

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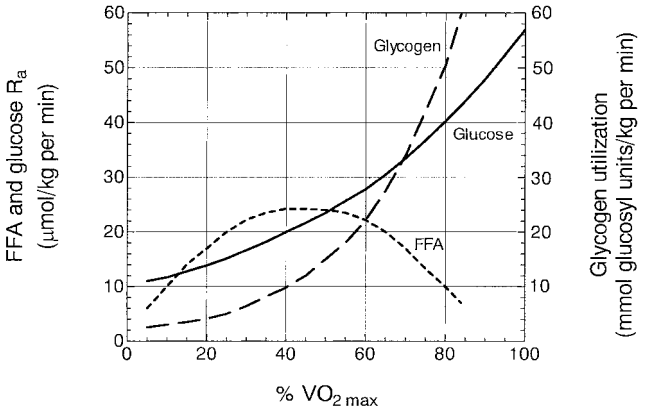

FIGURE 1—Blood glucose and free fatty acid flux rates (Ra) and net muscle glycogenolysis as a function of relative exercise intensity. $\dot{V}O_{2max}$, maximal oxygen uptake. Redrawn from reference 4 and reproduced with permission of the American Physiological Society.

sions. Although fasting increases the availability of plasma free fatty acids (FFA) and rates of FA oxidation during low- to moderate-intensity exercise, such an intervention does not have a positive effect on exercise capacity, largely due to a reduction in endogenous glycogen stores (20). Caffeine ingestion stimulates lipolysis, enhances rates of FA oxidation and decreases muscle glycogen utilization during exercise (9). However, the ergogenic effects of this substance are multifactorial and probably not directly related to, or even dependent on, enhanced rates of fat metabolism (28). Although ingestion of L-carnitine has been purported to increase FA metabolism by increasing the transport of long-chain fatty acids across the mitochondrial membrane, there is little evidence that either FA transport or oxidation are up-regulated by L-carnitine (23). For these reasons, this article focuses on the effects of oral fat ingestion protocols and intravenous (i.v.) infusion of fat emulsions on metabolism and exercise capacity in humans. Although i.v. infusion contravenes the International Olympic Committee's doping regulations, this technique has the advantage of acutely elevating arterial FFA levels without additional substrate or hormonal changes. As such, this procedure affords insight into the biochemical regulation of CHO-lipid interaction in skeletal muscle during exercise.

INGESTION OF MCT SOLUTIONS

MCTs contain FAs with a chain length of C6–10 and because of their relatively small molecular size are more soluble than LCTs. MCTs empty rapidly from the stomach and directly enter the systemic circulation through the portal vein. Unlike LCTs, they are less dependent on carnitine palmitoyltransferase I (CPT I) to cross the inner mitochondrial membrane. These physical properties have lead to the suggestion that MCTs could be a valuable source of energy for contracting skeletal muscle during submaximal exercise.

Massicotte et al. (34) were the first to determine the effect of MCT ingestion during exercise on metabolism. They compared the oxidation of ingested MCT labeled with ^{13}C with an isoenergetic amount of exogenous [^{13}C] glucose during 2 h of submaximal cycling (Table 1). The contribution from MCT and glucose oxidation was similar, representing 7–8% of total energy expenditure. Neither MCT nor glucose ingestion reduced endogenous carbohydrate utilization (34).

Recently, Jeukendrup and coworkers (29–31) investigated the effects of MCT ingestion on muscle metabolism and exercise performance (Table 1). In their first investigation (29), they reported that when MCT (10 $g \cdot h^{-1}$) was co-ingested with CHO during 3 h of low-intensity cycling, ~70% of the MCT was oxidized compared with only 33% when it was ingested alone. Toward the end of exercise, the rate of MCT oxidation closely matched the rate of ingestion. Notwithstanding, the contribution from ingested MCT to total energy expenditure was only 7% a figure identical to that reported by Massicotte et al. (34). In a subsequent study (30), these workers examined the effects of MCT ingestion (10 $g \cdot h^{-1}$) on muscle glycogen utilization during 3 h of cycling. MCT ingestion did not alter muscle glycogen disappearance, even when subjects commenced exercise with low glycogen stores (Table 1).

Given that MCT ingestion does little to alter patterns of substrate oxidation during exercise, it is not surprising that the majority of studies report no effect on exercise capacity (Table 1). To date, only one investigation has reported a beneficial effect of MCT ingestion on FA metabolism and performance (48). Van Zyl et al. (48) found that the ingestion of large (~30 $g \cdot h^{-1}$) amounts of MCT raised serum FA concentration, reduced (calculated) muscle glycogen utilization, and improved the performance of a 40-km cycle time-trial undertaken after 2 h of submaximal exercise. That study, however, is the exception. More to the point, the ingestion of large (>15 $g \cdot h^{-1}$) amounts of MCT are likely to produce gastrointestinal disturbances in the majority of athletes.

INGESTION OF LONG-CHAIN TRIGLYCERIDE (LCT) SOLUTIONS

One reason why the ingestion of MCT solutions before and/or during submaximal exercise do not alter rates of fat oxidation is that when consumed in tolerable quantities, they often fail to result in an substantial elevation in FFA concentration. In contrast, the ingestion of LCT solutions/meals before exercise (in combination with i.v heparin administration) can markedly increases FA availability (Table 2).

Costill et al. (8) were the first to report that, compared with a control condition (glucose ingestion), a combination of fat feeding and i.v. heparin administration before exercise stimulated lipolysis, elevated plasma FFA levels, and decreased muscle glycogenolysis by ~40% during 30 min of submaximal treadmill running (Table 2). A later study from the same lab (49) also found glycogen "sparing" with fat feeding and i.v heparin during 60 min of moderate-intensity cycling (Table 2). Even during intense (>80% of maximal oxygen uptake [$\dot{V}O_{2max}$]) exercise, there is still a reduction in the rate of total CHO oxidation provided there is an adequate supply of FA to the working muscle (22).

TABLE 1. Effect of medium-chain triglyceride (MCT) ingestion on metabolism and exercise performance.

Subject Characteristics	Ingestion Protocol	Exercise/Performance	Metabolic Effect	Reference
8 ET cyclists/triathletes $\dot{V}O_{2max}$ 4.7 ± 0.1 L·min^{-1}	MCT + CHO (250 mL·15 min^{-1} of 4.2% MCT + 6% CHO) CHO (250 mL·15 mm^{-1} 6% CHO) PLA (250 mL·15 min^{-1} water)	Cycle TT (35 kJ·kg^{-1} BM) MCT and CHO < PLA (169 ± 7 vs 166 ± 7 vs 178 ± 11 min, $P < 0.05$)	CHOox: MCT vs CHO, NS FATox: MCT vs CHO, NS Plasma FFA: MCT vs CHO, NS	1
12 UT $\dot{V}O_{2max}$ 3.8 L·min^{-1}	MCT (25 g) 1 h preexercise	1-h cycling @ 60% $\dot{V}O_{2max}$ (167 W)	CHOox and FATox: MCT vs CHO, NS Muscle glycogen use: MCT vs CHO, NS	12
9 ET $\dot{V}O_{2max}$ 4.8 L·min^{-1}	MCTL (1.72%) + CHO (10%); MCTH (3.44%) + CHO (10%); CHO (10%) ingested as 400-mL bolus then 100 mL·10 min^{-1}	2-h cycling @ 63% $\dot{V}O_{2max}$ then 40-km TT MCTL vs MCTH vs CHO, NS (38.7 ± 3 vs 38.5 ± 2.2 vs 39.7 ± 2.3 km)	CHOox: NS; FATox: NS Serum B-hydroxybutyrate: MCTH > MCTL > G	16
7 ET cyclists $\dot{V}O_{2max}$ 4.6 ± 0.3 L·min^{-1}	MCT (~25 g) + 54 g CHO 1 h preexercise	2-min cycling @ 60% $\dot{V}O_{2max}$ 28-min cycling @ 84 ± 1% $\dot{V}O_{2max}$	Glucose R_d: MCT vs CHO, NS Muscle glycogen use: MCT vs CHO, NS	26
10 T	MCT (~30 g) 1 h preexercise	1 h @ 70% $\dot{V}O_{2max}$	CHO/FATox: MCT vs CHO, NS	27
8 ET triathletes/cyclists $\dot{V}O_{2max}$ 5.5 ± 0.1 L·min^{-1}	MCT (27 g MCT + 87 g CHO/90 min) or CHO (87 g CHO/90 min) as a 4 mL·kg^{-1} bolus then 2 mL·kg^{-1}·20 min^{-1}	10-min cycling @ 100 W 90-min cycling @ 60% $\dot{V}O_{2max}$	CHOox: MCT vs CHO, NS FATox: MCT vs CHO, NS	29
9 ET triathletes/cyclists $\dot{V}O_{2max}$ 5.5 ± 0.1 L·min^{-1}	MCT (29 g MCT + 149 g CHO/180 min) or CHO (149 g CHO·180 min^{-1}) as 4 mL·kg^{-1} bolus then 2 mL·kg^{-1}·20 min^{-1}	180-min cycling @ 57 ± 2% $\dot{V}O_{2max}$	CHOox: MCT vs CHO, NS FATox: MCT vs CHO, NS Muscle glycogen use: MCT vs CHO, NS	30
7 ET cyclists	MCT (85 ± 3 g) MCT (85 ± 3 g) + CHO (170 ± 6 g) CHO (170 ± 6 g)	2-h cycling @ 60% $\dot{V}O_{2max}$ then 15 min cycle TT (highest average power output) CHO + MCT and CHO (314 W) > MCT (264 W; $P < 0.05$)	CHOox: MCT < CHO + MCT and CHO ($P < 0.05$)	31
6 UT $\dot{V}O_{2max}$ 4.2.1 L·min^{-1}	MCT (25 g) 1 h preexercise or CHO (57 g) during exercise (125 mL H_2O) + 7.1 g CHO·15 min^{-1}	2-h cycling @ 65% $\dot{V}O_{2max}$	CHOox: MCT vs CHO, NS FATox: MCT vs CHO, NS [FFA] MCT > CHO ($P < 0.05$)	34
9 UT $\dot{V}O_{2max}$ 3.8 ± 0.5 L·min^{-1}	400-kcal test solution ingested 1 h preexercise MCT (43 g) CHO (~100 g glucose)	Cycle time to exhaustion @ 60% $\dot{V}O_{2max}$ CHO vs MCT, NS (110 ± 4 min vs 108 ± 5 min)	RER: MCT < CHO (90–150 min, ($P < 0.05$) Blood ketone concentration: MCT 5-fold > CHO ($P < 0.05$)	44
6 ET cyclists $\dot{V}O_{2max}$ 5.5 ± 0.1 L·min^{-1}	400-mL bolus then 100 mL·10 min^{-1} MCT (86 g) MCT (86 g) + CHO (200 g) CHO (200 g)	2-h cycling @ 60% $\dot{V}O_{2max}$ then 40-km cycle TT MCT > MCT + CHO and CHO (72.1 ± 0.6 vs 65.1 ± 0.5 vs 66.8 ± 0.4 min; $P < 0.05$)	CHOox: MCT and MCT + CHO < CHO ($P < 0.05$). Plasma glucoseox: MCT < MCT + CHO and CHO (5.0 ± 1.0 vs 7 ± 1.0 mmol·L^{-1}; $P < 0.05$)	48

ET, endurance trained; T, trained; UT, untrained; $\dot{V}O_{2max}$, maximal O_2 uptake; MCT, medium-chain triglyceride; CHOox, carbohydrate oxidation; FATox, fat oxidation; TT, time-trial; FFA, free fatty acid; R_d, rate of disappearance; BM, body mass; RER, respiratory exchange ratio; NS, not significantly different; All values are mean ± SEM.

TABLE 2. Effect of long-chain triglyceride (LCT) ingestion on metabolism and exercise performance.

Subject Characteristics	Ingestion Protocol	Exercise/Performance Task	Metabolic Effect	Reference
6 ET runners, 1 UT $\dot{V}O_{2max}$ 4.2 ± 0.1 L·min^{-1}	LCT meal 4–5 h preexercise, then i.v. heparin (2000 U) 30 min preexercise CHO (75 g glucose) 45 min preexercise	30-min running @ 68% $\dot{V}O_{2max}$	Plasma FFA: LCT > CHO (1.0 vs 0.2 mM, $P < 0.05$) Muscle glycogen use: LCT < CHO (↓ 40%, $P < 0.05$)	8
7 ET cyclists/triathletes $\dot{V}O_{2max}$ 5.2 ± 0.6 L·min^{-1}	LCT drink (1.2 g·kg^{-1} BM) 90 min preexercise, then i.v. heparin (2000 U) 15 min preexercise CHO drink (2.5 g·kg^{-1}) 90 min preexercise	20-min cycling @ 80% $\dot{V}O_{2max}$ then 600-kJ cycle TT LCT vs CHO: NS (320 ± 16 vs 324 ± 15 W)	Plasma FFA: LCT > CHO (1.3 vs 0.2 mM, $P < 0.001$). RER: LCT < CHO (0.94 vs 0.97, $P < 0.01$). CHOox: LCT ↓ 10% vs CHO ($P < 0.05$)	22
8 ET cyclists/triathletes $\dot{V}O_{2max}$ 4.3 ± 0.2 L·min^{-1}	LCT drink (1.2 g·kg^{-1} BM) 1 h preexercise, then i.v. heparin (2000 U) 15 min preexercise CHO drink (2.6 g·kg^{-1} BM) 90 min preexercise	2-h cycling @ 70% $\dot{V}O_{2max}$ then 7 kJ·kg^{-1} BM cycle TT LCT > CHO: (33.0 ± 8.5 vs 30.4 ± 7.5 min, $P < 0.05$)	Plasma FFA: LCT > CHO (1.3 vs 0.4 mM, $P < 0.01$) RER: LCT < CHO (0.88 ± 0.05 vs 0.92 ± 0.03, $P < 0.01$)	28
9 T $\dot{V}O_{2max}$ 3.81 ± 0.14 L·min^{-1}	LCT (30% CHO, 61% fat, 9% protein) or high-CHO meal (79% CHO, 10% fat, 11% protein) 4 h preexercise (4,700 kJ)	2-h cycling @ 67% $\dot{V}O_{2max}$ then ~80% $\dot{V}O_{2max}$ until exhaustion LCT 141 vs CHO 138 min: NS	RER: LCT < CHO first 60 min ($P < 0.05$) [FFA]: LCT > CHO ($P < 0.01$)	37
10 T runners $\dot{V}O_{2max}$ 4.3 ± 0.2 L·min^{-1}	LCT (30% CHO, 61% fat, 9% protein) or high-CHO meal (79% CHO, 10% fat, 11% protein) 4 h preexercise (4,700 kJ)	2-h cycling @ 65% $\dot{V}O_{2max}$ then ~80% $\dot{V}O_{2max}$ until exhaustion. LCT 122 vs CHO 128 min: NS	RER: <LCT than CHO for first 40 min Serum [FFA]: LCT > CHO ($P < 0.05$) [*B*-hydroxybutyrate]: LCT > CHO ($P < 0.05$)	38
6 T $\dot{V}O_{2max}$ 4.76 L·min^{-1}	LCT (90% fat) + heparin or CHO (70% CHO) 4 h preexercise	Cycling to exhaustion @ ~70% CHO 118 vs LCT 128 min ($P < 0.01$)	CHOox: LCT vs CHO, NS (362 vs 383 g) FATox: LCT vs CHO, NS (93 vs 68 g)	39
5 UT $\dot{V}O_{2max}$ 3.3 ± 0.6 L·min^{-1}	LCT drink (90 g fat, >90% saturated) ~3 h preexercise, then i.v. heparin (2000 U) 15 min preexercise	60-min cycling @ 70% $\dot{V}O_{2max}$	Plasma FFA: LCT > CON (1.7 vs 0.3 mM, $P < 0.01$) Muscle glycogen use: LCT < CON (↓ 28%, $P < 0.05$)	49
8 ET cyclists $\dot{V}O_{2max}$ 5.2 ± 0.2 L·min^{-1}	LCT (80 g fat, 50 g CHO, 14 g protein) or CHO meal (3 g fat, 215 g CHO, 26 g protein) 4 h preexercise	90-min cycling @ 70% $\dot{V}O_{2max}$, 10-km TT LCT vs CHO, NS (290 ± 29 vs 276 ± 33 W)	CHOox: LCT vs CHO, NS FATox: LCT vs CHO, NS Plasma [FFA]: LCT vs CHO, NS	50

ET, endurance trained; T, trained; UT, untrained; $\dot{V}O_{2max}$, maximal O_2 uptake; LCT, long-chain triglyceride; CHOox, carbohydrate oxidation; FATox, fat oxidation; TT, time-trial; FFA, free fatty acid; BM, body mass; RER, respiratory exchange ratio; NS, not significantly different; Values are mean ± SEM.

On the other hand, several studies have reported only small differences in the rates of substrate oxidation in response to high-fat meals ingested 2–4 h before submaximal exercise (Table 2). Disparity in results between investigations could be due to a combination of factors including the training status of subjects, the exercise mode and intensity, and differences in meal composition that may have influenced the time course and degree to which FA availability was increased.

In contrast to the inconsistent effect of LCT ingestion on metabolism, the majority of studies find little ergogenic effect of LCT feedings on exercise capacity (Table 2). To date, only Pitsiladis et al. (39) have reported an improved submaximal cycling time to exhaustion when trained subjects ingested a high-fat compared with a high-CHO meal 4 h preexercise. As there were no differences in the rates of CHO or fat oxidation between treatments, it is difficult to explain the potential mechanism(s) for the prolonged endurance found in that study (39).

INFUSION OF INTRALIPID (PLUS HEPARIN)

Most of the studies that have examined the effect of intralipid (20% triglyceride emulsion) plus heparin infusion on substrate metabolism during exercise have found marked reductions in the rates of whole-body CHO oxidation (Table 3). Furthermore, during moderate- to high-intensity running and cycling exercise lasting 15–60 min, the majority of investigations have reported reductions in muscle glycogen utilization, with the magnitude of "sparing" ranging from 16–48% compared with a control trial (Table 3). In those individuals who "spare" glycogen in the presence of elevated plasma FFA, the reduction in glycogenolysis occurs early during exercise and appears to be independent of starting muscle glycogen content (13). The strong evidence for glycogen sparing with intralipid infusion (Table 3) in the absence of a consistent ergogenic effect on performance is perplexing. In those studies that fail to observe a performance enhancement, it is likely that muscle glycogen availability wasn't the limiting factor during exercise. Alternatively, it could simply be that the various laboratory measures of "performance" were not sensitive enough to detect the small changes necessary to increase sustainable power output (see reference 22).

In contrast to the results of the large number of investigations that have found a reduction in CHO metabolism during exercise after intralipid-heparin administration (Table 3), one study utilizing low-intensity cycling (40) and another using the one-leg knee kicking model (18) report no difference in rates of CHO oxidation or muscle glycogenolysis. In both these latter studies (18,40), plasma FFA

TABLE 3. Effect of Intralipid infusion on metabolism and exercise performance.

Subject Characteristics	Ingestion Protocol	Exercise/Performance	Metabolic Effect	Reference
11 UT $\dot{V}O_{2max}$ 3.79 ± 0.63 L·min^{-1}	IL + Hep 20 min pre- and throughout exercise	15-min cycling @ 85% $\dot{V}O_{2max}$	Plasma [FFA]: IL vs CON (1.1 vs 0.3 mM, $P < 0.05$) Muscle glycogen utilization: (IL ↓ 48% in 7/11 subjects)	13
6 (2 T, 2 MT, 2 UT) $\dot{V}O_{2max}$ 4.2 ± 0.1 L·min^{-1}	IL + Hep 30 min pre- and throughout exercise	15-min cycling @ 85% $\dot{V}O_{2max}$	Plasma [FFA]: IL vs CON (1.0 vs 0.20 mM, $P < 0.05$) Muscle glycogen utilization: IL vs CON (IL ↓ 28% $P < 0.05$)	14
11 UT $\dot{V}O_{2max}$ 4.0 L·min^{-1}	IL + Hep 20 min pre- and throughout exercise	One-leg knee extension for 1 h @ 80% of maximal workload	Plasma [FFA]: IL vs CON (1.12 vs 0.54 mM, $P < 0.05$) Leg RQ: IL vs CON, NS (0.86 vs 0.87) Glucose uptake: IL ↓ 33%, $P < 0.05$) Muscle glycogen utilization: IL vs CON, NS	18
7 UT $\dot{V}O_{2max}$ 4.20 ± 0.23 L·min^{-1}	IL + Hep 30 min pre- and throughout exercise	10-min cycling @ 40% $\dot{V}O_{2max}$ 10-min cycling @ 65% $\dot{V}O_{2max}$	Plasma [FFA]: IL vs CON (0.99 vs 0.11 mM, $P < 0.01$) RER: IL vs CON (0.87 vs 0.91, $P < 0.05$)	35
8 UT $\dot{V}O_{2max}$ 3.96 ± 0.18 L·min^{-1}	IL + Hep 30 min pre- and throughout exercise	10-min cycling @ 40% $\dot{V}O_{2max}$ 60-min cycling @ 65% $\dot{V}O_{2max}$	RER: IL vs CON (0.92 vs 0.89 @ 40% $\dot{V}O_{2max}$) RER: IL vs CON (0.94 vs 0.91 @ 65% $\dot{V}O_{2max}$) FFA: IL vs CON (0.8 vs 0.2 mM, $P < 0.05$) Muscle glycogen utilization: IL ↓ 23% ($P < 0.05$)	36
10 UT $\dot{V}O_{2max}$ 3.82 ± 0.16 L·min^{-1}	IL + Hep 30 min pre- and throughout exercise SAL (saline infusion)	150-min cycling @ 44% $\dot{V}O_{2max}$	Plasma [FFA]: IL vs CON, NS (1.12 vs 0.78 mM) RER: IL vs SAL (0.88 vs 0.91 at 60–120 min, $P < 0.05$)	40
6 ET cyclists $\dot{V}O_{2max}$ 4.81 L·min^{-1}	IL for 2 h pre- and throughout exercise	30-min cycling @ 80–85% $\dot{V}O_{2max}$	Plasma [FFA]: IL vs CON (1.2 vs 0.2–0.3 mM, $P < 0.05$) CHOox: IL ↓ 11% vs CON ($P < 0.05$) FATox: IL ↑ 27% vs CON ($P > 0.05$) Muscle glycogen utilization: IL ↓ 11% vs CON	43
5 UT $\dot{V}O_{2max}$ 4.33 ± 0.18 L·min^{-1}	IL + Hep 30 min pre- and throughout exercise	60-min cycling @ 70% $\dot{V}O_{2max}$	Serum [FFA]: IL vs CHO (1.5–2.0 vs 0.30 mM, $P < 0.001$) RER: IL vs CHO, NS (0.89 vs 0.93) Muscle glycogen utilization: IL ↓ 16% vs CON	49

ET, endurance trained; T, trained; MT, moderately trained; UT, untrained; $\dot{V}O_{2max}$, maximal O_2 uptake; IL + Hep, 20% Intralipid plus heparin infusion; CHOox, carbohydrate oxidation; FATox, fat oxidation; TT, time-trial; FFA, free fatty acid; BM, body mass; RER, respiratory exchange ratio; RQ, respiratory quotient; NS, not significantly different. All values are mean ± SEM.

concentrations were high in the control trial (0.5–0.8 mM), making it likely that further increases in FFA levels (to ~1.1 mM) would be unlikely to further enhance FA uptake (47).

During exercise, increased fat availability enables a better match between energy supply and demand, resulting in a lower accumulation of AMP and Pi, a lower glycolytic flux, and a concomitant decrease in the rate of pyruvate formation. Accordingly, one might expect a reduction in the rate of oxidation of blood glucose during exercise. However, the effects of increased FFA provision on muscle glucose uptake during exercise are equivocal. Romijn et al. (43) reported that when FFA concentrations were elevated to 1–2 mM during intense cycling, by infusion of lipid plus heparin, there was a 15% reduction in calculated muscle glycogen utilization but no difference in Rd glucose (determined from stable-isotope tracer techniques). On the other hand, Hargreaves et al. (18) using one-leg knee extension exercise found that muscle glucose uptake was reduced by 33% when plasma FFA concentration was increased to ~1.1 mM despite no difference in leg respiratory quotient or muscle glycogen breakdown. The discrepancy in results is most likely due to differences in the exercise modes between studies: the knee-extensor model has increased muscle blood flow relative to power output compared with dynamic exercise such as cycling or running. Further investigations are needed to establish the effect of increased FFA provision on muscle glucose uptake during exercise.

SUMMARY

In the search for strategies to improve athletic performance, several procedures have been utilized to elevate plasma FFA concentration, increase FFA availability to skeletal muscle, and promote FA oxidation during exercise. Acute increases in FA delivery to the working muscle decrease muscle glycogenolysis (by 15–48%) during whole-body dynamic exercise at 65–90% of $\dot{V}O_{2max}$. However, the effects of elevated circulating FFA on the uptake and oxidation of blood glucose are equivocal. Despite marked alterations in substrate availability and significant changes in the patterns of substrate oxidation with increased FFA concentrations, exercise capacity is remarkably resistant to change.

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