Regulation of skeletal muscle carbohydrate oxidation during steady-state contraction

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THE REGULATION OF SUBSTRATE OxIDATION IN CONTRACTING SKELETAL MUSCLE has been the subject of intense investigation (2, 3, 11–13, 23). The glucose-fatty acid cycle (GFC) describes a mechanism for the regulation and integration of carbohydrate and lipid oxidation (24–26). According to the GFC, when the availability of nonesterified fatty acids (NEFA) increases, there is a concomitant reduction in carbohydrate oxidation (24–26). This is proposed to be a direct consequence of a reduction in the amount of pyruvate dehydrogenase complex (PDC) existing in its active, dephosphorylated form (PDCa) and is mediated by increases in the mitochondrial acetyl-CoA-to-CoASH ([acetyl-CoA]/[CoASH]) and NADH-to-NAD\(^+\) concentration ratios (24–26). In resting skeletal muscle the mechanisms underlying the regulation of substrate oxidation appear to be consistent with the operation of the GFC (16, 22, 24, 33). Indeed, recent work has demonstrated a reduction in PDCa when the [acetyl-CoA]/[CoASH] ratio is increased by acetate infusion (22). The effect of reduced plasma NEFA availability on resting skeletal muscle PDC status has not been examined in healthy volunteers. However, it has been demonstrated that inhibition of lipolysis failed to alter PDCa during euglycemic conditions in resting skeletal muscle from patients with non-insulin-dependent diabetes mellitus (33).

When lipid availability has been increased during exercise, a reduction in muscle glycogen utilization or muscle carbohydrate oxidation has often (10, 22), although not always (13, 27), been observed. Furthermore, when lipid availability has been reduced by using nicotinate, a more rapid rate of muscle glycogen utilization and whole body carbohydrate oxidation has been observed during prolonged exercise (3, 5, 12). Importantly, it appears that nicotinate inhibits intramuscular and adipose lipolysis (12). In all these cases (3, 5, 12, 18, 19) the regulatory mechanism attributed to mediating the increase in carbohydrate oxidation has been the GFC. However, PDCa has never been assessed under conditions of reduced lipid availability, such that the operation of the GFC in contracting skeletal muscle has not been established and the regulatory mechanisms controlling substrate oxidation during exercise remain unclear (10, 22, 23). In particular, those studies that have demonstrated a glycogen-sparing effect of lipid infusion and simultaneously assessed PDCa and the [acetyl-CoA]/[CoASH] ratio have failed to establish PDC as the regulatory mechanism for their observations (10, 22). When PDC has been activated using dichloroacetate (DCA), blood lactate concentration was reduced during submaximal exercise (6); however, the effect of this reduction on muscle carbohydrate oxidation has not been established.

It was our aim, therefore, to examine the role of lipid availability and PDC activation status on carbohydrate utilization during moderately intense submaximal skeletal muscle contraction. This intensity reflects the most common workload utilized where the GFC has been interpreted to operate (12, 18, 19). This was achieved by using nicotinate, which inhibits hormone-sensitive lipase-mediated lipolysis and hence NEFA availability to the contracting muscle (5, 12, 15). Hormone-sensitive lipase is the main mediator of lipolysis in adipose and skeletal muscle tissue (34). In addition, PDC was activated using sodium DCA at a dose that maximally activates the enzyme complex (29). We hypothesized that if PDC was directly responsible for regulating steady-state carbohydrate oxidation, then this would be most evident when the enzyme complex was maximally activated.
METHODS

Animals. Eighteen female beagle dogs (Zeneca Pharmaceuticals, Alderley Park, Cheshire, UK) weighing 13.9 ± 1.1 kg and aged 12.2 ± 0.9 mo were divided into three groups: saline control (n = 6), nicotinate (n = 6), and DCA (n = 6).

Surgical procedures. After an overnight fast, each animal was premedicated with morphine sulfate (10 mg im). After 30 min, anesthesia was induced with pentobarbitone sodium (45 mg/kg body mass iv; Sagatal, Rhône Merieux, Harlow, UK) and maintained by intravenous infusion (0.11 ± 0.00 mg·kg⁻¹·min⁻¹). The animals were then artificially ventilated, and surgical procedures were carried out as described previously (32). Briefly, the right brachial artery was cannulated for recording of systemic blood pressure, and the left brachial artery and vein were cannulated for collection of arterial blood samples and infusion of saline, nicotinate, or DCA. The gracilis was vascularly isolated, with only the supply from the brachial artery and to the femoral vein left intact. Blood flow was measured using an electromagnetic flow probe (10-mm circumference; Carolina Medical Electronics, King, NC) placed around the femoral artery. In situ calibration of the flow probe was completed at the end of the experiment with use of the dog's own blood (timed collection), and zero flow was determined by occluding blood flow distal to the flow probe at intervals during the experiment. The popliteal artery was catheterized for recording gracilis muscle perfusion pressure. Heparin was infused (Multiparin, 1 U·kg⁻¹·min⁻¹ iv) for the duration of the experiment. The distal tendon of the muscle was attached to an isometric force transducer (model FTC 10, Grass, Quincy, Medfield, MA). The animals were then infused with saline (45 ml), nicotinate (45 mg/kg), or DCA (300 mg/kg) over a period of 45 min.

Muscle stimulation parameters. The resting length of the muscle was altered to obtain a standard resting tension of 300 g. At 60 min after the onset of infusion, muscle contraction was induced via electrical stimulation of the obturator nerve (model S88 stimulator, Grass). Square-wave impulses of 0.1-ms duration, 3-Hz frequency, and 10-V intensity were applied for 20 min, which results in a steady-state maximal oxygen consumption (VO₂max) of ~80%. It was determined in a pilot study that a stimulus intensity of 10 V resulted in maximal twitch force production, indicating that complete muscle fiber recruitment was achieved.

Blood collection and analysis. Arterial and venous blood samples, obtained at rest and during the stimulation protocol (between minutes 10–12 and 18–20), were taken from the brachial artery and femoral vein and used for blood pH, Pco₂, and Po₂ determination (model 280 blood-gas system, Ciba-Corning, Medfield, MA). Hemoglobin and total oxygen saturation were also assessed using a CO-oximeter (model 482, Instrumentation Laboratory, Lexington, MA). Further blood samples (1 ml) were collected in tubes containing 3.2% trisodium citrate, and after centrifugation, plasma was used for analysis of lactate, NEFA, and glucose. Plasma samples for glucose analysis were kept on ice, and glucose was measured spectrophotometrically at the end of each experiment (Glucose Autostat GA1120, Clandon, Aldershot, UK). Plasma samples for lactate (lactate reagent kit, Sigma Chemical, Poole, UK) and NEFA (NEFA C kit, Wako Chemicals, Neuss, Germany) were frozen for later spectrophotometric analysis. For the saline and nicotinate groups, the blockage of a venous catheter resulted in arteriovenous differences being available only from five of the six experiments in each case. When this happened an average value for glucose uptake and lactate efflux, calculated from the respective groups, was used to calculate total carbohydrate oxidation rates.

Muscle collection and analysis. A resting muscle biopsy was obtained at the end of the infusion period by use of the needle biopsy technique of Bergström and Hultman (2). After 20 min of stimulation, the muscle was freeze-clamped during contraction and a thin piece of muscle was excised, divided into two portions, and stored under liquid nitrogen. Subsequently, one portion was freeze-dried, dissected free from visible connective tissue and blood, powdered, and extracted in 0.5 M perchloric acid containing 1 mM EDTA. After centrifugation, the supernatant was neutralized with 2.2 M KHC03 and used for spectrophotometric determination of ATP, phosphocreatine, creatine, and lactate (14). The supernatant was also used for the determination of free carnitine and acetylcarnitine by enzymatic assays with use of radioisotopic substrates, as described previously (7). Freeze-dried muscle powder was used for the determination of muscle glycogen (14). In the remaining portion of frozen muscle, PDC activation was assessed as described previously (9).

Calculations and statistics. Muscle carbohydrate utilization was calculated from changes in muscle glycogen concentration from rest and muscle glucose uptake during contraction. The latter was obtained during the last 10 min of contraction. Muscle lactate accumulation and muscle lactate production (calculated from arteriovenous differences and converted to mmol/kg dry muscle) were summed and, after conversion to glucosyl units (divided by a factor of 2), were subtracted from muscle carbohydrate utilization to provide an estimate of muscle carbohydrate oxidation during the 20-min contraction period (10, 32). Muscle carbohydrate oxidation can then be expressed as a rate per minute by dividing by 20. The estimate of carbohydrate oxidation was also converted to millimoles of acetyl-CoA per kilogram of wet muscle to give the calculated flux through PDC for direct comparison with the measurements of PDC. This was done by converting the rate of carbohydrate oxidation to wet muscle mass (by dividing by 4.3) and converting to acetyl-CoA (by dividing by a factor of 2). Changes in muscle acetyl carnitine during contraction were not taken into account in this calculation, because it is unclear what proportion of the acetyl groups was derived from carbohydrate. However, even if it were assumed that all acetyl carnitine was derived from carbohydrate, the changes during contraction did not significantly alter the calculated flux through PDC (calculation not shown).

Values are means ± SE. Comparisons between treatments were made using ANOVA. When a significant F value was found (P < 0.05), Tukey's post hoc test was used to locate the differences, and significance was accepted at the 5% level.

RESULTS

Contractile function. There was no significant difference in peak isometric tension between any of the groups (4,437 ± 259, 4,189 ± 212, and 3,662 ± 445 g/100 g tissue for control, nicotinate, and DCA, respectively). Isometric tension declined ~12% during the initial few minutes of contraction and thereafter remained relatively constant for the remainder of the stimulation period. No significant differences in isometric tension existed between any of the groups at the end of the 20-min contraction period (3,842 ± 317, 3,632 ± 250, and 3,335 ± 186 g/100 g tissue for control, nicotinate, and DCA, respectively).

Hemodynamics and plasma metabolites. There was no effect of nicotinate or DCA on muscle blood flow or perfusion pressure during contraction compared with the control group (Table 1). Nicotinate resulted in a
In control, nicotinate, and DCA groups 10 to 20 during stimulation of canine gracilis muscle.

Table 1. Blood and plasma parameters from minutes 10 to 20 during stimulation of canine gracilis muscle in control, nicotinate, and DCA groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 5)</th>
<th>Nicotinate (n = 5)</th>
<th>DCA (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow, ml·min⁻¹·100 g⁻¹</td>
<td>95.5 ± 13.6</td>
<td>85.2 ± 11.9</td>
<td>78.1 ± 9.5</td>
</tr>
<tr>
<td>Perfusion pressure, mmHg</td>
<td>123 ± 8.9</td>
<td>121.7 ± 3.5</td>
<td>127.3 ± 5.8</td>
</tr>
<tr>
<td>VO₂, ml·min⁻¹·100 g⁻¹</td>
<td>15.7 ± 2.4</td>
<td>13.5 ± 1.6</td>
<td>12.8 ± 1.5</td>
</tr>
<tr>
<td>Lactate efflux, mmol/kg dry muscle</td>
<td>4.7 ± 3.5</td>
<td>5.4 ± 4.5</td>
<td>9.7 ± 2.7</td>
</tr>
<tr>
<td>Glucose uptake, mmol/kg dry muscle</td>
<td>9.9 ± 2.8</td>
<td>12.9 ± 2.9</td>
<td>11.1 ± 3.7</td>
</tr>
<tr>
<td>NEFA uptake, mmol/kg dry muscle</td>
<td>2.1 ± 0.5</td>
<td>0.4 ± 0.2*</td>
<td>0.6 ± 0.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE of 2 samples taken between minutes 10–12 and minutes 18–20 of 20-min stimulation protocol. DCA, dichloroacetate; VO₂, O₂ consumption. Net glucose and nonesterified fatty acid (NEFA)/urate were assessed from arteriovenous differences × flow and converted to dry muscle weight. Net lactate release was assessed from venoarterial differences × flow and converted dry muscle weight. Lactate efflux, glucose uptake, and NEFA uptake were measured at minute 20. *Significantly different from control, P < 0.05.

Reduction in resting arterial NEFA concentration from 0.29 ± 0.05 to 0.09 ± 0.02 mmol/l (P < 0.05). This was lower than the NEFA concentration measured in the control group (0.23 ± 0.03 mmol/l, P < 0.05). Plasma NEFA concentration was also reduced by DCA from 0.24 ± 0.02 to 0.12 ± 0.01 mmol/l. Arterial NEFA concentration did not change further during the stimulation protocol in any of the groups. NEFA uptake was fourfold lower after nicotinate and threefold lower after DCA than in the control group during the 20-min contraction period (Table 1). Arterial lactate concentration was significantly reduced by DCA (0.4 ± 0.1 mmol/l, P < 0.05) but did not differ between control and nicotinate groups (1.6 ± 0.19 and 1.48 ± 0.26 mmol/l for control and nicotinate, respectively). There were no significant differences among the three groups in muscle lactate efflux or muscle glucose uptake (Table 1).

Muscle metabolites. Muscle ATP and phosphocreatine concentrations did not significantly differ between groups at rest or during contraction (Table 2). Nicotinate and DCA reduced resting muscle lactate concentration compared with the control group (Table 2). During contraction, DCA reduced lactate accumulation compared with the control and nicotinate groups. Resting muscle glycogen concentration was similar across groups, and utilization during contraction did not differ between groups (Table 2). Carbohydrate oxidation, calculated from glycogen utilization, glucose uptake, and muscle lactate production (see Methods), did not differ between groups over the 20-min stimulation period (Fig. 1). Nicotinate did not significantly affect PDCA at rest, whereas PDCA was 2.5-fold higher in the DCA group (1.9 ± 0.2, 1.7 ± 0.2, and 4.5 ± 0.4 mmol acetyl-CoA·min⁻¹·kg wet wt⁻¹ at 37°C for control, nicotinate, and DCA, respectively). During contraction, PDCA was significantly lower in the nicotinate group than in the control and DCA groups (Fig. 2; P < 0.05). There was no effect of nicotinate on muscle acetylcarnitine concentration at rest or during contraction; however, DCA increased acetylcarnitine concentration at rest by ~10-fold (Table 2). During contraction, the acetylcarnitine concentration fell in the DCA group, such that there was no difference in acetylcarnitine concentration between groups (Table 2). Free carnitine concentration was significantly lower in the DCA group at rest than in the control and nicotinate groups, but no differences were observed between groups during contraction (Table 2). The sum of the acid-soluble carnitine esters (acetylcarnitine + free carnitine) did not differ at rest or during contraction between groups (Table 2).

**DISCUSSION**

In accordance with the GFC (24–26), activating PDCA, by using DCA, would be expected to result in an increase in carbohydrate oxidation during steady-state skeletal muscle contraction. Similarly, a decrease in lipid availability during contraction would be expected to be accompanied by an increase in carbohydrate oxidation mediated through an increase in PDCA. However, when PDCA was converted to its active form before the onset of contraction, no alteration in the rate of carbohydrate oxidation during steady-state contraction was observed. Furthermore, we observed that PDCA was reduced during steady-state contraction when lipolysis was inhibited, yet the rate of carbohydrate oxidation was maintained. Because PDCA varied

### Table 2. Muscle metabolite concentrations in canine gracilis muscle at rest and during 20 min of stimulation in control and nicotinate- and DCA-pretreated muscles

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>DCA</th>
<th>Contraction</th>
<th>DCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Nicotinate</td>
<td>DCA</td>
<td>Control</td>
</tr>
<tr>
<td>ATP</td>
<td>26.6 ± 1.5</td>
<td>28.4 ± 1.1</td>
<td>26.4 ± 0.9</td>
<td>24.6 ± 1.1</td>
</tr>
<tr>
<td>PCr</td>
<td>56.7 ± 2.3</td>
<td>56.9 ± 1.6</td>
<td>55.1 ± 2.2</td>
<td>42.8 ± 5.4</td>
</tr>
<tr>
<td>Creatine</td>
<td>69.6 ± 2.3</td>
<td>69.4 ± 2.4</td>
<td>71.2 ± 2.2</td>
<td>83.5 ± 5.4</td>
</tr>
<tr>
<td>Lactate</td>
<td>12.3 ± 1.6</td>
<td>7.2 ± 0.6*</td>
<td>5.7 ± 1.6*</td>
<td>1.38 ± 1.6</td>
</tr>
<tr>
<td>Glycogen</td>
<td>258 ± 18</td>
<td>267 ± 16</td>
<td>247 ± 18</td>
<td>177 ± 22</td>
</tr>
<tr>
<td>Acetylcarnitine</td>
<td>2.0 ± 0.4</td>
<td>2.7 ± 0.2</td>
<td>19.2 ± 0.8†</td>
<td>8.5 ± 1.6</td>
</tr>
<tr>
<td>Carnitine</td>
<td>24.6 ± 1.1</td>
<td>23.2 ± 1.2</td>
<td>5.4 ± 1.2†*</td>
<td>14.7 ± 1.5</td>
</tr>
<tr>
<td>SAC + C</td>
<td>26.5 ± 1.3</td>
<td>25.9 ± 1.0</td>
<td>25.7 ± 1.3</td>
<td>23.2 ± 1.0</td>
</tr>
</tbody>
</table>

Values are means ± SE expressed as mmol/kg dry muscle. n = 6. SAC + C, sum of acetyl carnitine and free carnitine; PCr, phosphocreatine. Canine gracilis muscles were stimulated at 3Hz via obturator nerve for 20 min. *Significantly different from control (P < 0.05); †significantly different from nicotinate (P < 0.05).
greatly among the three groups but carbohydrate oxidation remained identical, it can be concluded that the GFC does not operate in skeletal muscle during submaximal steady-state contraction.

In resting muscle, PDC is thought to be responsible for the regulation of pyruvate decarboxylation and hence carbohydrate oxidation (24). The PDC exists in a dephosphorylated (active) form and a phosphorylated (inactive) form. The interconversion between the active and the inactive form of PDC is regulated by a phosphatase-kinase system, which is, in turn, subject to control by the end products of the PDC-catalyzed reaction, i.e., acetyl-CoA and NADH (1). During contraction, however, physiological activation of PDC is thought to be partly achieved through an increase in the intramitochondrial calcium concentration (1), although the in vivo importance of calcium in PDC activation has not been determined. It has also been suggested that other metabolites, such as pyruvate and ADP, have a regulatory influence on the degree of PDC activation during steady-state contraction (8, 10, 22).

DCA has been used to decrease lactate production at rest and during submaximal contraction, presumably by increasing PDC activation and theoretically flux through the PDC reaction (6, 17, 31). In addition, reducing the amount of acetyl-CoA derived from β-oxidation normally increases muscle glycogen oxidation during exercise (3, 19). This increase in glycogen oxidation has been explained by a decrease in the [acetyl-CoA]/[CoASH] ratio resulting from a reduction in lipid availability and, therefore, greater PDC activation (18). The importance of the [acetyl-CoA]/[CoASH] ratio as a regulator of PDC or carbohydrate oxidation during steady-state contraction has not, however, withstood investigation (8, 22).

During contraction the ratio of acetylcarnitine to free carnitine concentration reflects changes in the [acetyl-CoA]/[CoASH] ratio (7, 19). It would be expected that a high [acetyl-CoA]/[CoASH] ratio, represented in the current study by a high acetylcarnitine concentration, would result in the inhibition of PDC activation. However, it is clear from the current study that PDC can range from ~40 to ~100% activated during contraction with apparently similar [acetyl-CoA]/[CoASH] ratios. The [acetyl-CoA]/[CoASH] ratios are apparently similar, since in the present study acetylcarnitine concentration did not significantly differ between groups. Putman et al. (22, 23) also demonstrated that PDC activation was dissociated from changes in the [acetyl-CoA]/[CoASH] ratio during exercise. At rest the [acetyl-CoA]/[CoASH] ratio was altered by an infusion of acetate and PDCa was reduced, but these effects on the [acetyl-CoA]/[CoASH] ratio or PDCa did not persist during contraction (22). However, in these studies and in the present study, muscle biopsies were taken during steady-state contraction. It is possible that the [acetyl-CoA]/[CoASH] ratio may influence the rate of activation of PDC and hence influence carbohydrate utilization (21) and lactate production (30) during the initial period of contraction. Indeed, consistent with our previous data, DCA reduced the muscle "oxygen deficit" by ~40% (30, 31). It should be indicated that this reflects overall substrate delivery during the initial, non-steady-state situation and is not a relevant factor in consideration of the control of steady-state carbohydrate oxidation, as addressed by the GFC theory (24).

We found that when lipolysis was inhibited, so reducing the competition between acetyl-CoA derived from the PDC reaction and that derived from β-oxidation, activation of PDC was reduced. This is contrary to what would be expected if the GFC operated in contracting...
skeletal muscle (24–26). Despite this reduction in the enzyme activation status, flux through the PDC reaction was maintained during contraction; i.e., the rate of muscle carbohydrate oxidation did not differ between the control and nicotinate groups. Activation of PDC requires covalent modification of the enzyme complex, such that an accurate assessment of its degree of activation in vivo is achieved by in vitro assessment (1). Flux through PDC during contraction can be estimated from the amount of carbohydrate oxidized, and the calculated flux in all three groups was \( -2.0 \text{ mmol acetyl-CoA min}^{-1} \cdot \text{kg wet wt}^{-1} \). This estimated flux, however, is similar to the degree of activation of PDC in the nicotinate group only (Fig. 1). Indeed, the calculated flux in the control group represented only \( -60\% \) of the measured PDC activation, whereas the corresponding values in the nicotinate and DCA groups were \( -90\% \) and \( -40\% \) of the measured PDC activation, respectively.

In the present study we did not significantly increase muscle carbohydrate oxidation with nicotinate (numerically it was \( -18\% \) higher). This may be a reflection of the limited contribution of lipid oxidation under present stimulation intensity (\( -20\% \)). However, failure to observe the operation of the GFC is not restricted to the higher workloads [e.g., Ravussin et al. (27) utilized a workload of \( -40\% \text{VO}_2\text{max} \)]. Importantly, in the present study the activation of PDC during contraction was in excess of the required steady-state catalytic activity and appeared to be unrelated to the rate of carbohydrate oxidation during steady-state contraction.

From the above data it appears that PDC is not responsible for the regulation of carbohydrate oxidation during skeletal muscle contraction. It is important, however, at this point to discuss what factors may have been responsible for the changes in PDC activation status in the present series of experiments. First, the reduction in PDC activation during contraction suggests that PDC activation may be under control conditions, elevated when acetyl groups are also derived from lipid oxidation under premaximal exercise with elevated lipid availability (10, 22), however, no increase in the amount of PDC activation was observed. However, in these studies, PDC activation was essentially maximal in the control condition, such that any potentiation of PDC activation, through greater mitochondrial pyruvate accumulation, was unlikely to be observed (10, 22). In conclusion, despite the 50% range in the extent of PDC activation status, carbohydrate oxidation was similar across the three groups. It would appear, therefore, that, contrary to the operation of the GFC, the extent of PDC activation is not a major physiological regulator of carbohydrate oxidation during steady-state skeletal muscle contraction.

**Perspectives**

The role of the GFC, as proposed by Randle and co-workers in the early 1960s (25), has directed our understanding of the way in which oxidation of carbohydrate and lipid is regulated within skeletal muscle tissue. A key feature of the GFC is that glucose oxidation is inhibited by NEFA oxidation through an acetyl-CoA- and NADH-mediated inhibition of the PDC and an increase in cytosolic citrate concentration, which inhibits phosphofructokinase activity and hence glycolytic flux. In vitro evidence in support of these possibilities has been presented (1, 24–26), although the physiological significance of the concentration of citrate used in vitro to inhibit phosphofructokinase has been questioned (20).

Overall it appears that the GFC may operate in vivo in noncontracting skeletal muscle (16, 22, 24, 33). It is apparent, however, that during contraction the GFC does not operate in skeletal muscle (10, 22). Indeed, it has been demonstrated in the present study that the activation status of PDC can vary about twofold without influencing steady-state carbohydrate oxidation. We must consider alternative mechanisms for the integration of carbohydrate and lipid oxidation in contracting skeletal muscle, e.g., the role of carnitine availability in determining fatty acid transport across the mitochondrial membrane during steady-state contraction. We previously pointed out, as have others, that carnitine availability may be important in regulating carbohydrate metabolism early during exercise (8). However, the extent of the reduction in free carnitine concentration (or the increase in acetylcarnitine) during the first few minutes of submaximal contraction is a function of exercise intensity (8) and may thereafter be a determinant of the rate of carnitine-mediated transport of long-chain acyl groups across the mitochondrial membrane via carnitine palmitoyl-transferase I. This would provide a simple link between exercise intensity and the reduction in lipid oxidation rates observed at high work rates (28).
REFERENCES


