

Time course of exercise-induced decline in malonyl-CoA in different muscle types

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WINDER, W. W., J. AROGYASAMI, I. M. ELAYAN, AND D. CARTMILL. *Time course of exercise-induced decline in malonyl-CoA in different muscle types*. *Am. J. Physiol.* 259 (Endocrinol. Metab. 22): E266–E271, 1990.—Malonyl-CoA is a potent inhibitor of carnitine palmitoyltransferase I (CPT-I), the rate-limiting enzyme for fatty acid oxidation in mitochondria from liver of fed rats. Malonyl-CoA has also been demonstrated to inhibit skeletal muscle CPT-I. This study was designed to determine the rate of decline in malonyl-CoA in muscle during the course of a prolonged exercise bout. Adult male rats were anesthetized (pentobarbital sodium, intravenously) at rest or after running for 5, 10, 20, 30, 60, or 120 min on a treadmill (21 m/min, 15% grade). Malonyl-CoA was then quantitated in the soleus (type I fibers) and in the superficial white (type IIB) and deep red (type IIA) regions of the quadriceps. Malonyl-CoA decreased in red quadriceps from 2.8 ± 0.2 to 1.4 ± 0.2 pmol/mg after 5 min and to 0.9 ± 0.1 pmol/mg after 20 min of exercise. The concentration of malonyl-CoA remained at this level for the duration of the exercise bout (120 min). In white quadriceps, resting values of malonyl-CoA were lower than in red quadriceps, and a significant decline was not observed until 30 min of exercise. A significant decrease in the soleus was observed after 20 min of exercise. This decline in muscle malonyl-CoA may be an important signal for allowing increased fatty acid oxidation during long-term exercise.

fatty acid oxidation; carnitine palmitoyltransferase I; plasma free fatty acids; blood glucose; fructose 2,6-bisphosphate

MALONYL COENZYME A is a potent inhibitor of skeletal muscle carnitine palmitoyltransferase I (CPT-I), the rate-limiting enzyme for fatty acid oxidation in fed rats (15, 16, 18, 27, 31). A previous study in this laboratory showed a significant decline in gastrocnemius muscle malonyl-CoA concentration in response to 30 min of treadmill exercise (32). This observation implies that fluctuations in malonyl-CoA may be important in regulating the rate of fatty acid oxidation in skeletal muscle during exercise. In this study, the time course of this decline in muscle malonyl-CoA has been characterized in gastrocnemius (mixed fiber type), soleus (predominantly type I fiber type), the deep red region of the quadriceps (type IIA), and in the superficial region of the quadriceps (type IIB).

MATERIALS AND METHODS

Animal care. Male Sprague-Dawley rats (Sasco, Omaha, NE) were housed in individual cages in a tem-

perature- (19–21°C) and light-controlled (12:12 h light-dark cycle) room. All rats were run 5–10 min/day on a rodent treadmill (Quinton, Seattle, WA) for 2 wk, so that they were well accustomed to being handled and to running on the treadmill. With rats under light ether anesthesia, jugular catheters were surgically implanted 3 days before the final exercise test. The jugular catheters were utilized for rapid induction of anesthesia at the end of exercise. Rats were fed ad libitum on Wayne Rodent Blox (Chicago, IL). Rats weighed 376 ± 4 g at the time of death.

Rats were killed at rest or after running 5, 10, 20, 30, 60, or 120 min on a rodent treadmill at 21 m/min up a 15% grade. Rats were rapidly anesthetized by intravenous injection of pentobarbital sodium (4.8 mg/100 g body wt). To avoid variation caused by diurnal changes (6), the final exercise tests were between 10:00 A.M. and 12:00 noon. Resting rats were also killed at 12:00 noon to verify that changes seen during exercise were not a result of diurnal cycles.

Collection of blood and tissues. As soon as rats were anesthetized, the soleus, the gastrocnemius/plantaris, the superficial white region of the quadriceps (~500 mg), the red quadriceps (~300 mg) adjacent to the femur, and a piece of liver were isolated and frozen with stainless steel block tongs at liquid nitrogen temperature. These tissues were frozen in the order indicated within 2.5 min after injection of anesthetic. Blood was then collected via the abdominal aorta. A perchloric acid extract was made (0.5 ml blood added to 2.0 ml 10% perchloric acid) for determination of glucose. The remaining blood was heparinized and used for free fatty acid (FFA) determination. All tubes were kept on ice and were centrifuged immediately after collection of the blood. Plasma samples and perchloric acid extracts were stored at -20°C until the time of analysis. Muscle and liver samples were stored at -70°C until analyzed.

Analytical methods. Malonyl-CoA was determined by the method described by McGarry et al. (17) on neutralized 10% perchloric acid extracts of muscle. This assay measures malonyl-CoA-dependent incorporation of [^3H] acetyl-CoA into fatty acids. The reaction is catalyzed by a fatty acid synthase enzyme previously isolated by the procedure of Linn (14).

Muscle fructose 2,6-bisphosphate was determined in neutralized 0.05 N NaOH extracts by the method of Van Schaftingen et al. (29, 30).

Perchloric acid extracts were neutralized and analyzed

for glucose (5). Plasma FFA concentration was determined by the method of Novak (20). Liver and muscle glycogen were determined by the anthrone method (8).

Results are expressed as means \pm SE. Statistically significant differences between resting and exercised rats were determined by analysis of variance (ANOVA) followed by Fisher's least-significant differences test (21).

RESULTS

In resting rats, malonyl-CoA concentration in the white region of the quadriceps was only 28% of the concentration in the deep red region of the quadriceps (Fig. 1). The gastrocnemius concentration was midway between these two extremes. The soleus malonyl-CoA concentration approached that of the red quadriceps.

When two groups of resting rats were killed 120 min apart, an interval equivalent to the time the rats ran on the treadmill, no significant differences were observed in malonyl-CoA or fructose 2,6-bisphosphate content of any of the muscles examined (data not shown). Glycogen contents of the red and white regions of the quadriceps, the gastrocnemius, and of the liver were likewise not significantly different. Glycogen content of the soleus was 21% lower in the second sample (data not shown).

The pattern of decline in muscle malonyl-CoA during the course of a 120-min exercise bout is shown in Fig. 1. The most rapid decrease occurred in the red region of the quadriceps muscle. After 5 min of exercise, malonyl-CoA had decreased to 52% of the resting value. A plateau of 34% of the resting level was observed to occur after 20 min of exercise. A different pattern was observed in the white region of the quadriceps. After 5 min of exercise, malonyl-CoA concentration was 55% higher than at rest. It then returned to resting levels until 30 min, when a significant decline was observed. A progressive decrease occurred during the remainder of the exercise bout until a value of 25% of resting concentration was reached after 120 min. In the soleus, the lowest value reached was 61% of the resting concentration. No significant decrease was seen until 20 min of exercise. The gastrocnemius exhibited a pattern intermediate between the red and white regions of the quadriceps.

Glycogen content of the soleus, the red region of the quadriceps, and of the gastrocnemius decreased rapidly early during the course of the exercise bout (Fig. 2). Glycogen content of the white region of the quadriceps declined much less rapidly. Only a marginal decrease occurred until 30 min of exercise. Liver glycogen decreased from 327 ± 34 to 28 ± 6 μ mol glucose units/g over the course of the 2-h period of treadmill running.

Plasma FFA concentration was significantly increased during exercise (Fig. 3). The increase reached statistical significance after 20 min of running. Blood glucose increased slightly midway through the exercise bout and then began to decline after 120 min.

The pattern of change in fructose 2,6-bisphosphate concentration was similar in the red and white regions of the quadriceps (Fig. 4). A significant decrease was seen after 5 min of exercise, followed by a return to resting values. After 120 min of exercise, fructose 2,6-

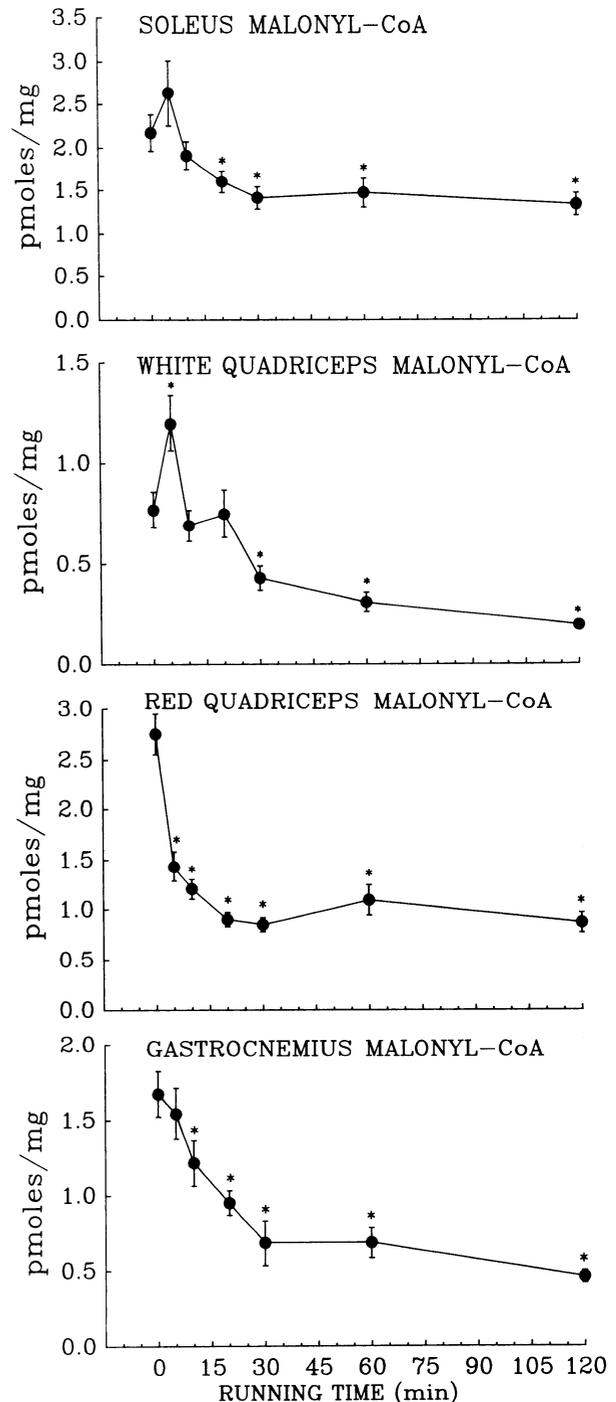


FIG. 1. Malonyl-CoA concentrations in different muscles during course of 120 min running on treadmill at 21 m/min up a 15% grade. Values are means \pm SE for 8-9 rats at each point. *Significantly different from resting value, $P < 0.05$. Resting values for different muscles are all significantly different from each other, $P < 0.05$.

bisphosphate was significantly higher than resting values in both the red and white regions of the quadriceps.

DISCUSSION

During prolonged exercise bouts, FFA oxidation is a major energy source for the working muscle (1, 13, 22-24). Muscle glycogen is utilized rapidly by the contracting muscles early during the course of a submaximal exercise

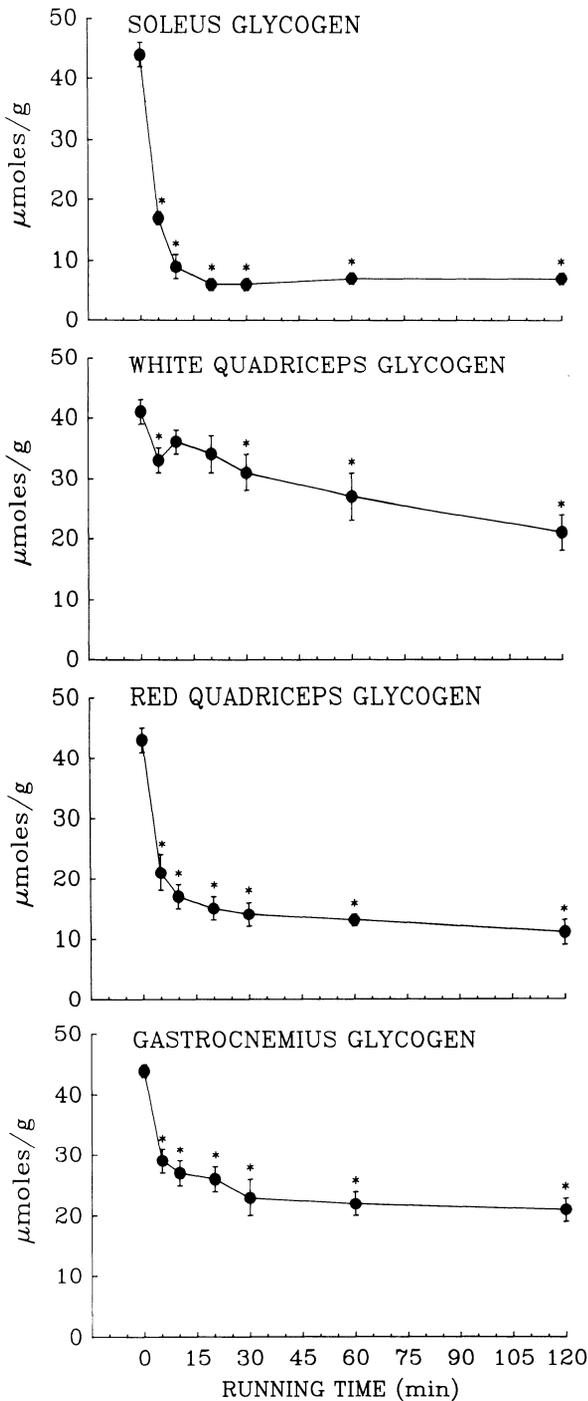


FIG. 2. Glycogen content (μmol glucose units/g wet wt) of different muscles during course of 120 min running on treadmill at 21 m/min up a 15% grade. See Fig. 1 legend for additional details.

bout, but glycogen utilization diminishes as blood-borne substrates (glucose and FFA) become available. Availability of FFA undoubtedly plays an important role in determining the substrate oxidation mix of the muscle (11, 12, 19, 25, 26). When plasma FFA are artificially increased in exercising rats, the rate of muscle glycogen utilization is diminished (11, 26). In isolated perfused rat hindlimbs, inclusion of high concentrations of oleate in the medium reduces the rate of glucose uptake and glycogen utilization (25).

In the liver, fatty acid oxidation and ketogenesis are

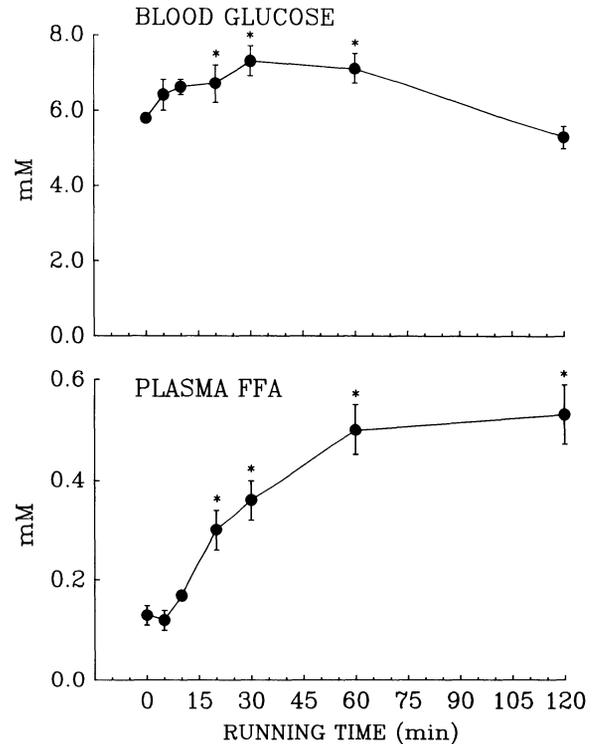


FIG. 3. Blood glucose and plasma free fatty acid (FFA) during course of 120 min running on treadmill at 21 m/min up a 15% grade. See Fig. 1 legend for additional details.

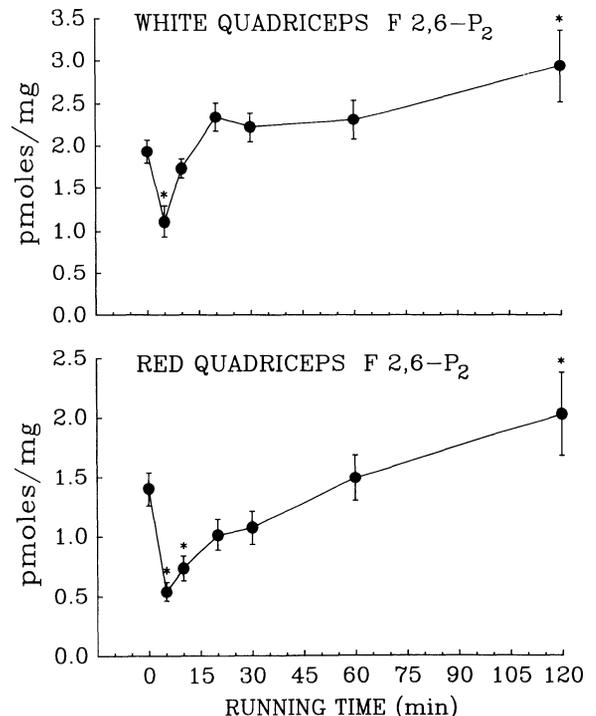


FIG. 4. Fructose 2,6-bisphosphate (F 2,6-P₂) content of red and white quadriceps during course of 120 min running on treadmill at 21 m/min up a 15% grade. See Fig. 1 legend for additional details.

influenced not only by availability of FFA but by control mechanisms within the hepatocyte. The CPT-I enzyme of liver is inhibited by malonyl-CoA, the first committed intermediate in the fatty acid synthesis pathway (15). During periods of prolonged fasting, during prolonged

exercise, or in the diabetic state, the liver content of malonyl-CoA is markedly reduced, thus relieving inhibition of the CPT-I enzyme and allowing fatty acid oxidation and ketogenesis to proceed (3, 4, 15). The liver content of malonyl-CoA is reduced when plasma glucagon is elevated, plasma insulin is depressed, liver glycogen is depleted, and plasma FFA concentration is elevated (15).

Intramuscular mechanisms also may be important in determining the substrate oxidation mix during exercise. The CPT-I enzyme of muscle is even more sensitive to inhibition by malonyl-CoA than is the liver enzyme (16, 18, 31). Malonyl-CoA is present in skeletal muscle, and the concentration decreases in response to fasting and exercise (16, 32). A citrate-dependent acetyl-CoA carboxylase has recently been found to be present in the cytosolic fraction of rat heart (28). Little is known concerning the pathway for synthesis or concerning the regulation of malonyl-CoA in skeletal muscle tissue.

From the present studies on the concentration of malonyl-CoA in the different muscle types at rest, the malonyl-CoA concentration appears to be correlated with the mitochondrial content of the muscle. When malonyl-CoA concentrations in soleus, red quadriceps, and white quadriceps are correlated with cytochrome *c* or cytochrome oxidase, values previously reported for these tissues (2, 33), [correlation coefficients of 0.99 ($P < 0.01$) and 0.99 ($P < 0.02$)] are obtained (Fig. 5). Malonyl-CoA values also appear to correlate well with carnitine palmitoyltransferase enzyme activities (from Ref. 2) in the different muscle types (Fig. 5). Thus muscle fibers, which

have a high capacity to oxidize fatty acids, also appear to have higher resting concentrations of malonyl-CoA. It is conceivable that muscles having a higher mitochondrial content would also have a greater capacity to generate citrate, the presumed substrate for extramitochondrial acetyl-CoA production. Citrate content has been reported to be greater in red quadriceps muscle than in white quadriceps after 30 min of exercise but not when at rest (26).

The most rapid decline in malonyl-CoA concentration during exercise occurs in the region of the muscle containing the fast-twitch red (type IIA) fibers. These are the fibers expected to be recruited early in an exercise bout of this intensity. The fast-twitch white fibers (type IIB) are less likely to be recruited at this work rate until later in exercise. These fibers have a lower oxidative capacity (thus being more dependent on glycolysis for energy production) than do the red fibers, yet they utilize little glycogen until late in the exercise bout. This provides evidence that white fibers are recruited to a lesser extent than the red fibers during work of this intensity. A significant decrease in malonyl-CoA does not occur in the white fibers until 30 min into the exercise session. These observations suggest that the decline in malonyl-CoA in the muscle during exercise may be mediated by a contraction-coupled mechanism. For example, the putative acetyl-CoA carboxylase could be allosterically inhibited by the increase in free calcium that accompanies muscle contraction. Alternatively, the carboxylase could be phosphorylated and inactivated by a calcium-dependent protein kinase. The enzyme involved in degradation of malonyl-CoA could also be activated by a similar mechanism.

Previous *in vitro* studies have indicated that the malonyl-CoA concentration required for 50% inhibition (I_{50}) of CPT-I in isolated skeletal muscle mitochondria is 34 nM (18). In the present study we report muscle concentrations of malonyl-CoA in the range of 200–1,500 nmol/kg in the different muscles at the end of a 2-h bout of exercise. If the CPT-I enzyme in the intact exercising muscle responds similarly to the enzyme in isolated mitochondria, it would be maximally inhibited by malonyl-CoA, even during long-term exercise. It is unclear at this time, however, whether the muscle CPT-I enzyme is exposed to the concentrations implied from total tissue content. A fraction of the total muscle malonyl-CoA may be bound to protein or located in intracellular compartments unavailable to the CPT-I enzyme. The muscle fatty acyl-CoA concentration may also be high enough during exercise to displace a significant fraction of malonyl-CoA from the enzyme. In liver, the sensitivity of CPT-I to malonyl-CoA inhibition has been reported to decrease in fasted rats (27). This may also be true of CPT-I in the muscle of exercising rats.

The significant increase in malonyl-CoA in the relatively inactive white fibers after 5 min of exercise may have been a consequence of a short-lived burst of glycolysis. The consequent rise in citrate may allow an increased rate of extramitochondrial acetyl-CoA production, thereby increasing substrate supply for the putative acetyl-CoA carboxylase. As implied from the glycogen

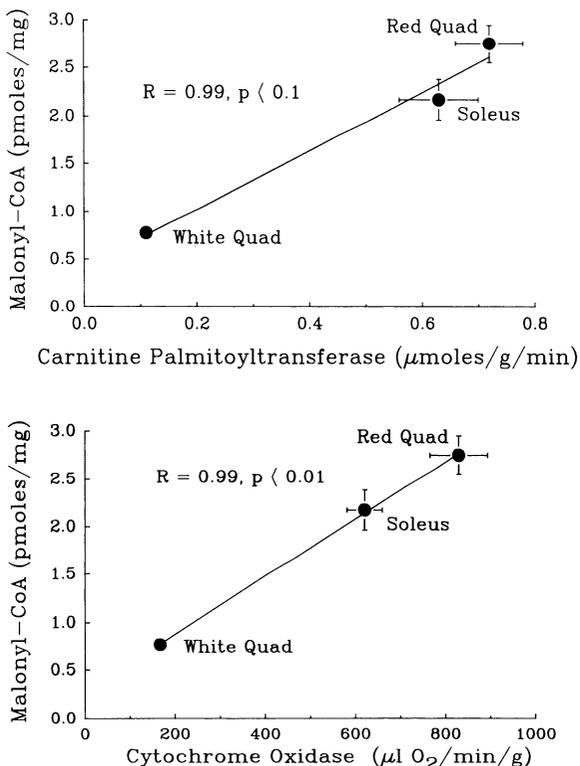


FIG. 5. Correlation between resting malonyl-CoA concentration and mitochondrial enzymes in red and white quadriceps and in soleus of rat. Values for carnitine palmitoyltransferase and cytochrome oxidase were taken from Ref. 2.

data, this burst of glycolysis also occurred in the contracting red quadriceps, but in this tissue, the elevation in free calcium may have prevented the synthesis or enhanced degradation of malonyl-CoA. In addition, citrate would more likely be metabolized in the mitochondria of active muscles, rather than diffusing into the sarcoplasm and becoming a source of acetyl-CoA for malonyl-CoA synthesis.

A striking correlation appears between glycogen content and malonyl-CoA in the red quadriceps ($r = 0.99$, $P < 0.001$) and in the gastrocnemius ($r = 0.85$, $P < 0.02$). Glycogen depletion appears to be an important factor in allowing high rates of fatty acid oxidation and ketogenesis in the liver (15). It may also be important in muscle in allowing the decline in malonyl-CoA. It should be clear from the data, however, that complete depletion of glycogen is not essential for allowing the exercise-induced decline in malonyl-CoA in muscle.

Incubation of hepatocytes in medium containing high concentrations of fatty acids causes a decrease in malonyl-CoA concentration of the hepatocytes, presumably due to direct inhibition of acetyl-CoA carboxylase by long-chain fatty acyl CoA derivatives (cf. Ref 15). In the present study, a marked decline in malonyl-CoA was observed in the red quadriceps and gastrocnemius before a significant rise in plasma FFA. Thus factors other than the increase in plasma FFA must be responsible for causing the initial decline in red quadriceps and gastrocnemius muscle malonyl-CoA.

A decline in plasma insulin concentration is considered to be important for allowing a maximal rate of hepatic ketogenesis. The well-known decrease in plasma insulin (34) could conceivably be involved in controlling malonyl-CoA concentration in muscle during exercise.

The decline in hepatic concentration of fructose 2,6-bisphosphate is considered to be an important regulatory change in inducing the decrease in malonyl-CoA in ketotic states. Fructose 2,6-bisphosphate is an allosteric activator of 1-phosphofructokinase in the glycolytic pathway (9, 10). A decrease in fructose 2,6-bisphosphate would be expected to reduce glycolytic flux and citrate synthesis, thereby decreasing availability of extramitochondrial acetyl-CoA for carboxylation to malonyl-CoA. The relationship between fructose 2,6-bisphosphate and malonyl-CoA in skeletal muscle is yet to be established. A previous report by this laboratory indicated no significant effect of 30 min of submaximal exercise on gastrocnemius muscle fructose 2,6-bisphosphate concentration (32). When the time course was examined in the present study, a significant decrease was observed early in exercise, and a significant increase was seen after 2 h of exercise in both red and white quadriceps. The increase in muscle fructose 2,6-bisphosphate late in exercise may be involved in allowing acceleration of glycolysis and lactate production as a source of gluconeogenic substrate for the liver after liver glycogen is depleted. Previous studies have indicated that the hepatic concentration of this compound is very low late in exercise after liver glycogen is depleted (34). Thus an apparent divergence in muscle and liver content of this regulator compound occurs at a time when the animal is dependent on glu-

coneogenesis for glucose production.

In summary, malonyl-CoA concentration decreases significantly in the deep red region of the quadriceps muscle after 5 min of treadmill exercise. No significant change was observed in the soleus until 20 min and in the superficial white region of the quadriceps until 30 min of exercise. This decrease in malonyl-CoA in red quadriceps occurs before any significant increase in plasma FFA. The decline in malonyl-CoA in the working muscle may be important in shifting the substrate oxidation mix from glycogen to fatty acids as the muscles continue to exercise.

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