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The dynamics of plasma free fatty acid metabolism during exercise*

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SUMMARY

Palmitic acid-1-C^{14} was given intravenously to volunteer subjects before, and toward the end of, 35–45 min of exercise. The fractional turnover rate and total turnover rates for plasma free fatty acids were greater during exercise. The concentration of free fatty acids in the plasma fell at the beginning of exercise, then rose and exceeded the resting levels. Immediately after exercise, there was a further abrupt rise and then another decline. The results indicate that exercise accelerates the efflux of plasma free fatty acids and then, secondarily, increases mobilization of free fatty acids from depots.

In recent years it has become evident that plasma free fatty acids (FFA) serve directly, along with glucose, as a major fuel for muscular contraction (1–9). Concomitants of FFA utilization by muscle are a change in concentration of plasma FFA and in turnover rate of FFA (5, 6, 9). Earlier work (6) has shown that vigorous exercise of relatively short duration (15 min) lowers the concentration of plasma FFA and that this lowering is accompanied by an increase in the turnover rate of plasma FFA. At the conclusion of exertion, the FFA concentration rises abruptly to higher than resting values. Further observations provided additional information; during more prolonged and less vigorous exercise, the initial FFA fall was less marked, and a gradual rise then took place[1] (9). Having noted that FFA might rise rather than fall under some circumstances, it became necessary to reexamine the problem of whether or not turnover rate of FFA is always increased during exercise or whether the increased turnover rate initially observed is a phenomenon that might accompany only the fall in FFA concentration with acute vigorous exercise. The purpose of the present investigation is to define more completely the kinetics of FFA mobilization during exercise and to establish the validity of the previous conclusion that exercise increases the turnover rate of plasma FFA.

METHODS

Five healthy male volunteers between the ages of 21 and 25 were selected. The subjects were permitted a low-fat, largely carbohydrate breakfast and were fasted thereafter until the completion of the procedure, which began in the early afternoon.

Indwelling arterial needles were inserted into a brachial artery and into a vein of the opposite arm. Following the needle insertions, the subjects were rested in the supine position in order to permit stabilization of plasma FFA levels. After the initial period of stabilization and with the subjects remaining at rest, arterial blood samples were drawn at 3- to 5-min intervals for determination of the concentration of plasma FFA by a modified Dole procedure (6, 10, 11). As in-

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[1] S. J. Friedberg. Unpublished observations.

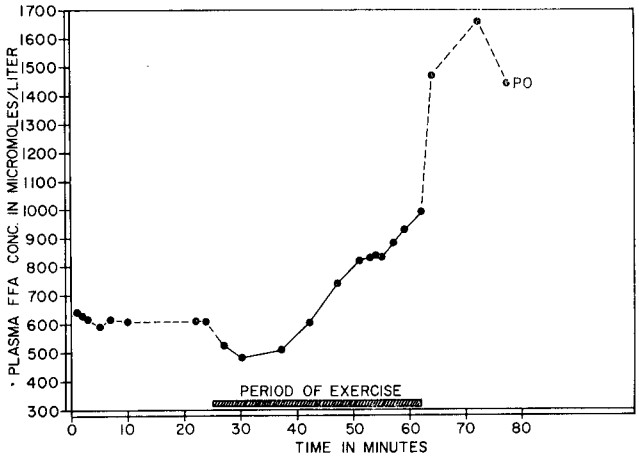

FIG. 1. Effect of exercise on concentration of plasma FFA.

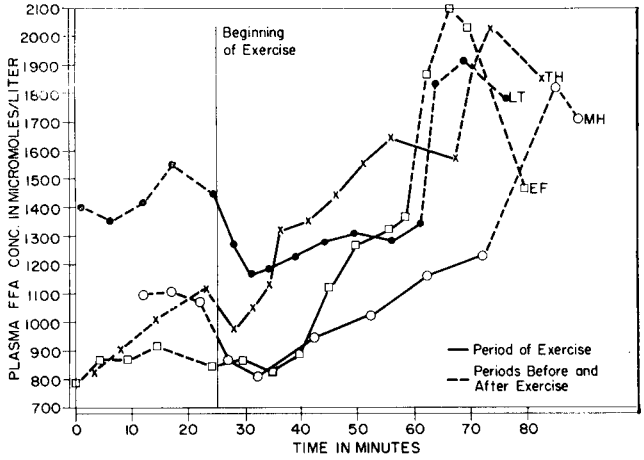

FIG. 2. Effect of exercise on concentration of plasma FFA.

dicated previously (6, 11), failure to remove lactic acid from serum obtained during exercise results in falsely elevated levels of plasma FFA. At the same time that the concentration of plasma FFA in resting subjects was being measured, 2 μc of albumin-bound palmitic acid-1-C^{14} (New England Nuclear Corp.), prepared as previously described (6), was injected rapidly through the indwelling venous needle and blood was drawn from the brachial artery at intervals of 1 min for a total period of 9 min in order to measure the rate of isotope disappearance. Radioactivity of plasma palmitic acid-1-C^{14} was determined in a liquid scintillation spectrometer as previously described (7).

Immediately following the resting period, the subjects began pedaling a stationary bicycle. The workload was held constant by maintaining a fixed resistance against the wheel and by having the subjects pedal at the rate of 72 cycles/min with the aid of a metronome. The amount of work done could not be measured, but the same resistance and rate were maintained for all subjects. These values were established initially so as to approach the maximum amount of work all participants could perform and still be able to continue exercising steadily for a period of 40–45 min. During the period of muscular work, arterial blood was drawn at intervals of 3–5 min for determination of the concentration of plasma FFA.

After 30–35 min of exercise, 2 μc of palmitic acid-1-C^{14} was again injected intravenously and arterial blood samples were again drawn every minute for 9 min to obtain another isotope-disappearance curve. Immediately prior to injection of the second dose of radiopalmitate, blood was drawn for determination of residual activity remaining from the first injection. The time of the second injection of tracer was selected to coincide with the period of maximum concentration of plasma FFA during exercise. During blood sampling, it was necessary for the subjects to stop pedaling for a few seconds for reinsertion of the inner stylette of the Cournand needle. At the conclusion of the exercise period, the subjects resumed the supine position and blood sampling was continued for 15 min for determination of the levels of plasma FFA.

RESULTS

The results of the effect of exercise on the concentration of plasma FFA are recorded in Figs. 1 and 2. During the initial period of rest, the concentration of plasma FFA remained relatively stable, except in subject TH. With the onset of exercise, there was an abrupt fall in FFA. This effect was not observed in subject EF.

Following the initial fall, plasma FFA began to rise and continued to do so throughout the period of exertion so that the eventual concentration exceeded the values at rest. In subject LT, who had a high initial resting level of FFA, this rise was slower and more gradual with the result that the FFA concentration at the end of the period of pedaling did not exceed that during the resting period. At the conclusion of exercise, there was a very abrupt rise in the FFA concentration, which began returning to lower levels after a few minutes.

As indicated in the previous section, the second injection of radiopalmitate was made during the last 10 min of exercise when, in most cases, the FFA concentration had risen to higher than resting values. Fig. 3 illustrates the disappearance from plasma of palmitic acid-1-C^{14} during rest and during exercise in the five subjects studied. Fig. 4 gives the mean curves

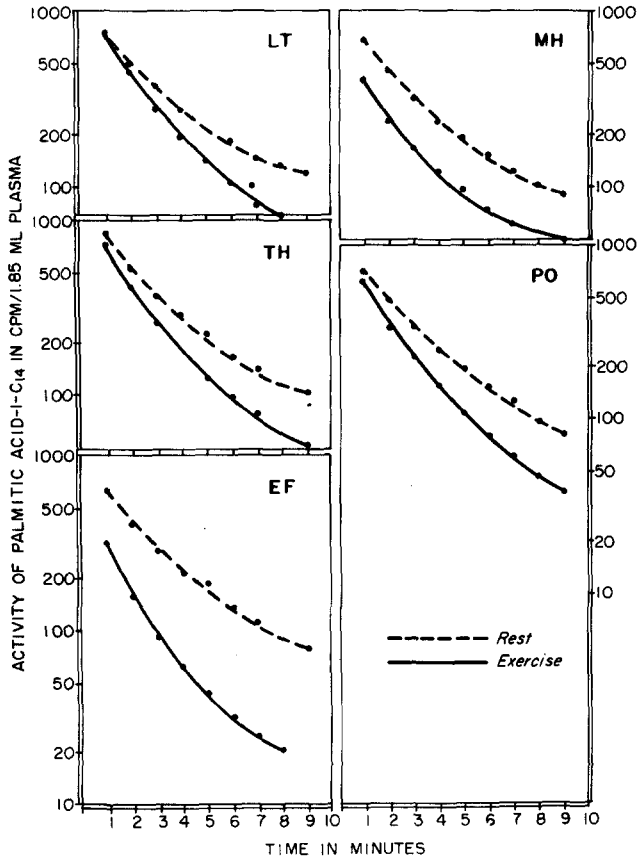

FIG. 3. Disappearance from plasma of palmitic acid-1-C^{14} during rest and exercise on five subjects.

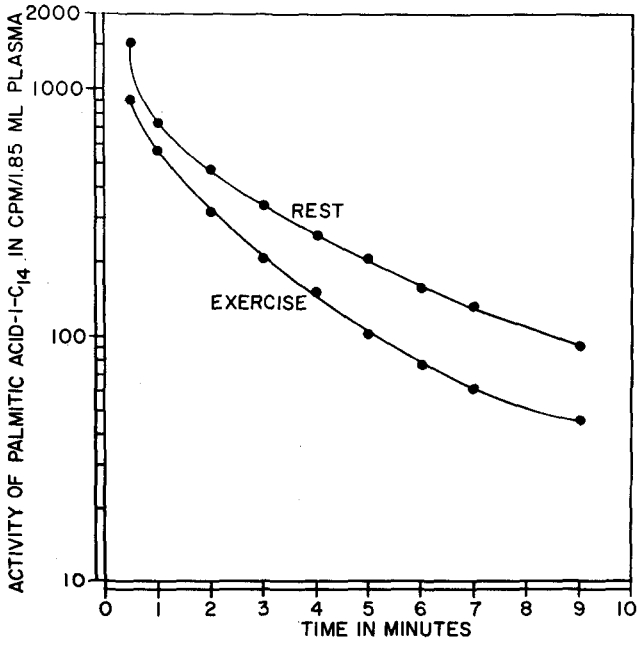

FIG. 4. Disappearance of palmitic acid-1-C^{14} during rest and exercise, from mean values of five studies.

during rest and exercise for the five studies. It can be seen that the albumin-bound radiopalmitate disappeared more rapidly during exercise than during rest.

DISCUSSION

Previous studies have shown that the initial fall in FFA concentration during exercise is accompanied by an accelerated disappearance of injected palmitic acid-1-C^{14} (6). This is interpreted to indicate that exercise accelerates the disappearance of plasma FFA—a finding that is consistent with the observation that human muscle extracts and oxidizes plasma FFA directly and that exercise markedly increases this oxidation (7, 8). Following the initial fall, and with the continuing exercise, there is a gradual rise in plasma FFA. This is interpreted to indicate that greater mobilization factors are now brought into play following, but not necessarily as a consequence of, increased utilization. The initial fall is felt to reflect the period of lag required for these new mobilization factors to become fully operative. The fact that FFA eventually rises is taken as evidence that mobilization factors now exceed those of utilization. In addition, the present study shows that accelerated disappearance of radiopalmitate is still in evidence while FFA is rising during exercise. Without the demonstration that turnover rates are increased during the phase of rising concentration of FFA, the other observations lose their significance and our previous concept of changes in FFA during exercise would not be tenable. It is clear, therefore, that utilization and fractional turnover rate of FFA continue to be increased even though mobilization factors have now made available increasing amounts of FFA. Immediately following cessation of exercise, there is an abrupt rise of plasma FFA—an event that fits the concept that increased utilization by muscle comes to an abrupt end and that mobilization factors again lag in re-establishing a new steady state. One should note particularly that the post-exercise rise is almost complete by the end of 3 min, an observation not made in our earlier studies. A more gradual post-exercise rise, on the other hand, would not fit this concept because of the known rapid flux of plasma FFA. As these mobilization factors are also reduced, the concentration of plasma FFA once again begins to decline toward the resting levels.

In interpreting the results of the present study, it is appropriate to consider the magnitude of the fractional turnover rates of plasma FFA during rest and during exercise. For the present purpose, only a qualitative statement of these values is necessary. Although a reasonable approximation of fractional turnover is

possible, the lack of linearity of the disappearance curves of palmitic acid-1-C^{14}, particularly during exercise, does not permit an accurate calculation. These problems have been pointed out in previous studies (4, 6), and are discussed below. In the present investigation, however, there can be little doubt that turnover rates of FFA during exercise are faster since both the concentration of plasma FFA and fractional turnover rate are increased.

Table 1 gives estimates of the fractional turnover rates in five studies during rest and during exercise calculated during both the second and third minutes. The difference between the resting and exercise curves is significant to less than the 0.01 level for the second minute, and to less than the 0.02 level for the third minute.

In dealing with disappearance curves in which transfer rates are known to be first order, and in which the curves are complicated by recirculation of label or the presence of more than one rate constant, the tangent to the steepest or earliest portion of such a curve will most closely represent the most rapid rate constant; i.e., the rate constant of transfer from the injected space. In the present problem, the earliest portion of the curves are obscured by the time required for intravascular mixing (12). Since the cardiac output during exercise may increase as much as 30-fold, intravascular mixing is probably complete before the end of the first minute. There is considerable justification in the assumption that the approximated rate constant determined from activities at 1 and 2 min is more realistic in this instance. This may not be so in the case of resting, when mixing may not be complete during this interval. In support of this interpretation, it can be seen that the slope is steepest during the second minute, at which time the concentration of radioactivity is lower than it is during rest.

The meaning of changes in concentration of plasma FFA and turnover rates of FFA with exercise must be considered in connection with the influence of concomitant circulatory changes. Alteration in blood volume during exercise would not be expected to produce changes in FFA concentration of the magnitude or direction observed in these studies. Ebert and Stead (13) found that exercise failed to mobilize any blood reserves in normal man and that, instead, there was a fall in plasma volume ranging from 220 to 590 ml during a period of strenuous exercise lasting 3–5 min. In our studies, a fall in FFA concentration was observed initially. If changes in FFA concentration had been the result of a loss of water from plasma as indicated by the rise in concentration of serum protein observed by Ebert and Stead, the result would have been an increase in FFA concentration. It is apparent, therefore, that the known changes in plasma volume during exercise would reduce the observed fall in FFA concentration during acute exercise and that the true FFA fall would be greater than that measured. It is also extremely unlikely that subsequent rise in FFA levels could be the result of a more gradual decrease in plasma volume. It is immediately apparent from examination of Fig. 1 that the changes in FFA concentration are of a magnitude incompatible with alterations in plasma volume.

TABLE 1. Calculated Fractional Disappearance Rates (K) of Plasma FFA During Rest and Exercise and Data Used for Calculations

Subject		Radioactivity 1 Min	Radioactivity 2 Min	Radioactivity 3 Min	K for 1–2 Min	K for 2–3 Min
		cpm/1.85 ml plasma			*mEq FFA/min*	
LT	Rest	750	500	375	0.405	0.263
	Ex.	750	450	275	0.511	0.491
TH	Rest	848	527	370	0.474	0.355
	Ex.	727	415	260	0.557	0.468
EF	Rest	650	414	290	0.449	0.355
	Ex.	323	160	93	0.700	0.541
MH	Rest	670	451	315	0.394	0.357
	Ex.	400	235	150	0.530	0.396
PO	Rest	694	487	333	0.349	0.378
	Ex.	619	333	226	0.617	0.387
Mean	Rest	722	476	337	0.414	0.343
	Ex.	564	319	201	0.583	0.462

The changes in distribution of blood volume, with a shift toward the exercising muscles and with extensive vascular dilation in these muscles, are well known. It is pertinent, however, to inquire about the effect that such vascular shunting might have on the concentration of FFA. In this connection, the changes in plasma concentrations of glucose (14, 15), triglycerides (6), and lactic acid (16) during exercise have been examined and in no way resemble the changes in FFA. Likewise, the behavior of injected materials such as Evans blue dye (12) or I^{131} albumin (17), which are only slowly removed from the vascular compartment, cannot be compared with the behavior of injected radiopalmitate.

Finally, it is pertinent to inquire into the factors that might be responsible for increased FFA mobilization from fat depots during increased muscular activity. At present, one can only speculate about these influences. The lag in mobilization of FFA suggests that a humoral rather than a nervous mechanism might be involved in releasing FFA from depots. Epinephrine and norepinephrine might, of course, play a role. These potent FFA mobilizers are known to be secreted in increased amounts during exercise (18). The increased uptake

might be due exclusively to the opening up of a greater endothelial surface made available by widespread capillary dilatation in exercising muscle and by the attendant increase in flow.

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