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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The effects of one 45 minute bout of high intensity eccentric exercise (250 Watts) were studied in 4 male runners and 5 untrained men. Plasma creatine kinase (CK) activity in these runners was higher ($p < 0.001$) than in the untrained men before exercise and peaked at 207 IU/ml one day after exercise, while in untrained men the maximum was 2143 IU/ml five days after exercise. Plasma interleukin-1 (IL-1) in the trained men was also higher ($p < 0.001$) than in the untrained men before exercise but did not significantly increase after

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exercise. In the untrained men, IL-1 was significantly elevated 3 hours after exercise ($p < 0.001$). In the untrained group only, 24-hour urines were collected before and after exercise while the men consumed a meat-free diet. Urinary 3-methyl-histidine/creatinine in the untrained group rose significantly from 126 umol/g before exercise to 180 umol/g ten days after exercise. The results suggest that in untrained men, eccentric exercise leads to a metabolic response indicative of delayed muscle damage. Regularly performed long distance running was associated with chronically elevated plasma IL-1 levels and serum CK activities without acute increases after an eccentric exercise bout.

HUMAN RESEARCH

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

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METABOLIC CHANGES FOLLOWING ECCENTRIC EXERCISE IN TRAINED AND UNTRAINED MEN

W.J. Evans[1], C.N. Meredith[1], J.G. Cannon[2], C.A. Dinarello[2], W.R. Frontera[1]
V.A. Hughes[1], B.H. Jones[3] and H.G. Knuttgen[3]

[1]USDA Human Nutrition Research Center on Aging
Tufts University
711 Washington Street
Boston, MA 02111

[2]Department of Medicine
Tufts University
136 Harrison Avenue
Boston, MA 02111

[3]U.S. Army Research Institute of Environmental Medicine
Natick, MA 01760

Address Correspondence to: W.J. Evans, Ph.D., Chief
Physiology Laboratory
USDA Human Nutrition Research
Center on Aging
Tufts University
711 Washington Street
Boston, MA 02111
(617) 956-0333

Running Head: Eccentric Exercise in Trained and Untrained Men

Abstract

The effects of one 45 minute bout of high intensity eccentric exercise (250 Watts) were studied in 4 male runners and 5 untrained men. Plasma creatine kinase (CK) activity in these runners was higher ($p < 0.001$) than in the untrained men before exercise and peaked at 207 IU/ml one day after exercise, while in untrained men the maximum was 2143 IU/ml five days after exercise. Plasma interleukin-1 (IL-1) in the trained men was also higher ($p < 0.001$) than in the untrained men before exercise but did not significantly increase after exercise. In the untrained men, IL-1 was significantly elevated 3 hours after exercise ($p < 0.001$). In the the untrained group only, 24-hour urines were collected before and after exercise while the men consumed a meat-free diet. Urinary 3-methyl-histidine/creatinine in the untrained group rose significantly from 127 umol/g before exercise to 180 umol/g ten days after exercise. The results suggest that in untrained men, eccentric exercise leads to a metabolic response indicative of delayed muscle damage. Regularly performed long distance running was associated with chronically elevated plasma IL-1 levels and serum CK activities without acute increases after an eccentric exercise bout.

Index Words: Eccentric exercise, interleukin-1, 3-methyl-histidine, creatine kinase, training.

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Introduction

All forms of exercise to which an individual is unaccustomed can cause delayed muscle soreness. This soreness, which appears 24 to 48 hours after strenuous exercise, has been associated with the eccentric component of muscular contractions (1,11,18). Following high intensity eccentric exercise, disturbances of the cross-striated band pattern with disruptions of the z-disks have been observed in human skeletal muscle (18,19,27). The myofibrillar damage is greater three days after the eccentric exercise than immediately after exercise, indicating that the degradation of contractile units is a delayed event (18,19). In rats subjected to downhill running, the histological damage found in muscles coincides with increased plasma levels of intracellular enzymes, such as creatine kinase (CK). This suggests that the elevation in plasma CK levels resulting from eccentric exercise may be an indirect measure of increased skeletal muscle cell permeability due to damage (3,4).

Additional indirect evidence for muscle damage following exercise in humans is the increase in urinary 3-methyl-histidine excretion (15). This amino acid is released principally from the breakdown of actomyosin, and although there are non-skeletal muscle pools of actomyosin that probably turn over at a faster rate, it is likely that the source of increased 3-methyl-histidine following exercise is skeletal muscle (15).

The chemical mediators for increased breakdown of muscle and connective tissues after eccentric exercise have not been identified. Interleukin-1 (IL-1), a protein secreted by phagocytic cells (8); IL-1 stimulates muscle proteolysis *in vitro* (5) via prostaglandin E_2-mediated increases in lysosome function (30). IL-1 activity increases in human plasma following submaximal exercise (8) and may be one of the adaptive responses that modulates protein turnover during recovery from exercise.

Delayed muscle soreness is much more apparent in untrained subjects that in persons accustomed to regular exercise (18). The purpose of this study was to examine the effects of a bout of high intensity eccentric exercise on plasma CK activity and IL-1 levels, in sedentary men and in endurance trained runners, to determine whether previous training changed the metabolic response to eccentric exercise. In addition, urinary 3-methyl-histidine excretion was measured in the untrained men, as an indirect index of the rate of actomyosin breakdown.

Methods

Five untrained men (VO_2 max 42 $\pm$ 3 ml. kg^{-1} . min^{-1}) and four highly trained endurance runners (VO_2 max 66 $\pm$ 5 ml . kg^{-1} . min^{-1}) volunteered for this study.

The study design was explained to all subjects and informed consent was obtained. The experiment was approved by the Tufts University Human Investigation Review committee and Human Use Review Committee of the U.S. Army Research Institute of Environmental Medicine.

All of the subjects exercised on a cycle ergometer designed for eccentric leg exercise (24), at an intensity of 250 Watts for 45 minutes. The untrained subjects were asked to remain inactive for seven days prior to and fourteen days after the exercise. The trained subjects remained inactive for only two days prior to and two days after eccentric exercise, to avoid the metabolic changes associated with detraining (10.

The 5 untrained men were told that they could consume as many calories from non-meat sources as they pleased. They were also instructed by a registered dietition what food to eat to insure an adequate protein intake diet while collecting 24-hour urines during the 3 week period of the study. Urines were not collected on the trained subjects.

Samples: The 24-hour urines from the untrained men were collected throughout the study and aliquots were frozen at -20° until analysis. Venous blood samples were obtained for CK activity and IL-1 analysis on the day of exercise, at times immediately before (pre-exercise), immediately after, 3 hours after and 24 hours after exercise. Blood samples collected 2,3,4,6,8,10 and 14 days after the exercise bout were analyzed for CK activity. Plasma samples were frozen at -20° until analysis.

Analyses: CK activity was measured spectrophotometrically (Sigma Kit N° 45-UV). IL-1 activity was measured by the ability of Sephadex G-50 chromatographed plasma fractions to increase thymocyte proliferation and results were expressed as percent of basal thymocyte proliferation (7). Urinary 3-methyl-histidine was measured by HPLC (36) and urinary creatinine by colorimetric methods (17).

Statistical analysis: Results are presented as mean and standard error of the mean. Differences between trained and untrained men were assessed by analysis of variance.

Results

The VO_2 of the subjects during the eccentric exercise (250 watts) did not differ between the two groups (VO_2 = 1.17 L . min^{-1} or 17.6 ml . Kg^{-1} .min^{-1}). This represented 42% VO_2 max in the untrained men and 27% VO_2 max in the runners. While no objective measurement of muscle soreness was made, it was clear that the eccentric exercise bout produced extreme muscle soreness in the untrained men, limiting their mobility for one to two days. However, the distance runners experienced only mild soreness that did not affect their locomotion.

The patterns of change in plasma CK activities between the trained and the untrained men were strikingly different (Figure 1). When compared to the untrained men, pre-exercise CK levels were significantly higher ($p < 0.001$) in the runners. In the untrained men, mean total CK activities were significantly increased ($p < 0.01$) three hours after exercise and increased progressively for 5 days afterwards, reaching a peak value that was 33 times greater than the baseline level. Plasma CK activities in the untrained men did not return to baseline until 9 days after the eccentric exercise bout. In the trained men, however, the increase in plasma CK activities was significant only at 24 hours after the exercise bout, reaching a maximum value 2.3 times greater than the pre-exercise level. Plasma CK levels returned to pre-exercise values before the trained men resumed normal running activity 2 days after the eccentric exercise bout.

Urinary 3-methyl-histidine/creatinine ratios, measured in the untrained men only, are shown in Figure 2. The ratio rose progressively for 10 days after exercise and was significantly higher than baseline level on days 10, 11 and 12 after exercise. The 3-methyl-histidine/creatinine ratio for days 13 and 14 was not different from the value on day 0.

Plasma IL-1 activities immediately after and 24 hours after exercise were not significantly different from baseline values, in either group. Figure 3 shows the individual values for IL-1 obtained at baseline and at 3 hours after exercise, in the trained and untrained men. All 5 of the untrained men showed an increase in IL-1 3 hours after exercise ($p < 0.001$), while only 1 of the 4 trained men showed a post-exercise increase. In the trained men, baseline IL-1 levels were significantly higher ($p < 0.001$) than in the untrained men.

Discussion

Intense muscle soreness and impaired locomotion were found one and two days after the eccentric exercise only in the untrained men. The physiological reasons for this are not clear, as the absolute exercise intensity was the same for all subjects. The differences in soreness may be related to different degrees of muscle damage. Friden (18) has shown that eccentrically trained subjects experience little muscle damage when subjected to high intensity eccentric exercise. The substantial eccentric component involved in long distance running seems to produce a similar effect. Schwane and Armstrong (31) reported that training rats by uphill, level or downhill treadmill running effectively eliminated increase in plasma CK activity due to downhill running. They also concluded that the eccentric component of running produced the training effect.

Exercise-induced increases in plasma activities of enzymes found in skeletal muscle have been attributed to skeletal muscle damage (9). However, this association has not been proven. Nevertheless, the delayed increase in plasma CK following eccentric exercise in animals or humans has been shown to coincide with ultrastructural changes in muscle (3,26,27). The differential effects of the exercise on the two groups were more clearly demonstrated in the changes in plasma CK activities. The higher pre-exercise CK activities found in the trained men are consistent with resting values reported for endurance runners before competition (2). After the exercise, the runners demonstrated only small increases in plasma CK activities 24 hours post-exercise, while all of the other samples were not significantly different from baseline. Schwane and co-workers (32) found a similar pattern of CK release after downhill running in moderately trained men. In the untrained subjects, on the other hand, the eccentric exercise resulted in extreme changes

in plasma CK activity that did not return to pre-exercise levels for ten days. The fact that plasma CK activity continued to rise for five days may indicate continued skeletal muscle cell leakage following a single bout of eccentric exercise. It is also interesting to note that the CK activities in these subjects remained significantly elevated well after the occurrence of peak muscle soreness (48 hours post-exercise). The magnitude and duration of the CK release was significantly greater than the responses typically observed following concentric exercise (2,23,34). Newham and co-workers (26) examined plasma CK activity following stepping exercise and also found a large delayed increase in some of his subjects, peaking at five days, while other subjects, performing the same exercise, had a much smaller increase, peaking 24 to 48 hours after exercise. The differences may have been dut to the fitness level or previous exercise history of their subjects which were not reported.

Elevated plasma IL-1 levels have previously been demonstrated following a single bout of concentric exercise in both sedentary and moderately trained men and women (8). The high pre-exercise IL-1 levels in the runners of this study suggest that repeated bouts of endurance exercise chronically elevated IL-1. The runners refrained from strenuous physical activity for 48 hours prior to the eccentric exercise bout, which in the case of untrained sujbects, was sufficient time for exercise-induced IL-1 activities to return to normal. It is impossible to know if the elevated IL-1 levels in the runners was a result of training or of their previous exercise session.

Elevated IL-1 activity may account for several responses which have been observed following high intensity exercise or training (21,21,25, 35). These responses are similar in kind to the so called "acute phase" response to infection. The IL-1 responses to exercise and those found in febrile patients are similar (6). However, the acute phase responses observed after exercise

are much smaller than those associated with infection. Since IL-1 stimulates muscle proteolysis in vitro (5), elevated plasma IL-1 may represent an adaptive response which modulates muscle protein turnover during recovery from exercise. IL-1 influences muscle protein metabolism in several ways. It accelerates muscle proteolysis by promoting the generation of prostaglandin E_2 which in turn increases lysosome function (14,30). IL-1 has been demonstrated to stimulate insulin secretion (20). IL-1 also stimulates fibroblast proliferation (37), collagenase production and osteoclast activity (13) and thus may be of importance in the homeostasis of several aspects of the musculo-skeletal system. Although IL-1 is rapidly cleared from the circulation, it has been shown to initiate changes in cellular metabolism that do not require its continued presence (13).

Dohm and co-workers recently reported an exercise-induced increase in urinary 3-methyl-histidine levels in both trained and untrained subjects following exercise (15). They also reported increased resting urinary 3-methyl-histidine levels, indicating increased actomyosin turnover, in trained when compared to untrained subjects. Their findings of chronically increased actomyosin turnover may be related to the chronic mild muscle damage induced by the eccentric exercise component of running and jumping. A possible mediator for increased actomyosin turnover could be the elevated baseline IL-1 levels seen in the runners in the present study which is known to accelerate muscle proteolysis. Other investigators have examined urinary 3-methyl-histidine levels in response to exercise and have found either no change (17,29) or small increases (15,16,33). However, these results were based on shorter periods of observation following less severe exercise intensities. In the present study, the urinary 3-methyl-histidine/creatinine ratio showed a delayed increase, urinary losses were not significantly

different from pre-exercise values until nine days post-exercise. These data are in support of investigations examining ultrastructural changes in skeletal muscle following eccentric exercise (18,27). These studies have found a characteristic pattern of damage, with biopsies taken two to five days after the exercise displaying significantly more cellular disruption than biopsies taken immediately after exercise. A recent study indicates that lengthening contractions result in greater injury to skeletal muscle fibers than isometric or shortening contractions (28). An increasing amount of fiber degeneration and infiltration of macrophages peaking three days after muscle contraction was also shown (28). This is consistent with the results of Vihko and co-workers (35) showing an increase in lysosomal enzyme activity following exhaustive exercise, with peak activity seen three to four days post-exercise.

In summary, a sequence of events following eccentric exercise was observed in untrained men which included an immediate increase in the proteolysis-inducing factor, IL-1, a later increase in CK, and a greatly delayed increase in urinary 3-methyl-histidine. These changes are likely due to skeletal muscle damage which results in a delayed increase in skeletal muscle protein breakdown as suggested by the increased urinary 3-methyl-histidine/creatinine ratio. These responses were attenuated or absent in the trained runners. The biochemical mediators, and the physiological reasons for the minimal effects found in the trained runners remain to be explored.

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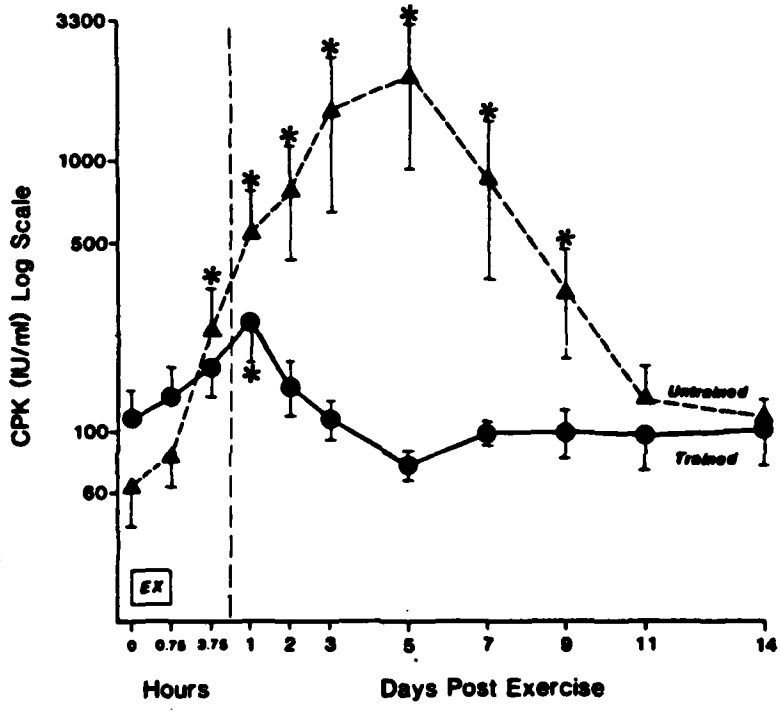
Figure Legends

Figure 1. Plasma CK activities following 45 minutes of eccentric exercise. In the runners, activities were significantly different ($p<0.01$) from pre-exercise levels 24 hours after exercise only. In the untrained men, CK activities were significantly greater than the pre-exercise value 3 hours post exercise and remained elevated for nine days after exercise. Pre-exercise CK levels were significantly higher in the runners. * Indicates difference ($p<0.05$) from pre-exercise mean.

Figure 2. Urinary 3-methyl-histidine levels (expressed per gram creatinine) in the untrained men. The levels rose progressively after the eccentric exercise and were significantly different ($p<0.05$) from pre-exercise on days 10, 11 and 12 post exercise.

Figure 3. Interleukin-1 activity as percent change from control thymocyte cultures (7) pre and 3 hours post eccentric exercise in each of the trained and untrained men. The untrained men demonstrated a significant ($p<0.007$) elevation in plasma IL-1 activity 3 hours post exercise while the runners showed no consistent change. The pre-exercise IL-1 levels of the runners were higher ($p<0.001$) than those of the untrained men.


3300
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CPK (IU/ml) Log Scale
Untrained
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0.75
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1
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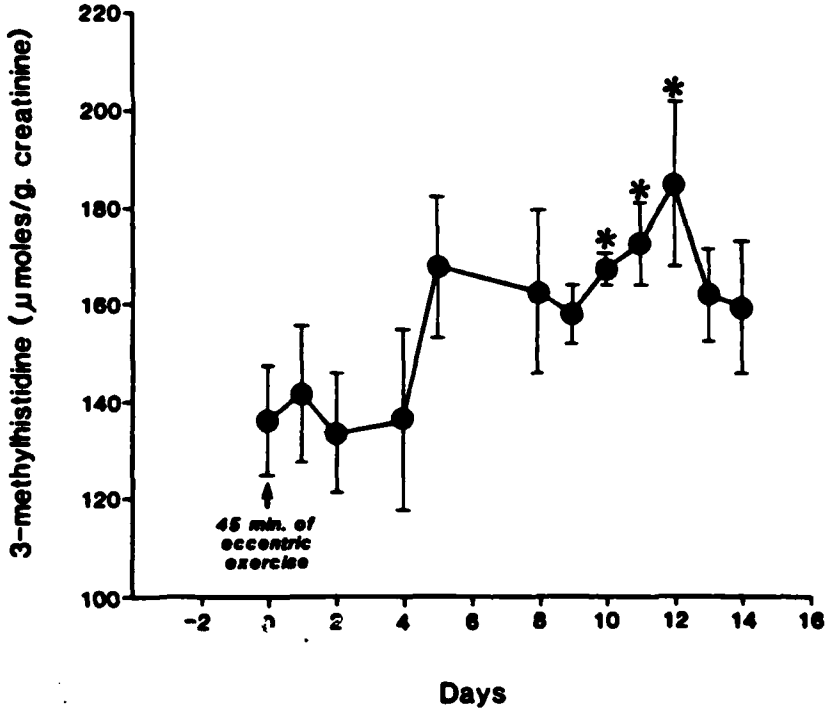
11
14
Hours
Days Post Exercise

Figure 1


3-methylhistidine (μmoles/g. creatinine)
220
200
180
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6
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14
16
Days

Figure 2

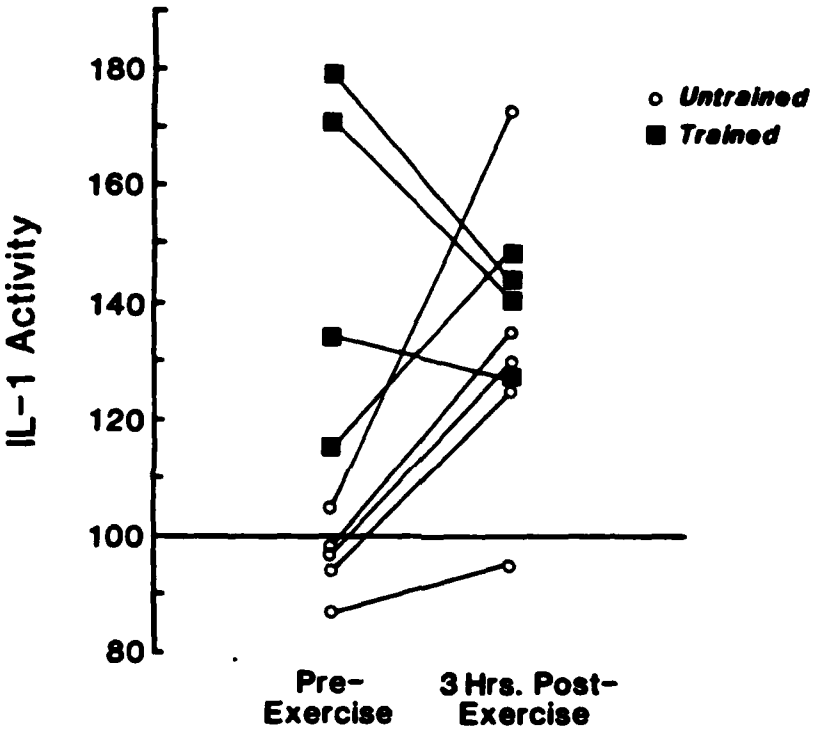

Figure 3

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