Urate uptake and lowered ATP levels in human muscle after high-intensity intermittent exercise

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Hellsten, Y., B. Sjödin, E. A. Richter, and J. Bangsbo. Urate uptake and lowered ATP levels in human muscle after high-intensity intermittent exercise. Am. J. Physiol. 274 (Endocrinol. Metab. 37): E600–E606, 1998.—The exchange of purines in exercised and rested muscle and their relation to muscle ATP levels after intense intermittent exercise were investigated. Seven subjects performed one-legged knee extensor exercise on the following two occasions: without (control; C) and with (high purines; HP) additional arm exercise. There was a greater net release of hypoxanthine by the exercised muscle during the recovery period in HP compared with C (185 ± 44 vs. 101 ± 30 [SE] µmol/kg muscle; P < 0.05). During recovery, the arterial urate concentration was higher in HP compared with C (peak: 585 ± 48 vs. 355 ± 20 µmol/l; P < 0.05). The exercised but not the rested muscle extracted a marked amount of urate (330 µmol/kg muscle) from plasma in the HP trial. Muscle ATP levels after 90 min of recovery in HP were lower than at rest (24.3 ± 0.6 vs. 20.1 ± 1.1 mmol/kg dry wt). The present data suggest that a single session of long-term high-intensity intermittent exercise causes a significant release of purines from the muscle into blood, which contributes to a sustained lowered level of the muscle ATP concentration. Furthermore, intensely exercised muscle extracts urate when plasma urate is elevated, an event that may be of importance for the replenishment of oxidized muscle urate stores.

hypoxanthine; adenine nucleotides; antioxidant; adenosine 5’-triphosphate

DURING EXERCISE of high intensity, adenine nucleotides in muscle are degraded with the consequent formation and intracellular accumulation of IMP. A fraction of IMP produced is further degraded to nucleotide bases that are released into the bloodstream mainly as hypoxanthine (9). The release of hypoxanthine from intensely exercised muscle has been calculated to amount to a low percentage of the net IMP accumulation (3), representing a seemingly negligible loss of nucleotides that rapidly could be restored via purine salvage or de novo synthesis. In accordance, studies have shown that the muscle adenine nucleotide concentration returns to preexercise levels within minutes after a single intense exercise session of short duration (17). Nevertheless, two recent investigations have demonstrated that intense exercise performed regularly over one to several weeks can lead to around a 20% decrease in the resting levels of muscle adenine nucleotides, of which at least a part has been attributed to a repeated loss of purines from the muscle (11, 20). These findings suggest that the determining factor for the extent of purine release from muscle may be the repetition of intense exercise. The magnitude of purine release from muscle after one session of repeated intense exercise and its possible effect on muscle ATP levels has, however, not been examined.

The elevations in plasma hypoxanthine after intense exercise have a direct implication on plasma urate levels as the liver oxidizes hypoxanthine to urate and releases it into the bloodstream at a rate proportional to the increase in plasma hypoxanthine (9). The release of purines from muscle and the consequent large formation of urate during and after intense exercise could be considered wasteful, as it represents a loss of useful nucleotide precursors. However, urate may be of importance in protecting tissues against reactive oxygen species (4). In a recent study, we found a decrease in muscle urate during intense exercise and a parallel increase in the urate oxidation product allantoin, probably formed by the presence of free radicals in the muscle (7). As the human muscle cells cannot produce urate, the replenishment of oxidized intramuscular urate stores may occur via uptake of urate from plasma by the muscle. In one study, we observed an uptake of urate by muscle after short-term cycling exercise followed by a period of ischemia (9), whereas, in another study in which subjects performed one-legged knee extensor exercise, no urate uptake was found by muscle after exercise (3). The plasma urate concentration in these two studies differed markedly due to the difference in muscle mass involved in the exercise. One possibility is that uptake of urate by muscle is dependent on the concentration of plasma urate. It is therefore of interest to know whether uptake of urate by muscle after exercise is determined by an elevation in plasma urate.

The present study examined hypoxanthine and urate exchange in the rested and exercised muscle, as well as the consequence of purine release for muscle ATP levels, after one intense intermittent exercise session. Subjects performed one-legged exercise without and combined with two-arm exercise to allow for the examination of the effect of plasma hypoxanthine, urate, and hormonal levels on the exchange of hypoxanthine and urate by muscle.

METHODS

Subjects

Seven, healthy male subjects ranging in age from 19 to 28 yr with an average height of 178 (range: 173–185) cm and an average weight of 69.3 (63.1–78.2) kg volunteered to participate in the experiment. The subjects participated regularly in physical activity but were not competitive. The maximum oxygen uptake of the subjects was 4.26 (3.72–4.93) l/min. The
subjects were fully informed of any risks and discomforts associated with the experimental procedures before giving their informed consent to participate. The study was approved by the local ethics committee.

Procedures

Subjects performed one-legged exercise in the supine position on an ergometer that permitted the exercise to be confined to the quadriceps muscle (1). They also performed arm cranking in an upright position. The subjects practiced the exercise on more than four separate occasions, and, in the final preexperiment, the subjects completed the entire protocol for the experiments except for the invasive procedures.

Protocol

About 3 h before an experiment, the subjects had a light breakfast consisting of a few slices of bread with marmalade and 300–500 ml of juice. The subjects reported to the laboratory 2 h before the experiment. After 30 min of rest in the supine position, a catheter was placed in the femoral artery of the experimental leg under local anesthesia. The tip was positioned 1–2 cm proximal to the inguinal ligament. A catheter was also placed in the femoral vein of the experimental and the rested leg, with the tip of the catheter positioned ~1–2 cm distal to the inguinal ligament. A thermistor for measurement of blood temperature was inserted through the femoral venous catheter and was advanced 8–10 cm proximal to the tip.

The exercise and tissue sampling protocol is shown in Fig. 1. After the placement of the catheters, the subjects rested in the supine position for ~1 h. Then, the subjects performed intense intermittent one-legged knee extensor exercise for ~100 min. The exercise was performed on two occasions separated by 7–14 days. On one occasion (high purine, HP), intense arm exercise was performed between the leg exercise bouts to raise the blood purine and catecholamine concentrations, and, on the other occasion, no arm exercise was performed (control, C). The same leg was exercising in the C as in the HP experiment, and the order of the two experiments was randomized. The intermittent leg exercise consisted of a 10-min warm-up period with the experimental leg at an intensity of 10 W followed by a 33-min rest period. Then the subjects performed an exhaustive exercise bout [power output: 61.4 ± 3.7 (SE) W; exercise duration: 4.67 ± 0.55 (C) and 3.46 ± 0.28 (HP) min]. After 4.5 min of rest, the subjects then exercised at an intensity of 61.4 ± 3.7 W for 1 min and, after another 2 min of rest, at an intensity of 36.8 ± 2.2 W for 5 min. After five such periods with 1 and 5 min of exercise, the subjects exercised the leg at an intensity of 61.4 ± 3.7 W for 2.5 min. The kicking frequency during the exercise was 60 revolutions per minute. In HP, the subjects also performed arm cranking at an upright position at an intensity of 137 ± 3 W (frequency: 60 cranks/min) in between the leg exercise.

In each condition (C and HP), muscle biopsies were obtained from muscle vastus lateralis of the exercising leg before and immediately after the long-term intermittent exercise as well as after 5, 30, and 90 min of recovery. For the exercising leg, blood samples of 3–4 ml volume were drawn simultaneously from the femoral artery and vein at rest, at the end of the long-term intermittent exercise, and at 1, 2.5, 3.5, 5, 8, 10, 15, 20, 30, 45, 60, 75, and 90 min of recovery. Blood from the femoral vein of the rested leg was drawn before and at the end of exercise and at 5, 10, 20, 30, 45, and 60 min after exercise. Blood flow was measured immediately before blood sampling in the exercising leg. An occlusion cuff placed just below the knee was inflated (220 mmHg) during blood sampling and blood flow measurements.

Measurements and Analysis

Blood flow. Femoral venous blood flow was measured by the thermodilution technique (2). Briefly, ice-cold saline was infused at a constant rate into the femoral vein for 10–15 s to achieve changes in blood temperature of 0.8–1.0°C. At rest and in late recovery, when the blood flow was low, a 30- to 45-s infusion period was used (16).

Blood analysis. A part of each blood sample was centrifuged rapidly, and the plasma was collected and stored at −20°C until analyzed.

Muscle mass. The mass of quadriceps femoris muscles was estimated based on Simpson's rule, which included measurements of thigh length, multiple circumferences of the thigh, and the skin fold thickness (13). The mean knee extensor mass of the experimental leg was 3.0 kg, with a range of 2.7–3.4 kg.

Muscle biopsies. Muscle biopsy samples were analyzed for total water by weighing the samples before and after freeze drying. Changes in muscle variables were calculated on dry weight basis and normalized to the water content of resting muscle. This enables a comparison of quadriceps muscle metabolite concentrations and the magnitude of exchange of metabolites between muscle and blood. Muscle ATP and IMP concentrations were determined on five of the subjects by a method for HPLC (23), modified as previously described (10). Hematocrit determinations were made in triplicate using microcentrifugation.

Calculations

Leg substrate exchange. Net purine exchange in the thigh was calculated by multiplying the blood flow by the difference between femoral artery and femoral venous concentrations of the variables. For each individual, leg blood flow of the active leg at each time point was determined as the average of the

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Fig. 1. Schematic representation of the experimental protocol.
measurements obtained in C and HP. This appears valid, as the average differences of the measurements obtained in C and in HP were <0.5 and 0.3 l/min in the first and the late phase of recovery, respectively, and no systematic differences were observed. A continuous blood flow curve was constructed for each subject by linear connection of the consecutive data points to obtain time-matched values for the blood flow measurements. No difference between "time-matched" and measured blood flow was larger than 0.3 l/min during early recovery, whereas the difference was <0.1 l/min in late recovery.

Total exchange of substrates. The total exchange of purines during the first 5 min the next 25 min or the last 60 min of recovery are given by the time integral

$$\int_{x}^{y} f(t) \, dt$$

where x is 0, 5, or 30 min, y is 5, 30, or 90 min, and f(t) is exchange of one of the variables at a given time (t) during recovery. In practice, the exchange was determined as the area under the f(t) curve, with time on the x-axis. The curves are produced on the assumption that there was a linear relationship between two measured values.

Comments to methods. In the present experiment, plasma purines rather than whole blood purines were determined. Thus, to estimate the exchange of hypoxanthine over the legs, hypoxanthine was measured in plasma and whole blood of three subjects performing bouts of 2 min intense cycling interspersed by 15 min of rest. Blood samples were collected from an arm vein before and on several occasions after each cycling bout. Blood samples were divided into two of which one part was immediately extracted with 0.8 M perchloric acid and placed on ice and the other fraction was immediately centrifuged for 60 s at 10,000 rpm in a Dich centrifuge (Ole Dich instrument makers), plasma was separated from the erythrocytes, and each fraction was immediately extracted. Hematocrit was determined on all original blood samples, and hemoglobin was determined on the whole blood samples. Hypoxanthine concentration was determined on extracts of whole blood and plasma, neutralized with 1.5 M KOH. The erythrocyte hypoxanthine concentration was estimated by subtracting the plasma hypoxanthine concentration from the whole blood concentration, taking into account the hematocrit value.

Figure 2 shows that the distribution of hypoxanthine in plasma versus erythrocytes was similar over a range from 2 to 60 µmol/l. The curve equation was $$y = 1.003x - 1.203$$, and the correlation between the concentration of hypoxanthine in plasma versus erythrocytes was $$r^2 = 0.898$$ ($$P < 0.001$$). These results suggest that plasma values of hypoxanthine can be used to represent whole blood values.

Statistics. The data from C and HP were compared by two-way analysis of variance with repeated measures, and the Newman-Keuls test was used to locate differences. Differences between the recovery and the resting values or nil were determined by paired t-tests. Pearson's product moment correlation ($$r$$) was used to assess the distribution of hypoxanthine in blood and the relationship between urate exchange and catecholamine levels. The significance level was set at $$P < 0.05$$.

RESULTS

Blood Flow

Leg blood flow was 0.44 ± 0.03 l/min at rest, 4.03 ± 0.39 l/min at the end of the exercise session, and 2.59 ± 0.31, 1.59 ± 0.22, 1.12 ± 0.09, 0.94 ± 0.05, 0.76 ± 0.05, 0.62 ± 0.05, 0.53 ± 0.06, and 0.48 ± 0.02 l/min at 1, 2.5, 5, 7.5, 10, 20, 75, and 90 min in recovery, respectively.

Hypoxanthine

The arterial concentration of hypoxanthine at the end of exercise was greater in HP compared with C ($$60.1 ± 7.4$$ vs. $$17.8 ± 2.0$$ µmol/l; $$P < 0.05$$; Fig. 3A). In both C and HP, there was a significant (compared with nil) release of hypoxanthine from the exercising leg muscles at the end of exercise ($$14.2 ± 3.9$$ (C) and $$16.0 ± 2.0$$ (HP) µmol/min) and during 45 min of recovery ($$P < 0.05$$; Fig. 3B). The total release of hypoxanthine from the exercised leg during recovery was greater in HP than in C ($$P < 0.05$$; Table 1). In HP, there was a release ($$P < 0.05$$) of hypoxanthine from the resting leg that was smaller than that of the active leg ($$P < 0.05$$; Fig. 3C). No exchange of hypoxanthine by the inactive leg was observed in C (Fig. 3C).

Urate

The arterial concentration of urate increased from a resting level of 284 ± 14 µmol/l to a peak level of 355 ± 20 µmol/l at 60 min in recovery in C, and the corresponding values in HP were 307 ± 14 and 585 ± 48 µmol/l, respectively (Fig. 4A). In HP, there was an uptake of urate during the first 10 min in recovery ($$P < 0.05$$), with the highest rate of uptake ($$61.4 ± 7.4$$ µmol/min) occurring 1 min after exercise (Fig. 4B). The total uptake of urate in the exercised muscle during recovery was greater in HP than in C ($$P < 0.05$$; Table 1).

There was no exchange of urate in the resting leg during either of the two experiments (Fig. 4C).
Catecholamines

The epinephrine concentration at 1.5 and 5 min of recovery was higher (P < 0.05) in HP than in C (0.45 ± 0.09 vs. 0.21 ± 0.04 and 0.36 ± 0.11 vs. 0.21 ± 0.05 ng/ml, respectively), whereas no differences were observed at 30 and 90 min (0.25 ± 0.06 vs. 0.26 ± 0.07 and 0.18 ± 0.02 vs. 0.19 ± 0.06 ng/ml, respectively). Throughout recovery, the norepinephrine concentration was higher (P < 0.05) in HP than in C (1.94 ± 0.50 vs. 0.76 ± 0.23, 1.04 ± 0.19 vs. 0.44 ± 0.06, 0.31 ± 0.03 vs. 0.51 ± 0.09, and 0.41 ± 0.10 vs. 0.24 ± 0.03 ng/ml, for 1.5, 5, 30, and 90 min of recovery, respectively). At rest, the epinephrine and norepinephrine concentrations in C and HP were 0.15 ± 0.02 vs. 0.26 ± 0.020 and 0.17 ± 0.02 vs. 0.30 ± 0.06 ng/ml, respectively. There was a correlation between the exchange of urate and the plasma epinephrine and norepinephrine in recovery.

Table 1. Net total exchange of hypoxanthine and urate of the active thigh during 90 min of recovery from long-term intermittent one-legged knee extensor exercise without and with interspersing arm exercise

<table>
<thead>
<tr>
<th>Time of Recovery, min</th>
<th>0–5</th>
<th>5–30</th>
<th>30–90</th>
<th>0–90</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>HP</td>
<td>C</td>
<td>HP</td>
</tr>
<tr>
<td>Hypoxanthine release, μmol</td>
<td>56 ± 13</td>
<td>49 ± 8</td>
<td>187 ± 54†</td>
<td>277 ± 60†</td>
</tr>
<tr>
<td>Urate uptake, μmol</td>
<td>42 ± 71</td>
<td>188 ± 64*†</td>
<td>7 ± 46</td>
<td>330 ± 109*†</td>
</tr>
</tbody>
</table>

Values are means ± SE. C, control experiment without interspersing arm exercise; HP, experiments with interspersing arm exercise.

*Significant difference (P < 0.05) between C and HP. †Significantly different from nil.
ery in HP (r = 0.929; P > 0.05 and r = 0.98; P < 0.01, respectively).

**Muscle Nucleotides**

The muscle ATP concentration decreased 9% in the active leg during exercise in C (P < 0.05; Table 2) and 17% in HP (P < 0.05; Table 2). In HP, the muscle ATP concentration after 90 min of recovery was 9% lower than the preexercise value (P < 0.05). The change in ATP in recovery from exercise in C was similar to that in HP; however, the ATP value at 90 min of recovery was not significantly different from that at rest (P > 0.05).

The concentration of IMP in the muscle after exercise was similar in C and HP (Table 2).

**DISCUSSION**

The present study demonstrates that a single session of long-term high-intensity intermittent exercise can lead to a marked release of purines from the exercised muscle and a lowering of muscle ATP levels, lasting for more than 90 min after exercise. Furthermore, after exercise, the muscle extracts urate from plasma, an event associated with a high arterial urate concentration.

**Muscle Hypoxanthine Exchange and ATP Levels**

Hypoxanthine was released from the exercised muscle during more than 45 min of recovery in HP, with a total net release corresponding to ~3% of the adenine nucleotide pool. The actual release from the muscle was probably substantially greater, since hypoxanthine also was released during exercise, which was evident from the elevated plasma hypoxanthine values at the end of exercise. The purge release in the present study is greater than has previously been reported after one session of high-intensity exercise (9, 18), which suggests that long-term high-intensity intermittent exercise induces a recurring degradation of nucleotides with a consequent considerable formation of hypoxanthine.

Upon termination of exercise, the muscle ATP level was ~17% lower than resting values in HP. Reamination of accumulated IMP increased the ATP levels by <7%, and at 90 min in recovery the muscle ATP levels were still 2.5 mmol/kg dry wt (9%) lower (P < 0.05) than preexercise values. The change in muscle ATP in recovery from exercise in C was similar to that in HP; however, the 90-min ATP value in C was not significantly different from that at rest. The finding of a sustained lowered level of muscle ATP is in agreement with previous studies involving periods of regularly performed sessions of intense exercise, after which the resting muscle ATP concentrations were found to be reduced by ~20% (11, 20). The observed lowered resting levels of ATP can in part be explained by the release of hypoxanthine from the active muscle during and in recovery from exercise. However, because the hypoxanthine release in recovery amounted to 0.5 mmol/kg dry wt, it seems unlikely that the entire difference in ATP levels between the preexercise and the 90-min recovery biopsies can be explained by hypoxanthine release. Thus there appears to be a yet unidentified additional pathway for ATP degradation in the muscle that causes a loss of muscle nucleotides.

The rested leg released hypoxanthine during the recovery phase in the HP experiment but not in the C experiment. This finding indicates that the release of purines from muscle may be regulated by some blood-borne factor in which the greater muscle mass involved in the HP condition may have led to a greater increase in this factor, influencing hypoxanthine release from both the exercised and the rested leg. Norepinephrine and epinephrine are possible candidates, as the plasma catecholamine level was greater in HP compared with C in recovery and as there was a relationship between the urate uptake in HP and the plasma catecholamine level. However, this possibility needs to be examined further.

The present results clearly show that plasma hypoxanthine is not utilized for nucleotide resynthesis by exercised or rested muscle in recovery from exercise despite very high arterial hypoxanthine concentrations. These observations are in agreement with findings in animal studies showing that most tissues, including resting skeletal muscle, only utilize a small amount of extracellular hypoxanthine for nucleotide resynthesis, the remainder being oxidized to urate and allantoin (15, 22). Our data suggest that nucleotides lost from the muscle during exercise, to a major extent, therefore, must be resynthesized via the de novo pathway from ribose 5-phosphate. A fraction of purines formed during exercise is probably also salvaged intracellularly in the muscle via the hypoxanthine phosphoribosyltransferase pathway, as has been indicated by the finding of an enhanced hypoxanthine phosphoribosyltransferase activity in muscle after intense training in humans (8).

**Exchange of Urate in Exercised and Rested Muscle**

In a recent study, we demonstrated that intense cycle exercise can lead to depletion of urate in the muscle to ~20% of the resting value, with a parallel increase in the oxidation product of urate, allantoin (7). It was also shown that the muscle urate concentration returned to

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**Table 2. Muscle ATP and IMP concentrations in the exercised muscle before, at the end of, and in recovery from long-term intermittent one-legged knee extensor exercise without and with interspersing arm exercise**

<table>
<thead>
<tr>
<th>Time</th>
<th>ATP</th>
<th>IMP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C (mmol/kg dry wt)</td>
<td>HP (mmol/kg dry wt)</td>
</tr>
<tr>
<td>Preexercise</td>
<td>23.5 ± 0.7</td>
<td>24.3 ± 0.6</td>
</tr>
<tr>
<td>End of exercise</td>
<td>21.5 ± 1.1*</td>
<td>20.1 ± 1.1*</td>
</tr>
<tr>
<td>Recovery, min</td>
<td>21.3 ± 0.8*</td>
<td>20.6 ± 0.8*</td>
</tr>
<tr>
<td>5</td>
<td>22.0 ± 0.7*</td>
<td>21.4 ± 1.2*</td>
</tr>
<tr>
<td>30</td>
<td>21.6 ± 0.9</td>
<td>21.8 ± 0.6*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Units are mmol/kg dry wt. *P < 0.05, significantly different from preexercise.
preexercise levels within the first few minutes of recovery (7). In the HP experiment, there was a significant uptake of urate in the exercised muscle during the first 10 min in recovery. The total uptake of urate corresponded to ~330 µmol/kg wet wt, which is close to the concentration of urate in muscle at rest (21). As xanthine dehydrogenase is absent in human skeletal muscle cells and low in activity in the muscle microvasculature (6), the replenishment of urate stores via urate forma-

tion within the muscle tissue is probably negligible. The present results suggest, therefore, that uptake of urate from plasma is the main mechanism behind the replenishment of oxidized intracellular muscle urate stores.

The uptake of urate from plasma occurred only in the exercised and not the rested leg and only in the HP condition, which indicates that the uptake of urate by muscle is not solely a consequence of an increased urate concentration gradient between muscle and blood, es-

established by the elevation in plasma urate levels after exercise. An increase in the concentration of urate in plasma appeared, however, to be necessary for uptake of urate to occur, as urate extraction was evident only in the HP experiment in which plasma urate levels in recovery were higher than in the C experiment. Necess-

ity of an elevated plasma urate concentration for extraction could explain why the muscle releases some of its nucleotide pool in the form of hypoxanthine, precursor of urate, into blood during exercise. In this context, it is of interest to note that exercise to exhaus-

tion induces a marked increase in plasma urate, of ~100 µmol/l or more, for a wide range of exercise intensities (12). Apart from the requirement of a urate gradient between plasma and muscle, a mechanistic explanation for urate flux through the muscle mem-

brane is presently not available. A urate transporter/ channel has, however, recently been discovered in several tissues, including skeletal muscle (14), and it is possible that it provides the molecular mechanism behind muscle urate exchange.

The increase in plasma urate after strenuous exer-

cise originates from the liver, which extracts and oxida-

izes plasma hypoxanthine released from exercising muscle (9). The present study shows that hypoxanthine released from the muscle may enter the muscle again as urate, probably for replenishment of intracellular urate stores, oxidized by reactive oxygen species. It may be speculated that the reason for urate formation occurring in the liver as opposed to the muscle is because of the harmful property of the enzyme involved in the oxidation of hypoxanthine to urate, xanthine dehydrogenase. Xanthine dehydrogenase may, during various conditions, including metabolic stress, be con-

verted to an oxidase form that generates reactive oxygen radicals. Therefore, a high activity of this enzyme may be harmful to a tissue such as muscle, which is subjected to large alterations in metabolic demand.

The present study demonstrates that one session of long-term, high-intensity intermittent exercise can lead to a substantial loss of nucleotide precursors from the exercised muscle into the blood and a sustained lowering of muscle adenine nucleotide levels. Uptake of hypoxanthine from blood does not appear to be an important salvage pathway for muscle nucleotides, as both exercised and nonexercised muscle released hy-

poxanthine in recovery despite high plasma hypoxan-

thine concentrations. Exercised muscle extracts urate from plasma after high-intensity intermittent exercise, with the probable purpose to restore urate levels, which may be depleted due to free radical-induced oxidation of urate in the muscle.

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