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Curcumin effects on inflammation and performance recovery following eccentric exercise-induced muscle damage

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¹Division of Applied Physiology, Department of Exercise Science, Arnold School of Public Health and the ²Department of Pathology, Microbiology and Immunology, School of Medicine, University of South Carolina, Columbia; and ³Department of Microbiology and Molecular Medicine, Clemson University, Clemson, South Carolina

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Davis JM, Murphy EA, Carmichael MD, Zielinski MR, Groschwitz CM, Brown AS, Gangemi JD, Ghaffar A, Mayer EP. Curcumin effects on inflammation and performance recovery following eccentric exercise-induced muscle damage. *Am J Physiol Regul Integr Comp Physiol* 292: R2168–R2173, 2007. First published March 1, 2007; doi:10.1152/ajpregu.00858.2006.—Downhill running is associated with fiber damage, inflammation, delayed-onset muscle soreness, and various functional deficits. Curcumin, a constituent of the Indian spice turmeric has been investigated for its anti-inflammatory activity and may offset some of the damage and functional deficits associated with downhill running. This study examined the effects of curcumin on inflammation and recovery of running performance following downhill running in mice. Male mice were assigned to downhill placebo (Down-Plac), downhill curcumin (Down-Cur), uphill placebo (Up-Plac), or uphill curcumin (Up-Cur) groups and run on a treadmill at 22 m/min at -14% or $+14\%$ grade, for 150 min. At 48 h or 72 h after the up/downhill run, mice (*experiment 1*) underwent a treadmill performance run to fatigue. Another subset of mice was placed in voluntary activity wheel cages following the up/downhill run (*experiment 2*) and their voluntary activity (distance, time and peak speed) was recorded. Additional mice (*experiment 3*) were killed at 24 h and 48 h following the up/downhill run, and the soleus muscle was harvested for analysis of inflammatory cytokines (IL-1 β , IL-6, and TNF- α), and plasma was collected for creatine kinase analysis. Downhill running decreased both treadmill run time to fatigue (48 h and 72 h) and voluntary activity (24 h) ($P < 0.05$), and curcumin feedings offset these effects on running performance. Downhill running was also associated with an increase in inflammatory cytokines (24 h and 48 h) and creatine kinase (24 h) ($P < 0.05$) that were blunted by curcumin feedings. These results support the hypothesis that curcumin can reduce inflammation and offset some of the performance deficits associated with eccentric exercise-induced muscle damage.

inflammatory cytokines; fatigue; mice; nutraceutical; phytochemicals

IT IS WELL KNOWN THAT INTENSE exercise can induce muscle damage and inflammation depending on exercise mode, intensity, and duration (30, 40). Exercise with a large eccentric component (lengthening of a muscle that is actively developing tension) produces the greatest muscle fiber damage, inflammation, delayed-onset muscle soreness (DOMS), and various functional deficits. It is now thought that many of these responses to muscle-damaging exercise may be triggered by a large increase in inflammatory cytokines in the working muscle, plasma, and perhaps even the brain (13, 30, 32, 40).

Exercise-induced increases in inflammatory cytokines, such as IL-1 β , TNF- α , and IL-6 were originally thought to be expressed only in immune cells, but now are known to be expressed, to varying degrees, in many other tissues. These cytokines are regulated by a variety of stimulators and suppressors within the inflammatory pathways. The NF- κ B and activator protein-1 (AP-1) mediated cytokine pathways and the cyclooxygenase-2 (COX-2) prostaglandin cascade are the most well studied pathways (12). Muscle damage with the production of free radicals in response to unaccustomed exercise can trigger these pathways that lead to increased inflammatory cytokine production, pain, and performance deficits in muscle function (4).

Recent evidence suggests that various herbal extracts including tumeric (*Curcuma longa* rhizomes) have potent anti-inflammatory activity in a variety of inflammation models (1). The anti-inflammatory properties of tumeric have been attributed to its constituent curcumin. Evidence suggests that in some experimental conditions, curcumin can have similar anti-inflammatory activity as some of the common nonsteroidal anti-inflammatory drugs (NSAIDs) like indomethacin, Vioxx, Celebrex, and ibuprofen, but without many of the side effects, such as gastrointestinal distress and cardiovascular complications (14, 22). The molecular basis of the anti-inflammatory properties of curcumin is linked to its effects on several targets, including transcription factors, growth regulators, and cellular signaling molecules. Curcumin is reported to directly influence the activity of various inflammatory regulators; it has been shown to reduce NF- κ B activation, AP-1 binding to DNA, as well as to decrease the production of the enzyme COX-2, all of which play a pivotal role in the inflammatory cascade (11, 15, 18, 33, 41). In addition, several studies have shown that curcumin can indirectly inhibit these inflammatory regulators through its ability to scavenge free radicals (6, 28). However, to date there are no reports of the potential benefits of curcumin on inflammation and subsequent recovery of performance following eccentric exercise-induced muscle damage.

The purpose of this study was to evaluate the potential benefits of curcumin supplementation using an eccentrically biased downhill treadmill running model. This model of exercise-induced muscle damage, inflammation, and functional deficits is well characterized in rodents (2, 7, 19, 20, 30, 34). The strength of this model is that the “control” condition is uphill running that requires more energy and is physically more

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demanding, but produces little or no muscle damage and inflammation. Recently, we have shown that both voluntary (wheel) and involuntary (treadmill) running is significantly reduced for up to 4 days following a bout of downhill running in mice (8). And further, we have suggested that the performance deficits are at least partially explained by inflammation including increases in brain IL-1 β (8, 9). We hypothesized that the anti-inflammatory activity of curcumin would hasten recovery of running performance due to a reduction in inflammation-induced deficits in regeneration of muscle fibers, soreness, and central nervous system fatigue.

METHODS

Animals

Male Institute of Cancer Research mice, 8 wk of age, were purchased from Harlan Sprague-Dawley Labs and were acclimated to our facility for a period of at least 3 days prior to any experimental intervention. Mice were housed individually in regular cages or cages that contained a running wheel (Mini-Mitter, Bend, OR). All mice were cared for in the animal facility at the University of South Carolina Medical School. Mice were maintained on a 12:12-h light-dark cycle in a low-stress environment (22°C, 50% humidity, and low noise) and given food (Purina Chow) and water ad libitum. All experimental trials were performed at the end of the active dark cycle (0700). The University's Institutional Animal Care and Use Committee approved all aspects of this experimental protocol.

Curcumin Treatment

Mice were randomly assigned to one of four groups: downhill placebo (Down-Plac), downhill curcumin (Down-Cur), uphill placebo (Up-Plac), or uphill curcumin (Up-Cur). All mice were acclimated to a 0.5-g highly palatable rodent food pellet (Research Diets) for a period of 3 days. Mice were given either a food pellet containing 10 mg of curcumin powder (Down-Cur and Up-Cur) or placebo [food pellet without curcumin (Down-Plac and Up-Plac)] daily for 3 consecutive days prior to the up/downhill run. Animals typically (>90%) consume the entire pellet within 30 min with no differences between the placebo and curcumin pellet. This was confirmed in these animals during the acclimation period. Mice that did not ingest the food pellet within 30 min of it being dropped into the cage were excluded (<5%).

Exercise Protocol

The initial up/downhill run consisted of 150 min of running on a motorized treadmill. For this session, all mice were placed on a stationary rodent treadmill for a few minutes to allow them to become familiar with the running environment prior to a progressive ramping of speed and grade during the first 20 min of exercise. Instead of a typical acclimation period that runs between a few days to several weeks we incorporated this brief acclimation period in the exercise bout to prevent any adaptation to the running protocol that is known to significantly dampen the muscle-damaging effects. After the first 20 min, mice were running at 22 m/min at a grade of -14% or +14%. The strength of this model is that the control condition is uphill running that requires more energy and is physically more demanding but produces little or no muscle damage and inflammation. Mice were gently hand-prodded occasionally to maintain running status; no electric shock was used in these experiments, as mice generally respond to a gentle tap on the tail or hindquarters.

Experiment 1. Treadmill run to fatigue. A subset of mice ($n = 64$) [Down-Plac ($n = 16$), Down-Cur ($n = 16$), Up-Plac ($n = 16$), and Up-Cur ($n = 16$)] were used to assess recovery of running performance following the up/downhill run, these mice were run to fatigue on a motorized treadmill at 36 m/min and 8% grade at either 48 h ($n =$

8/group) or 72 h ($n = 8$ /group) post-up/downhill run. Fatigue was defined as the time when mice were no longer able or willing to keep up with the treadmill speed, despite continued gentle hand prodding for a period of 1 min (8) (Fig. 1).

Experiment 2. Voluntary wheel running activity. A second subset of mice ($n = 61$) [Down-Plac ($n = 16$), Down-Cur ($n = 18$), Up-Plac ($n = 13$), and Up-Cur ($n = 14$)] were used to assess recovery of voluntary activity following the up/downhill run. Immediately following the up/downhill run the animals were placed back into activity wheel cages to which they had become acclimated over the past 7 days. Mice were acclimated to the running wheels for 7 days prior to the collection of baseline levels (defined as the average activity for 3 days prior to the up/downhill run), typically running behavior increases over time for ~7 days after which it reaches a plateau, which is relatively constant for 4–8 wk. Voluntary wheel running activity was measured automatically for 7 consecutive days via computer using Vital View physiological and behavioral monitoring software (Mini-Mitter). However, only data collected during the “active” dark period (1900–0700) were analyzed. Earlier experiments in our lab have shown that voluntary wheel running activity is minimal during the “inactive” light period (0700–1900), (~300 m vs. 6000 m during the “active” dark period from 1900–0700). Voluntary activity was quantitated for total distance (Distance), time on wheel (Time), and peak speed (P-Speed) as calculated using the following equations: Distance = (number of wheel rotations during a 2-min interval) \times [circumference of the running wheel (0.7581 m)]; Time = [(number of 2-min intervals where wheel rotations were > 0) \times 2]; P-Speed = {(95th percentile of rotations during a given time interval) \times [circumference of wheel (0.7581 m)/2]} (24). Data are represented as the average of each 2-min interval collected over the 12-h active dark cycle and is expressed as a percentage of baseline (average of data collected for 3 days prior to up/downhill run) (Fig. 1).

Experiment 3. Muscle cytokine and plasma creatine kinase analysis. A third subset of mice ($n = 96$) [Down-Plac ($n = 24$), Down-Cur ($n = 24$), Up-Plac ($n = 24$), and Up-Cur ($n = 24$)] were killed at 24 h or 48 h following the up/downhill run for blood and muscle collection. Animals were killed by halothane overdose, and blood was collected from the inferior vena cava with a heparinized syringe and spun in a microcentrifuge at 4,000 rpm for 15 min. Plasma was then stored at -80°C until assayed for creatine kinase via an *N*-acetylcysteine-activated kinetic assay (Diagnostic Chemicals, Prince Edward Island,

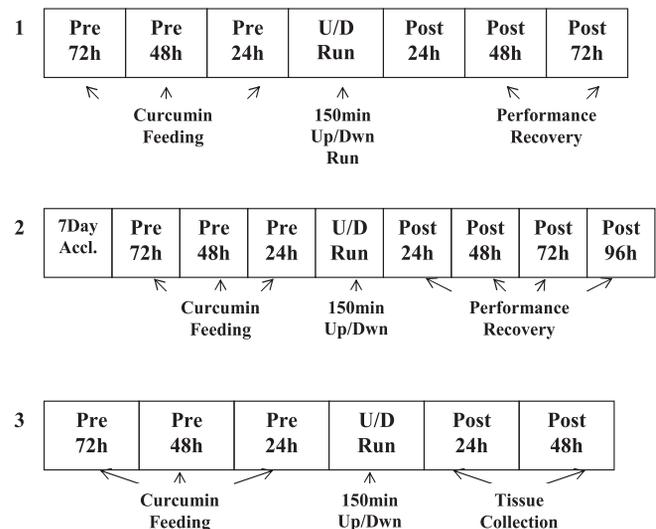


Fig. 1. Experimental design schematic for *experiment 1*, treadmill run to fatigue; *experiment 2*, voluntary wheel running activity; and *experiment 3*, muscle cytokine and plasma creatine kinase analysis. U/D, Up/Down, up/downhill run.

Canada). Immediately following the blood collection, the soleus muscle from both legs was immediately removed, cleaned of residual blood, and flash frozen in liquid nitrogen. They were then stored at -80°C for analysis of cytokine (IL-1 β , IL-6, and TNF- α) protein concentration. The right and left soleus muscles from two mice of the same group were pooled to obtain enough tissue for analysis of the three cytokines. Each pool was added to 0.8 ml of Iscoves culture medium containing 5% fetal bovine serum and a cocktail enzyme inhibitor (10 mM EDTA, 5 mM benzamide HCl, and 0.2 mM PMSF). The tissue was homogenized by using a polytron, and total protein was mechanically dissociated from the tissue by using an ultrasonic cell disruptor. Sonicated samples were centrifuged at 10,000 rpm at 4°C for 10 min, and the supernatants were removed and stored at 4°C prior to the assay of IL-1 β , IL-6, and TNF- α via ELISA (R&D Systems, Minneapolis MN). The assay was performed according to the manufacturer's instructions. Total soluble protein was also determined by using supernatant of sonicated samples via bicinchoninic acid protein assay (Rockford, IL). Cytokine levels are expressed as a picogram per 100 micrograms of total protein. Creatine kinase was measured in plasma according to manufacturer's instructions (Diagnostic Chemicals) with modification for use with a microplate. Briefly, creatine kinase was measured by recording the change in absorbance, after the slope had stabilized, at 340 nm at 1-min intervals until the absorbance change was constant. Creatine kinase was calculated by the rate of increase in absorbance at 340 nm due to the formation of NADPH. Creatine kinase activity is expressed as units per liter (Fig. 1).

Statistical Analysis

Data were analyzed using a two-way ANOVA (exercise \times treatment). All data were analyzed using commercial software (SigmaStat, SPSS, Chicago, IL). Statistical significance was set with an alpha value of $P < 0.05$. Post hoc analysis was done by utilizing Student-Newman-Keuls tests. Data are presented as means \pm SE.

RESULTS

Treadmill Running Performance

As compared with uphill running, downhill running significantly reduced treadmill run times to fatigue at 48 h (<0.001) and 72 h (<0.001) following the run (Fig. 2). Curcumin treatment for 3 days prior to the up/downhill run blocked the over-100% reduction in treadmill run times associated with downhill running ($P < 0.01$). There was no effect of curcumin in the uphill runners.

Voluntary Wheel Running Activity

Downhill running also reduced voluntary wheel running (distance and time, but not peak speed) compared with uphill runners ($P < 0.05$), although this effect was less in magnitude than the reduction in treadmill running performance. Curcumin feedings completely blocked this reduction in wheel running. Total running distance for Down-Plac during the first active cycle (1900–0700) following the downhill run (0700–0930) was $\sim 75\%$ of baseline (mean of 3 active cycles prior to the up/downhill run) ($P < 0.05$) (Fig. 3A). This improved to 80% for the active cycle on *day 2* ($P < 0.1$) and returned to baseline on *day 3*. There was no difference from baseline in the curcumin-fed group following either the downhill or uphill run. Time on the wheel was also reduced during each of the first two active cycles following the downhill run ($P < 0.05$) (Fig. 3B). This effect was also blocked by curcumin feedings.

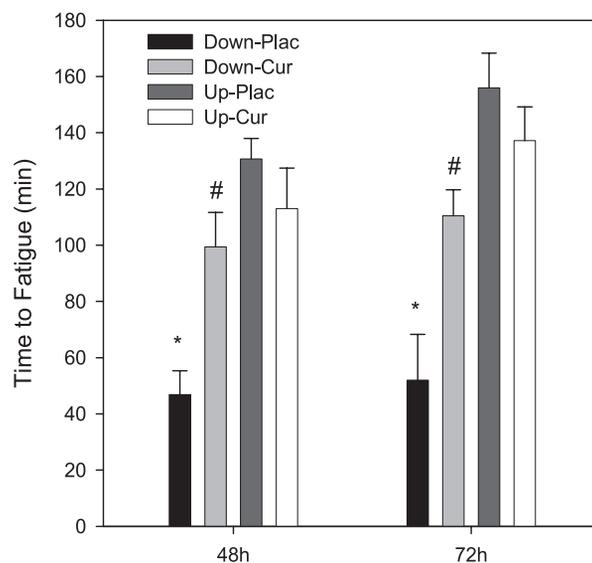


Fig. 2. Treadmill fatigue times at 48 h and 72 h following the up/downhill run. Each bar represents mean \pm SE time to fatigue ($n = 8/\text{group}$). * $P < 0.001$ for Down-Plac vs. Up-Plac. # $P < 0.01$ for Down-Cur vs. Down-Plac. Down-Plac, downhill placebo; Down-Cur, downhill curcumin; Up-Plac, uphill placebo; Up-Cur, uphill curcumin.

There was no effect of either downhill running or curcumin on peak speed (data not shown).

Creatine Kinase

Plasma creatine kinase was significantly elevated (over 100%) in Down-Plac at 24 h, but not 48 h following the initial run compared with Up-Plac ($P < 0.01$). Curcumin treatment blunted this increase in creatine kinase ($P < 0.05$) (Fig. 4). Again, there was no effect of curcumin in the uphill runners.

Muscle Cytokine Analysis

Figure 5 shows the effects of curcumin on inflammatory cytokine concentrations in the soleus muscle. The effects of downhill running on soleus muscle IL-1 β , IL-6, and TNF- α concentration were similar with generally smaller effects at 24 h than 48 h. Downhill running was associated with a small but statistically insignificant increase in IL-1 β ($P = 0.1$) at 24 h (Fig. 5A), whereas at 48 h there was a significant increase in IL-1 β in Down-Plac vs. Up-Plac ($P < 0.05$). Curcumin feedings offset this increase in IL- β in the downhill group ($P < 0.05$). Curcumin similarly blunted the increases in IL-6 (Fig. 5B) and TNF- α (Fig. 5C) at 24 h ($P < 0.1$) and 48 h ($P < 0.05$).

DISCUSSION

The induction of mechanical damage and inflammatory cytokines in skeletal muscle following a bout of eccentrically biased exercise (downhill running) is typically associated with a reduction in muscle-specific performance during the normal progression of tissue regeneration. Recently, we have shown a decrease in whole body exercise (both treadmill running and voluntary wheel running) following a bout of downhill running in mice (8, 9). The primary results of this study suggest that the anti-inflammatory phytochemical curcumin can speed recovery

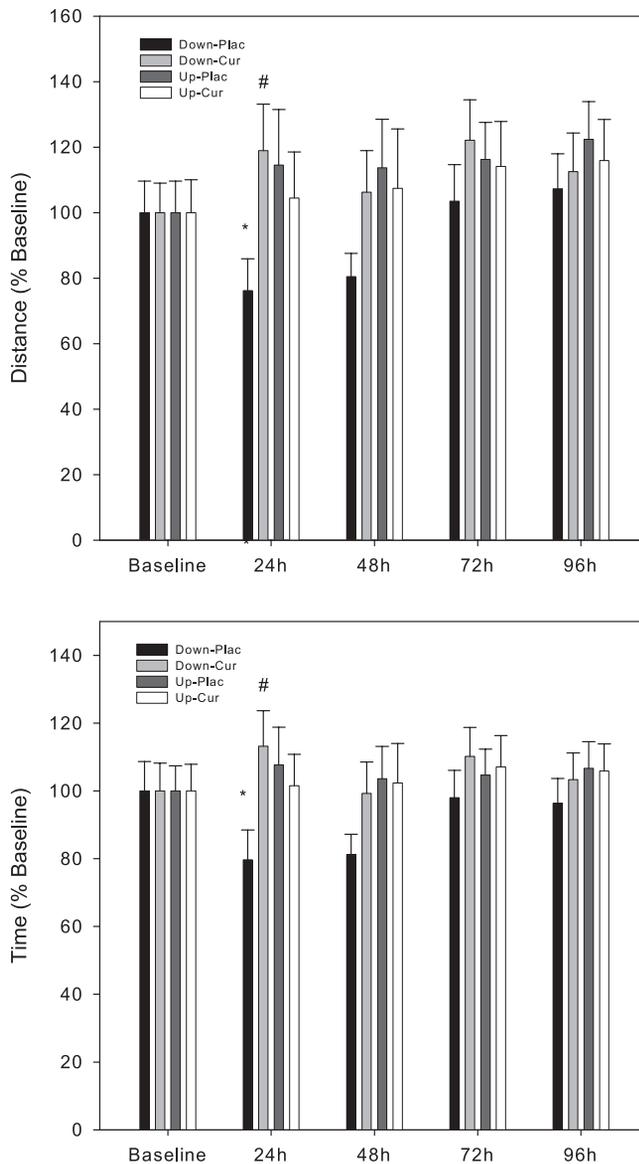


Fig. 3. Distance (A) and time (B) on activity wheel for each of the 4 consecutive days following the up/downhill run. Each bar represents the mean \pm SE distance (A) and time (B) during 12-h active cycle (1900–0700). Values expressed as %baseline (mean of 3 active cycles prior to up/downhill run) ($n = 13$ – 18 /group). * $P < 0.05$ for Down-Plac vs. Up-Plac. # $P < 0.05$ for Down-Cur vs. Down-Plac.

of both voluntary (wheel running) and involuntary (treadmill) running performance following exercise-induced muscle damage. The performance effects are reflected by a reduction in plasma creatine kinase and inflammatory cytokine concentrations (IL-1 β , IL-6, and TNF- α) in soleus muscle, which are typically associated with muscle damage and inflammation. Others have shown a beneficial effect of curcumin on enhancement of muscle regeneration after trauma (37), but this is the first study to show a benefit of curcumin on whole body exercise performance following exercise-induced muscle damage.

Both concentric and eccentric muscle contractions can induce muscle damage and muscle-specific functional deficits, albeit to different degrees. Eccentric contractions, defined as a muscle that is lengthening while tension is still developing, is

known to produce the most damage and DOMS (2). This has repeatedly been indicated by histology (16), increased damage and inflammation markers, such as creatine kinase (17), C-reactive protein (27), and inflammatory cytokines (38), along with reduced muscle endurance/power (31) and increased pain (DOMS) (17, 31). This phenomenon is well studied, but has for the most part been confined to contrived lab experiments involving single muscle groups in humans and rodents, and overall physical performance was not addressed. The fact that curcumin appears capable of enhancing a behavioral response (spontaneous running) implies an important central nervous system (CNS) component (e.g., drive, motivation) that may be related to less pain and perhaps reduced inflammatory cytokines. Support for a CNS effect involving the inflammatory cytokine IL-1 β comes from studies showing that delayed recovery of both voluntary and involuntary running performance following exercise-induced muscle damage is associated with increased IL-1 β concentrations in various brain regions (8), and this effect can be reversed with intracerebral ventricular administration of an IL-1 β antagonist (9). The mechanical damage can result in a variety of inflammatory responses, initially due to infiltrating cells, such as neutrophils and macrophages within the muscle that result in increased muscle, blood, and even brain concentrations of inflammatory cytokines. These responses can have profound effects on both physical and mental function (fatigue, perceived discomfort, impaired mood, and perhaps other cognitive deficits) (13, 30, 32, 40).

Scientific investigation into the development of new anti-inflammatory drugs has increased dramatically in recent years. The outcome has been a wide variety of NSAIDs like indomethacin, Vioxx, Celebrex, and ibuprofen, which are often used to reduce muscle and joint pain (22, 29, 39). However, a major drawback to chronic ingestion of many of the NSAIDs, such as practiced by many athletes and military personnel, is the degradation of the mucosa lining of the stomach, leading to

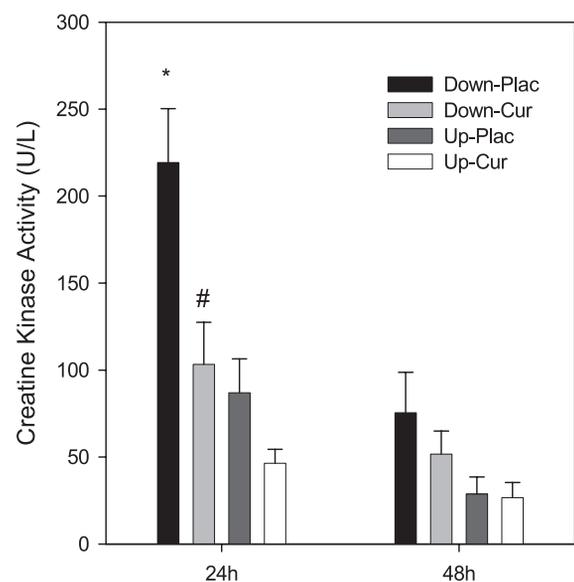


Fig. 4. Plasma creatine kinase concentration at 24 h and 48 h following the up/downhill run. Each bar represents the mean \pm SE creatine kinase concentration ($n = 12$ /group). * $P < 0.01$ for Down-Plac vs. Up-Plac. # $P < 0.05$ for Down-Cur vs. Down-Plac.

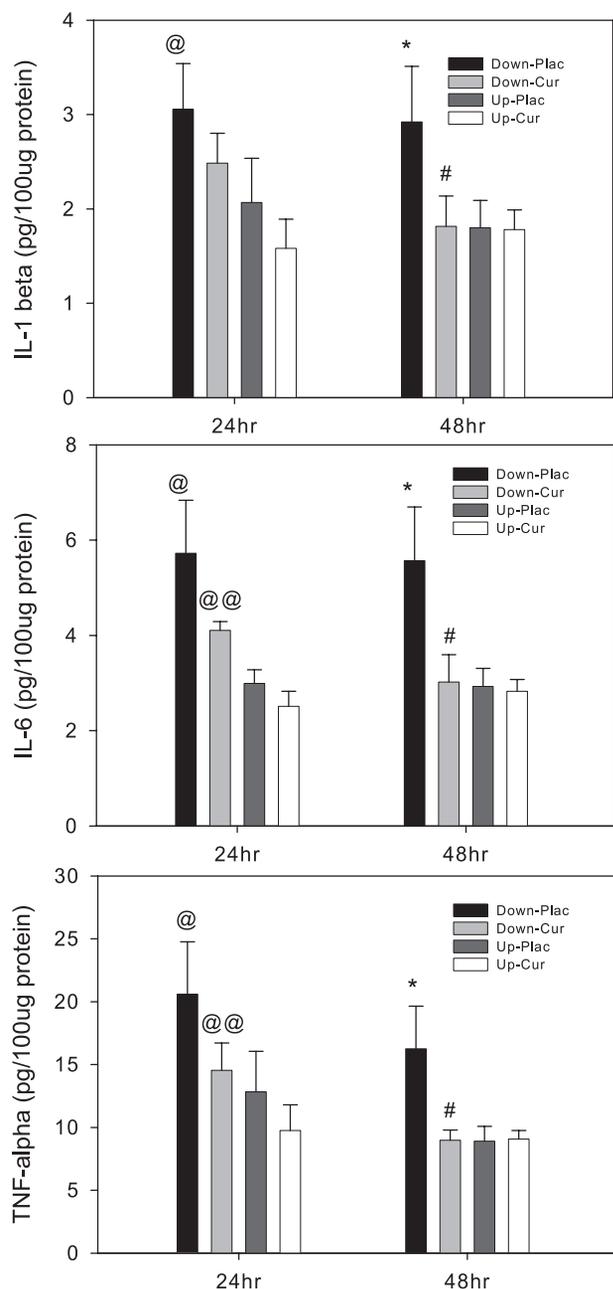


Fig. 5. IL-1 β , IL-6, and TNF- α protein concentration in soleus muscle at 24 h and 48 h following the up/downhill run. Each bar represents the mean \pm SE protein concentration ($n = 6$ /group). * $P < 0.05$ for Down-Plac vs. Up-Plac. # $P < 0.05$ for Down-Cur vs. Down-Plac. @ $P < 0.1$ for Down-Plac vs. Up-Plac. @@ $P < 0.1$ for Down-Cur vs. Down-Plac.

gastrointestinal ulcers and unexpected and potentially deadly bleeding, as well as increased risk of other cardiovascular events (14, 22, 29, 39). We have shown that the NSAID ibuprofen does not alter DOMS or creatine kinase following an ultramarathon competition (23). Furthermore, repeated use of NSAIDs may not be appropriate in the context that some inflammatory components are needed for both repair and adaptation (21). As a result, the use of mild natural anti-inflammatory agents, such as curcumin, are generating much interest. Our results suggest that curcumin can enhance performance recovery following muscle-damaging exercise, which is of

great potential benefit to athletes and military personnel who are often exposed to unusually stressful exercise conditions on a recurrent basis.

The molecular basis of the anti-inflammatory properties of curcumin has been attributed to its effects on several targets including transcription factors, enzymes, and cellular signaling molecules, including NF- κ B, AP-1, and COX-2. Curcumin has been shown to directly inhibit activation of transcription factors NF- κ B and AP-1 (15, 18, 33, 35). NF- κ B and AP-1 play critical roles on the cells of the immune system through the regulation of various inflammatory cytokines (10, 36). In nonstimulated cells, NF- κ B is held in the cytosol through interaction with inhibitor κ B (I κ B) inhibitory proteins. Following exposure to inflammatory stimuli, I κ B is phosphorylated and degraded, resulting in liberation of the NF- κ B dimers (p50 and p65), which can now be translocated to the nucleus where transcription of the target gene is induced (3). It has been proposed that curcumin directly inhibits I κ B kinase (IKK) activity, which prevents the phosphorylation and degradation of I κ B α , thereby blocking NF- κ B activation, which, in turn, leads to decreased transcription of various inflammatory cytokine genes (25). The suppressed activation of AP-1 by curcumin is thought to occur via binding to its DNA motif (5, 18) or inhibition of *c-fos* and *c-jun*, components of the AP-1 pathway (26). It is also possible that curcumin can act indirectly to inhibit NF- κ B and AP-1 through its ability to scavenge reactive oxygen species, which can decrease the oxidative stimulus for activation of NF- κ B and AP-1 (6, 28).

Curcumin has also been reported to suppress COX-2, the key enzyme in the formation of prostaglandins, a family of compounds derived from arachidonic acid through the COX pathway (11, 18, 41). Prostaglandins are potent mediators in the inflammatory response. The mechanisms for the curcumin-induced reduction in COX-2 have not yet been elucidated; however, it is thought to be mediated by its effects on NF- κ B and AP-1 (18). As opposed to the NSAID drugs, which specifically target COX-2 inhibition, curcumin's effects appear to be more specifically targeted at NF- κ B (15, 18, 33, 35), and therefore, their anti-inflammatory effects may come with less potential for serious side effects.

In conclusion, these results suggest that ingestion of the common food constituent curcumin can offset the muscle-damaging effects of downhill running on inflammation and whole body exercise performance. This benefit was shown for both externally motivated treadmill running, as well as voluntary wheel running, a distinction that could be helpful in determining the underlying mechanisms (i.e., CNS vs. peripheral). These extend previous data showing a beneficial effect of curcumin on muscle regeneration after trauma that was linked to its anti-inflammatory activity (37). These findings may have important ramifications with respect to novel nutritional strategies that enhance performance recovery following stressful endurance events, such as those commonly undertaken by athletes and military personnel. NSAIDs are typically used for this purpose but have not been shown to be particularly effective and may be associated with serious side effects.

GRANTS

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