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Curcumin attenuates oxidative stress following downhill running-induced muscle damage

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ABSTRACT

Downhill running causes muscle damage, and induces oxidative stress and inflammatory reaction. Recently, it is shown that curcumin possesses anti-oxidant and anti-inflammatory potentials. Interestingly, curcumin reduces inflammatory cytokine concentrations in skeletal muscle after downhill running of mice. However, it is not known whether curcumin affects oxidative stress after downhill running-induced muscle damage. Therefore, the purpose of this study was to investigate the effects of curcumin on oxidative stress following downhill running induced-muscle damage. We also investigated whether curcumin affects macrophage infiltration via chemokines such as MCP-1 and CXCL14. Male C57BL/6 mice were divided into four groups; rest, rest plus curcumin, downhill running, or downhill running plus curcumin. Downhill running mice ran at 22 m/min, −15% grade on the treadmill for 150 min. Curcumin (3 mg) was administered in oral administration immediately after downhill running. Hydrogen peroxide concentration and NADPH-oxidase mRNA expression in the downhill running mice were significantly higher than those in the rest mice, but these variables were significantly attenuated by curcumin administration in downhill running mice. In addition, mRNA expression levels of MCP-1, CXCL14 and F4/80 reflecting presence of macrophages in the downhill running mice were significantly higher than those in the rest mice. However, MCP-1 and F4/80 mRNA expression levels were significantly attenuated by curcumin administration in downhill running mice. Curcumin may attenuate oxidative stress following downhill running-induced muscle damage.

1. Introduction

Downhill running including eccentric muscle contraction induces muscle damage, and generates reactive oxygen species (ROS) and inflammatory cytokines in animal and human experiments. Previous studies indicated that gene expression of inflammatory cytokines such as TNF-α and IL-1β in skeletal muscle was elevated by downhill running in human [1,2]. In addition, recent studies reported that hydrogen peroxide and inflammatory cytokine production in skeletal muscle was increased after downhill running in rodents [3,4]. Moreover, macrophages and neutrophils are present in skeletal muscle after downhill running [5–7]. Therefore, macrophages and neutrophils may play an important role in oxidative stress and inflammation following downhill running-induced muscle damage.

Although infiltration of macrophages into tissues is mediated by chemokines such as monocyte chemoattractant protein (MCP)-1 and CXCL14 [8], plasma concentration of MCP-1 was elevated by downhill running [9]. In addition, MCP-1 and MCP-1 receptor (CCR2) knockout mice attenuated macrophage infiltration in skeletal muscle after muscle damage induced by cardiotoxin injection [10]. Therefore, MCP-1 may induce macrophage infiltration, and modulate inflammation and oxidative stress after downhill running. In addition, it was shown that COX-2 modulated macrophage infiltration after muscle damage, and COX-2 inhibitor treatment attenuated infiltration of macrophages and neutrophils after lacerate-induced muscle damage [11]. COX-2 knockout mice showed less macrophage infiltration of lacerate-induced muscle damage [12]. Therefore, COX-2 may also induce macrophage infiltration,

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and modulate inflammation and oxidative stress after downhill running. Recently, it is reported that these inflammatory mediators such as TNF-α and COX-2 up-regulate expression of catabolic condition inducer such as atrogin1/MAFbx and MuRF1 in skeletal muscle, and induce muscle protein degradation [13–15]. Hydrogen peroxide also induced expression of atrogin1/MAFbx and MuRF1 in skeletal muscle myotubes [16,17]. Therefore, macrophages may be required for inflammation- and oxidative stress-induced muscle protein degradation.

Curcumin, an important constituent of *Curcuma longa*, possesses anti-oxidant and anti-inflammatory actions. It is shown that curcumin has been used to treat a variety of inflammatory conditions and chronic diseases [18]. In addition, curcumin has beneficial effects in conditions such as injured skeletal muscle. Interestingly, it is shown that curcumin reduces inflammatory cytokine concentration in skeletal muscle after downhill running [19]. These results indicate that curcumin may possess effective anti-inflammatory action after muscle damage. Downhill running-induced muscle damage also causes oxidative stress. However, it is not known whether curcumin affects oxidative stress following downhill running-induced muscle damage. Therefore, the purpose of this study was to investigate the effects of curcumin on oxidative stress following downhill running-induced muscle damage. In addition, we investigated to examine whether curcumin affects macrophage infiltration via suppression of chemokines such as MCP-1 and CXCL14 expression. We hypothesized that curcumin would suppress macrophage infiltration and oxidative stress.

2. Methods

2.1. Animals

Male C57BL/6 mice (n = 52) were purchased from Kiwa Laboratory Animals (Wakayama, Japan) at 9 weeks of age, and mice were housed together in one cage in controlled environment under a light–dark cycle (lights on at 9:00 and off at 21:00). The experimental procedures followed the Guiding Principles for the Care and Use of Animals in the Waseda University Institutional Animal Care and Use Committee and were approved (10K001). All mice were randomly divided into four groups: Rest (n = 12), Rest plus Curcumin (n = 12), Downhill running (n = 14), or Downhill running plus Curcumin (n = 14) group. All groups were allowed to eat food freely.

2.2. Downhill running protocol

All mice were initially acclimated to running on a motorized treadmill (Natsume, Kyoto, Japan) at 20 m/min, 0% grade for 20 min/day for 1 week. On the day of the experiment, the downhill running groups of mice ran at 22 m/min, −15% grade on the treadmill for 150 min.

2.3. Preparation of curcumin powder

We developed a highly absorbable curcumin formulation (THERACURMIN®) using microparticle and surface processing techniques. Curcumin powder was prepared by Theravalues (Tokyo, Japan). Curcumin powder was extracted from Indian turmeric by using alcohol. THERACURMIN® was prepared as follows; first, gum ghatti, mainly consists of polysaccharides, obtained from the exudation of ghatti trees, was dissolved in water to make gum ghatti solution. Curcumin powder was mixed into this solution, and water and glycerin was added to adjust the weight. This mixture was ground by a wet grinding mill, and then, dispersed by a high-pressure homogenizer. After this procedure, stable THERACURMIN® was obtained. THERACURMIN® consisted of 10 w/w% of curcumin, 2% of other curcuminoids such as demethoxycurcumin and isdemethoxycurcumin, 46% of glycerin, 4% of gum ghatti, and 38% of water.

2.4. Curcumin administration

Newly developed microparticle curcumin (named THERACURMIN®: 3 mg) was dissolved with normal saline (PBS) to the concentration of 15 mg/ml solution. Curcumin was administered in oral administration immediately after downhill running. PBS was administered to the control group mice. All mice were killed at 24 h after curcumin injection.

2.5. Plasma creatine kinase and lactate dehydrogenase activity measurement

Mice were anaesthetized by breathing of isoflurane (Abbott, Tokyo, Japan). Abdominal vein blood samples were collected in heparin tube, and plasma was stored at −80 °C. Plasma creatine kinase (CK) activity was measured with CK Test Wako (Wako Pure Chemical Industries, Tokyo, Japan). Plasma lactate dehydrogenase (LDH) activity was measured with LDH·J Test Wako (Wako Pure Chemical Industries).

2.6. Hydrogen peroxide assay

To examine hydrogen peroxide levels in gastrocnemius of mice, skeletal muscle was homogenized in Tissue Protein Extraction Reagent (T-PER) with Protease inhibitor (Thermo, Rockford, Illinois, USA). Protein concentration was measured using BCA Protein Assay (Thermo). Hydrogen peroxide level was measured with SensoLyte ADHP Hydrogen Peroxide Assay Kit (Fremount, California, USA)

2.7. Real-time quantitative PCR

To measure mRNA expression in gastrocnemius of mice, it was quickly immersed in RNAlater (Applied Biosystems, Carlsbad, CA) and stored at −80 °C. Total RNA was extracted using RNeasy Fibrous Tissue Mini Kit (Qiagen, Valencia, CA, USA) and RNase-Free DNase Set (Qiagen) according to the manufacturer's instructions and assessed for purity using the NanoDrop system (NanoDrop Technologies, Wilmington, DE). Total mRNA was reverse transcribed to cDNA using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems) according to the manufacturer's instructions. Polymerase chain reaction (PCR) was performed using the Fast 7500 real-time PCR system (Applied Biosystems) using Power SYBR® Green PCR Master Mix kits (Applied Biosystems). The thermal profiles consisted of 10 min at 95 °C for denaturing, followed by 40 cycles of 95 °C for 15 s, annealing at 60 °C for 1 min. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA was used as the housekeeping gene, and all data are represented relative to its expression (i.e., using standard curve methods) as fold change from the rest group. Specific PCR primer pairs for each studied gene are shown in Table 1.

2.8. Statistical analyses

All statistical analyses were performed using SPSS V17.0. The statistical significance of differences between groups on CK and LDH in plasma, hydrogen peroxide, and mRNA expression was determined using two-way ANOVA. In any analysis, if significant interactions were observed, then comparisons with the Tukey HSD post hoc test were performed.

Table 1
Primer sequences for real-time RT–PCR analysis.

Gene	Forward	Reverse
GAPDH	TGAAGCAGGCATCTGAGGG	CGAAGGTGGAAGAGTGGGAG
NADPH Oxidase	TTGGGTCAGCACTGGCTCTG	TGGCGGTGTGCAGTGCTATC
COX-2	AGAAGGAAATGGCTGCAGAA	GCTCGGCTTCCAGTATTGAG
MCP-1	CTTCTGGGCCTGCTGTTCA	CCAGCCTACTCATTGGGATCA
CXCL14	CCAAGATTCGCTATAGCGAC	CCTGCGCTTCTCGTTCCAGG
F4/80	CTTTGGCTATGGGCTTCCAGTC	GCAAGGAGGACAGAGTTTATCGTG

3. Results

3.1. Effects of downhill running and curcumin administration on plasma creatine kinase (CK) and lactate dehydrogenase (LDH) activities

To assess the effect of curcumin administration on downhill running–induced muscle damage, we examined plasma CK and LDH activities as muscle damage markers in plasma (Table 2). Plasma CK and LDH activities were significantly affected by downhill running. However, plasma CK and LDH activities were not significantly affected by curcumin administration [CK: an effect of downhill exercise: $F(1,48) = 10.7$, $P < 0.01$, curcumin: $F(1,48) = 0.001$, n.s., and exercise x curcumin interaction: $F(1,48) = 0.65$, n.s., and LDH: an effect of downhill exercise: $F(1,48) = 5$ .99, $P < 0.05$, curcumin: $F(1,48) = 0.007$, n.s., and exercise × curcumin interaction: $F(1,48) = 1.38$, n.s.].

3.2. Effects of downhill running and curcumin administration on hydrogen peroxide concentration and NADPH-oxidase mRNA expression

To identify the effect of curcumin administration on downhill running–induced oxidative stress, we examined hydrogen peroxide concentration and NADPH-oxidase mRNA expression in skeletal muscle (Fig. 1). Hydrogen peroxide concentration and NADPH-oxidase mRNA expression were significantly affected by downhill running [hydrogen peroxide: an effect of downhill exercise: $F(1,44) = 6.62$, $P < 0.05$, curcumin: $F(1,44) = 3.12$, n.s., and exercise × curcumin interaction: $F(1,44) = 4.89$, $P < 0.05$, and NADPH-oxidase: an effect of downhill exercise: $F(1,48) = 8.74$, $P < 0.01$, curcumin: $F(1,48) = 1.48$, n.s., and exercise × curcumin interaction: $F(1,48) = 5.95$, $P < 0.05$]. Hydrogen peroxide concentration in the downhill running mice was significantly higher than that in the rest mice ($P < 0.01$). However, hydrogen peroxide concentration was significantly attenuated by curcumin administration in the downhill running mice ($P < 0.01$, Fig. 1 A). Moreover, NADPH-oxidase mRNA expression in downhill running mice was significantly higher than that in the rest mice ($P < 0.01$). However, NADPH-oxidase mRNA expression was significantly attenuated by curcumin administration in the downhill running mice ($P < 0.05$, Fig. 1 B).

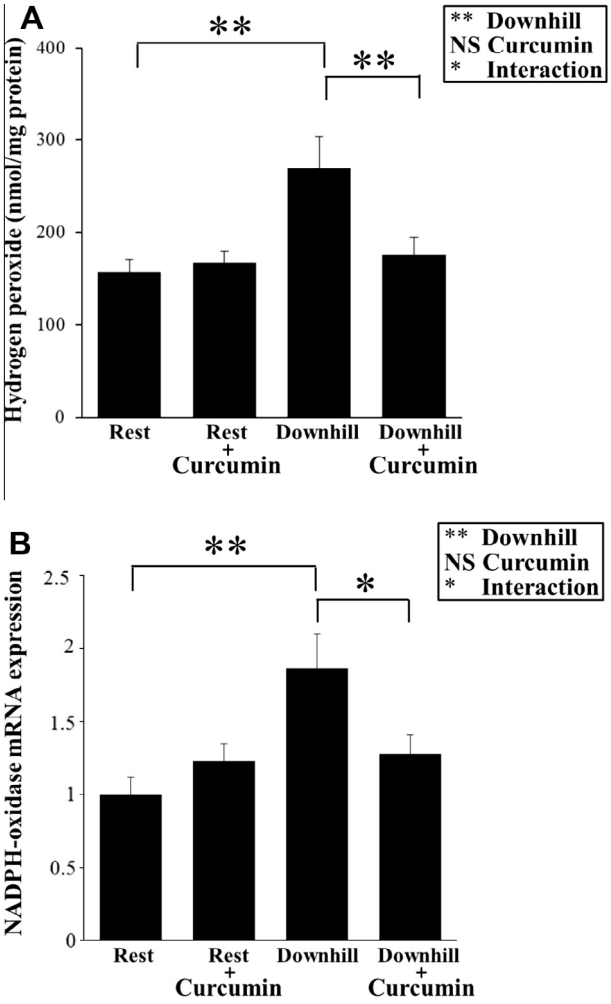

Fig. 1. Effects of downhill running and curcumin administration on hydrogen peroxide concentration and NADPH-oxidase mRNA expression in gastrocnemius muscle of mice. The values are the means ± SEM. Analyses were performed using 2-way ANOVA for multiple groups (boxed text). NS: not significant, $^{*}P < 0.05$, $^{**}P < 0.01$.

3.3. Effects of downhill running and curcumin administration on COX-2 mRNA expression

To identify the effect of curcumin administration on downhill running–induced inflammation, we examined COX-2 mRNA expression in skeletal muscle (Fig. 2). COX-2 mRNA expression levels were significantly affected by downhill running [an effect of downhill exercise: $F(1,48) = 10.04$, $P < 0.01$, curcumin: $F(1,48) = 0.002$, n.s., and exercise × curcumin interaction: $F(1,48) = 0.58$, n.s.].

Table 2
Effects of downhill running and curcumin administration on creatine kinase (CK) and dehydrogenase (LDH) activities in plasma of mice.

	Rest		Downhill running		Two-way ANOVA		
	PBS	Curcumin	PBS	Curcumin	Downhill	Curcumin	Interaction
CK (IU/L)**	148.8 ± 92.9	89.3 ± 40.3	336.9 ± 99.5	400.7 ± 124.7	$P < 0.05$	NS	NS
LDH (IU/L)*	313.0 ± 30.8	294.2 ± 15.0	526.7 ± 65.0	650.4 ± 120.6	$P < 0.01$	NS	NS

The values are the means ± SEM.
** $P < 0.01$, *<0.05: effect of downhill running.

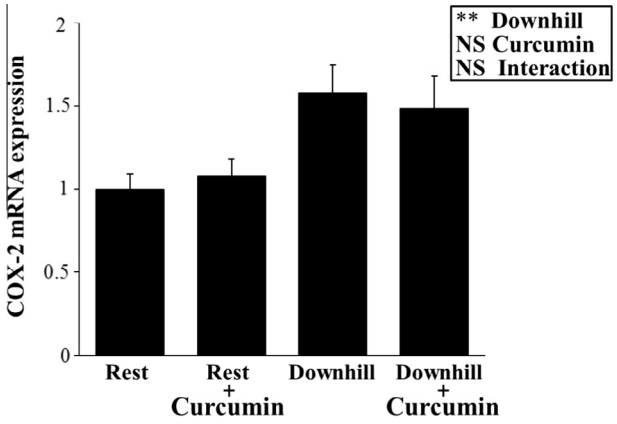

Fig. 2. Effects of downhill running and curcumin administration on COX-2 mRNA expression in gastrocnemius muscle of mice. The values are the means ± SEM. Analyses were performed using 2-way ANOVA for multiple groups (boxed text). NS: not significant, $^{**}P < 0.01$.

3.4. Effects of downhill running and curcumin administration on MCP-1 and CXCL14 mRNA expression

To identify the effect of curcumin administration on downhill running–induced macrophage chemokines, we examined MCP-1 and CXCL14 mRNA expression in skeletal muscle (Fig. 3). MCP-1 mRNA expression was significantly affected by downhill running and curcumin administration [an effect of downhill exercise: $F(1,48) = 19.3$, $P < 0.01$, curcumin: $F(1,48) = 4.59$, $P < 0.05$, and exercise × curcumin interaction: $F(1,48) = 2.87$, n.s.]. In addition, CXCL14 mRNA expression was significantly affected by downhill running [an effect of downhill exercise: $F(1,48) = 7.25$, $P < 0.01$, curcumin: $F(1,48) = 1.52$, n.s., and exercise × curcumin interaction: $F(1,48) = 1.14$, n.s.]. MCP-1 and CXCL14 mRNA expression in the downhill running mice was significantly higher than that in the rest mice ($P < 0.01$, Fig. 3 A and B). However, MCP-1 mRNA expression was not significantly changed by curcumin administration in the downhill running mice ($P < 0.01$, Fig. 3 A).

3.5. Effects of downhill running and curcumin administration on F4/80 mRNA expression

To investigate the effects on macrophage infiltration, we examined gene expression of F4/80 reflecting presence of monocytes and macrophages (Fig. 4). F4/80 mRNA expression was significantly affected by downhill running [an effect of downhill exercise: $F(1,48) = 12.14$, $P < 0.01$, curcumin: $F(1,48) = 3.15$, n.s., and exercise × curcumin interaction: $F(1,48) = 5.17$, $P < 0.05$]. F4/80 mRNA expression in the downhill running mice was significantly higher than that in the rest mice ($P < 0.01$, Fig. 4). However, F4/80 mRNA expression was significantly attenuated by curcumin administration in the downhill running mice ($P < 0.01$, Fig. 4).

4. Discussion

Muscle damage caused by downhill running leads to oxidative stress and inflammatory reaction. Indeed, it is shown that hydrogen peroxide and inflammatory cytokines such as TNF-α were increased by downhill running [3,4]. Recently, it is well known that curcumin possesses anti-oxidant and anti-inflammatory properties. In fact, it was shown that curcumin reduced inflammatory cytokine concentrations such as TNF-α and IL-1β in skeletal muscle after downhill running [19]. We have already found that curcumin concentration in the blood and skeletal muscle showed the highest

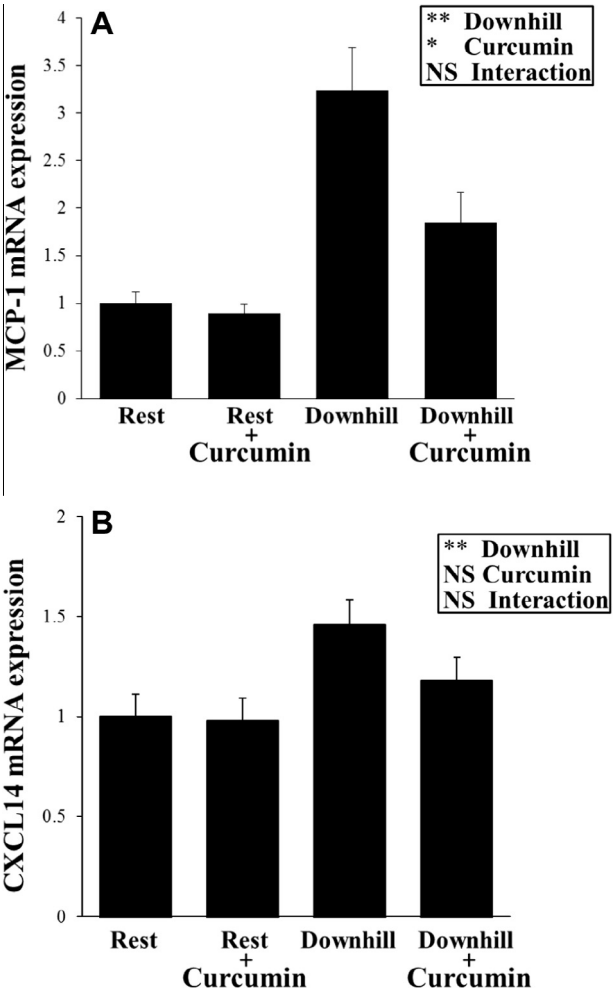

Fig. 3. Effects of downhill running and curcumin administration on MCP-1 (A) and CXCL14 (B) mRNA expression in gastrocnemius muscle of mice. The values are the means ± SEM. Analyses were performed using 2-way ANOVA for multiple groups (boxed text). NS; not significant, $^{**}P < 0.01$.

levels 3 h after oral administration of curcumin, and the large difference is maintained until after 24 h [20]. However, in this study, curcumin did not reduce plasma CK and LDH activities as muscle damage markers after downhill running. Therefore, curcumin administration immediately after downhill running may not prevent downhill running-induced muscle damage. On the other hand, we have shown that curcumin reduces hydrogen peroxide concentration and NADPH-oxidase gene expression in skeletal muscle after downhill running. Therefore, these results indicate that curcumin may also induce an anti-oxidant effect following downhill running-induced muscle damage. However, it is not known how curcumin affects oxidative stress following downhill running-induced muscle damage.

Interestingly, previous studies have shown that macrophages and neutrophils were infiltrated to skeletal muscle tissue after downhill running-induced muscle damage [5–7]. In addition, NADPH oxidase exists on membranes in macrophages and neutrophils, which induces hydrogen peroxide production [21]. Moreover, hydrogen peroxide produced by induced NADPH-oxidase mediates NF-κB signaling pathway activity, which induces expression of inflammatory mediators such as TNF-α [22,23]. Therefore, infiltration of macrophages and neutrophils may provide an important factor of oxidative stress and inflammatory reaction following downhill running-induced muscle damage. In the present study, we indicated that downhill running induced up-regulation of

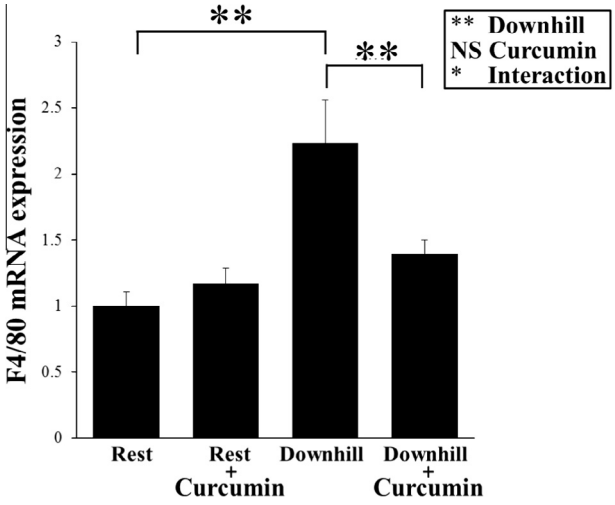

Fig. 4. Effects of downhill running and curcumin administration on F4/80 mRNA expression in gastrocnemius muscle of mice. Analyses were performed using 2-way ANOVA for multiple groups (boxed text). The values are the means ± SEM. NS: not significant, $^{*}P < 0.05$, $^{**}P < 0.01$.

F4/80 mRNA expression in skeletal muscle. On the other hand, curcumin administration decreased F4/80 mRNA expression after downhill running. Therefore, curcumin may attenuate macrophage infiltration in skeletal muscle after downhill running. Moreover, curcumin administration-induced suppression of hydrogen peroxide production and NADPH-oxidase expression may be caused by depression of macrophage infiltration in skeletal muscle after downhill running. The factors affecting the inhibition of macrophage infiltration in skeletal muscle by curcumin administration are presently unknown. MCP-1 and CXCL14 are secreted by various types of cells such as endothelial cells and myocytes, and serve as a chemotactic and activating factor for the recruitment of monocytes [8]. In fact, it is reported that MCP-1 and CCR2 knockout mice show attenuated macrophage infiltration in skeletal muscle after muscle damage by cardiotoxin injection [10]. In addition, COX-2 knockout mice also showed less macrophage infiltration of lacerate-induced muscle damage [12]. Therefore, COX-2 also modulates macrophage infiltration after muscle damage. In the present study, we suggested that downhill running not only induced up-regulation of the F4/80 mRNA, but also increased the mRNA expression of MCP-1, CXCL14 and COX-2. Therefore, chemokines (such as MCP-1 and CXCL14) and COX-2 may play a role in the infiltration of macrophages after downhill running-induced muscle damage. Curcumin suppresses macrophage infiltration in adipose tissue in obese mice [24]. In addition, previous studies have shown that curcumin inhibited MCP-1 production via suppression of NF-κB signaling pathway *in vitro* [25–27]. In addition, curcumin administration suppresses plasma concentration of MCP-1 in diabetic model rats [28]. However, the effects of curcumin administration on chemokines and COX-2 expression in skeletal muscle have been unclear until now. We observed that curcumin administration reduced MCP-1 mRNA expression in skeletal muscle after downhill running. On the other hand, CXCL14 and COX-2 mRNA expression did not change by curcumin administration after downhill running. Therefore, our study indicated that curcumin administration-induced depression of macrophage infiltration was caused by suppression of MCP-1 production in skeletal muscle after downhill running. MCP-1 is mainly induced by NF-κB signaling pathway [29]. On the other hand, COX-2 is induced not only by NF-κB signaling pathway, but also it is induced by several cytokines and growth factors [30,31]. Moreover, CXCL14 is induced by prostaglandin E2 production via COX-2 expression [32]. Interestingly, although NF-κB signaling in skeletal muscle is activated by downhill running [3], curcumin specifically inhibited activation of NF-κB signaling pathway. Therefore, curcumin may only inhibit MCP-1 mRNA expression.

The limitation of this study was that the present experiment was carried out without isolation of macrophages and myocytes from muscle tissue. Chemokines such as MCP-1 and CXCL14 were secreted by myocytes. In addition, reactive oxygen species such as hydrogen peroxide were secreted by macrophages and neutrophils. However, it is not clear whether which cells were affected by curcumin. Therefore, future studies need to examine this in detail using analyses of isolated macrophages and myocytes from muscle tissues.

5. Conclusion

Curcumin administration is considered to result in suppression of oxidative stress and inflammatory reaction. However, it has still been unclear whether curcumin administration attenuates oxidative stress following downhill running-induced muscle damage. The present study demonstrated that curcumin administration effectively suppressed downhill running-induced hydrogen peroxide production and NADPH-oxidase expression in skeletal muscle. Therefore, curcumin may be beneficial for the prevention of oxidative stress in downhill running-induced skeletal muscle damage.

Information about the contributions of each author

N.K. contributed to the conception and design of this study and to write the manuscript. K.K., M.T., M.T. and D.S. performed the experimental work and analysis of the results. Y.O., A.I. and H.Y. performed the experimental work and analysis of the results. K.S. has primary responsibility for final content.

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