

## Hypoxia with or without treadmill exercises affects slow-twitch muscle atrophy in a rat model of rheumatoid arthritis

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**INTRODUCTION:** In rheumatoid arthritis (RA), the control of arthritis has been improved by the development of drug therapy, but the loss of muscle mass, which is the cause of ADL impairment, is difficult to recover. We reported treadmill running in a rat model of RA inhibits the production of Cx43 and TNF- $\alpha$  in the synovial membrane, as well as the degeneration of articular cartilage and sub-chondral bones, and it prevents the atrophy of slow-twitch muscles. On the other hand, it is known that a sustained hypoxic environment suppresses synovitis and controls joint destruction in an animal model of RA. In addition, it is reported that hypoxia in muscles promotes muscle hypertrophy. In this study, we analyzed the effects of hypoxic environment with or without treadmill running on slow-twitch muscle fibers in a rat model of arthritis.

**METHODS:** Eight-week-old Dark Agouti rats were sensitized to type 2 collagen to produce rats with arthritis (CIA) and reared in a hypoxic chamber (O<sub>2</sub> 12%). Rats were randomly divided into the following three groups (N = 6 each): CIA rat normoxia-sedentary group (Normo-no), CIA rat hypoxia-sedentary group (Hypo-no), and CIA rat hypoxia-treadmill running group (Hypo-ex). Only the Hypo-ex group was forced to run from day 28 to day 42 on a treadmill device in hypoxia chamber. The running protocol used for this group had previously been reported to have an inhibitory effect on muscle atrophy in the rat RA model and was as follows: running 5 times/week, 12 m/min, and 30 min/day. All rats were euthanized 48 hours after running on day 42, and soleus muscles were harvested for histological analysis by laminin staining and mRNA analysis by real time RT-PCR.

**RESULTS SECTION:** The relative soleus weight values in the Hypo-no and Hypo-ex groups were 1.23- and 1.36-fold higher than the Normo-no group ( $p < 0.05$  and  $p < 0.01$ , respectively; Figure 1). The relative muscle cross-sectional area of the soleus in the Hypo-ex group was significantly increased compared to the Normo-no and Hypo-no groups (1.52- and 1.24-fold,  $p < 0.01$  and  $p < 0.05$ , respectively; Figure 2). No significant differences in soleus expression levels of HIF-1 $\alpha$  and atrogen-1, a marker of muscle protein degradation, among experimental groups were observed (Figure 3). However, the expression of p70S6K, a marker of muscle protein synthesis, was significantly higher in the Hypo-no (1.49-fold) and Hypo-ex (1.46-fold) groups than the Normo-no group ( $p < 0.05$  and  $p < 0.01$ , respectively).

**DISCUSSION:** In CIA rats, slow-twitch muscle atrophy could be prevented in hypoxic environment with or without treadmill running. Targeting the slow-twitch muscles in particular may lead to recovery from ADL disability.

**SIGNIFICANCE/CLINICAL RELEVANCE:** It may indicate that combining various exercise regimens with a hypoxic environment, especially for slow-twitch muscles, is effective in sarcopenia that occurs after inflammation.

### REFERENCES:

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### IMAGES AND TABLE

