

# Sustained hypoxia with treadmill running ameliorates destruction of articular cartilage in a rat model of rheumatoid arthritis

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**INTRODUCTION:** Rheumatoid arthritis (RA) impairs joint function because of joint destruction due to synovitis. Recently, the use of biological agent in the treatment of RA has markedly enabled suppression of joint destruction, however a different approach is required because of the duration of efficacy, side effects and economic burden. We focused on exercise therapy due to solve these problems<sup>1,2</sup>. We reported that sustained hypoxia suppresses joint destruction by control of synovitis in animal model of RA<sup>3</sup>, and also reported that moderate treadmill exercise can suppress arthritis as well<sup>1</sup>. In this study, we evaluate joint destruction in a collagen-induced arthritis (CIA) rat model by treadmill running under sustained hypoxia and the efficacy and safety of this treatment.

**METHODS:** 8 weeks old Dark Agouti rats were immunosensitized by type 2 collagen to create rat CIA models, and raised in a hypoxic chamber (O<sub>2</sub> 12%). We randomly divided all the sensitized rats into the following three groups (n= 6): the normoxia-no running group (Control), hypoxia-no running group (H-N), and hypoxia-treadmill running group (H-T). Only the H-T group was made to run on a treadmill in a hypoxic chamber from day 28 to 42. The running protocol for H-T group was as follows: 5 times/week, speed of 12 m/min, and 30 min/day<sup>1</sup>. All rats were sacrificed on day 44; 48 hours after running of on day 42, and we removed ankle joints, and performed histological analysis by Safranin O staining.

**RESULTS SECTION:** On day 14 and 16, at the time when inflammatory processes are strongest, joint swelling was suppressed in the H-N and H-T groups compared with the Control group. On day 44, joint destruction was suppressed compared with the Control group (Figure 2), and the Histological Score (0-3 points; from no damage to completely destroyed cartilage layers) was 2.33 for the Control group, 1.33 for the H-N group, 1.50 for the H-T group; the H-N and H-T groups improved compared with the Control group (p < 0.05, respectively; Figure 3). This study found no significant difference between the H-N and H-T groups.

**DISCUSSION:** We reported that sustained hypoxia ameliorated synovitis by downregulation of HIF-1 $\alpha$ , as a result, suppressed joint destruction<sup>3</sup>. In this study, the hypoxic environment induced had an effect of suppressing joint destruction with or without treadmill running. We expected a synergistic effect of sustained hypoxia and exercise therapy, but the exercise protocol<sup>1</sup> that had a therapeutic effect under normoxia could not be showed the synergistic effect. On the other hand, excessive exercise may have negative effect on the joints at the inflammatory phase, but this exercise in our study was safety without negative effect. So we believe that exercise therapy under hypoxia may be the innovative treatment for arthritis with maintaining muscle strength, however, we need to be examined the exercise protocol due to further suppressing of joint destruction.

**SIGNIFICANCE/CLINICAL RELEVANCE :**

Exercise therapy can be combined with hypoxia for joint destruction in inflammatory diseases, and has possibility to improve ADL further by maintaining muscle strength in addition to suppressing joint destruction.

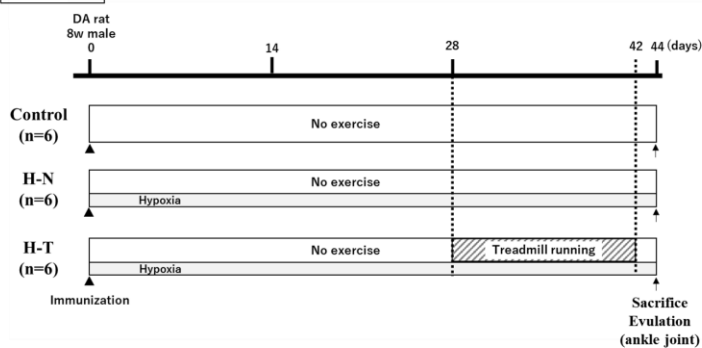
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- 1) Shimomura S, et al.: Int J Mol Sci 2018
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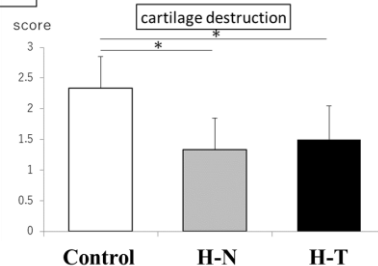
**ACKNOWLEDGEMENTS:** This research was subsidized by JSPS KAKENHI Grant Number 19K19914, 21K11172, 21K11292.

**IMAGES AND TABLE**

**Figure1**



**Figure3**



**Figure2**

**Safranin O staining**

