Low-to-Moderate Intensity Exercise Reverses Nerve Growth Factor Upregulation in Osteoarthritic Rats

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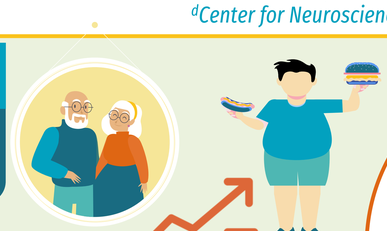
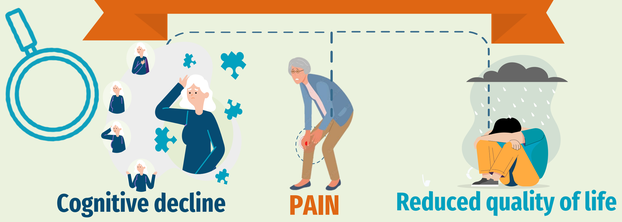
Aging population & ↑ obesity rates

In an era marked by an aging population and rising obesity rates, osteoarthritis (OA) has emerged as a leading cause of chronic pain and disability globally[1].



Osteoarthritis



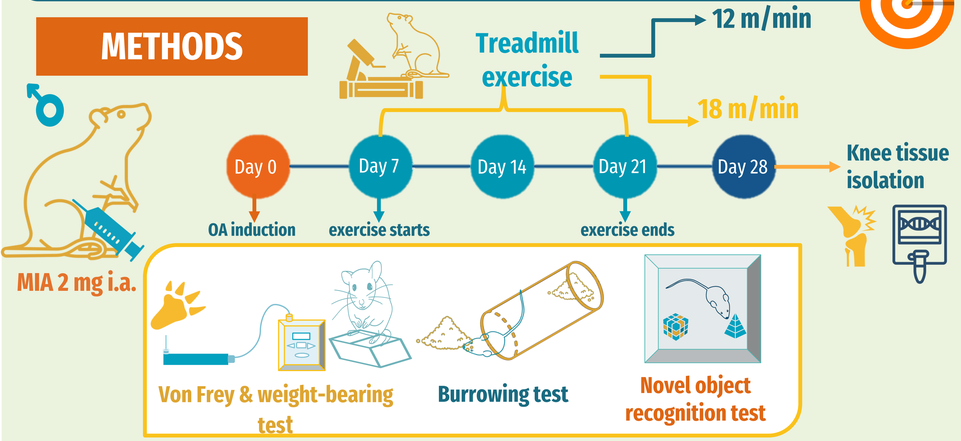
Exercise as a core therapy for OA management

Established treatment guidelines endorse exercise as a core therapy for OA management with/without pharmacological interventions[2,3]. In addition to pain relief, exercise may also improve mental health and cognitive function[4].

How exercise relieves pain is not yet fully understood.

We aimed to explore the effects of a two-week exercise intervention on pain-related behavior, general well-being, and cognitive function in an OA rat model. In particular, we wanted to elucidate the influence of exercise on molecular markers contributing to peripheral sensitization, cytokines (IL-1β and TNF-α) and nerve growth factor (NGF), a promising target for pain control in OA.

METHODS



- ❑ OA was induced by intra-articular injection of monoiodoacetate (MIA; 2 mg) in male Wistar rats. Sham-control rats received the same volume of saline injection[5].
- ❑ On day 7 post-MIA, rats were randomly assigned to low-to-moderate (12 m/min) or moderate-to-high (18 m/min) exercise intensity groups. Treadmill exercise, lasting 30 min/day for 5 consecutive days, followed by a 2-day rest was conducted over a two-week period.
- ❑ Behavioral tests were performed prior to OA induction and at weekly intervals until day 28.
- ❑ Pain-related behavior was assessed using the von Frey and weight-bearing test.
- ❑ General well-being was evaluated in the burrowing test.
- ❑ The cognitive performance of the rats was assessed on day 27 using the novel object recognition test (NORT).
- ❑ On day 28, animals were sacrificed and knee tissue was collected for qRT-PCR analysis of cytokines (IL-1β and TNF-α) and NGF.

RESULTS

Pain-related behavior

Both exercise intensities reversed MIA-induced mechanical hypersensitivity and weight-bearing deficits ($P \leq 0.027$ *vs.* MIA-control).

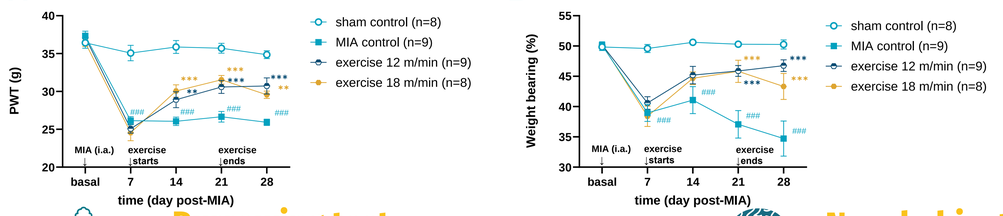


Fig. 1. Two-week exercise intervention of both low-to-moderate (12 m/min) and moderate-to-high (18 m/min) intensity reversed MIA-induced mechanical hypersensitivity (A) and weight-bearing deficits (B) in rats with MIA-induced OA. Results were presented as time-course data of paw withdrawal threshold (PWT) (A) and weight-bearing (%) (B) during the 28-day experiment (###P < 0.001 sham control *vs.* MIA control; *P < 0.05, **P < 0.01, ***P < 0.001 MIA control *vs.* exercise groups, two-way repeated measures ANOVA followed by Tukey *post-hoc* test).

Burrowing test

Higher exercise intensity depressed burrowing behavior on day 20 (P = 0.005 *vs.* sham control), while lower intensity exercise had no significant impact on burrowing ($P \geq 0.77$ *vs.* sham control).

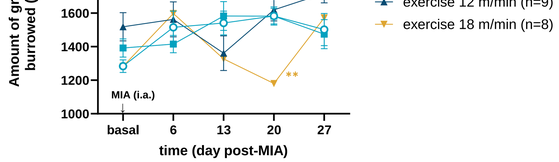


Fig. 2. The effects of two-week exercise intervention of low-to-moderate (12 m/min) and moderate-to-high (18 m/min) intensity on burrowing behaviour of rats with MIA-induced OA. Results were presented as time-course data of burrowing behaviour during the 28-day experiment (**P < 0.01 MIA control *vs.* exercise groups, two-way repeated measures ANOVA followed by Tukey *post-hoc* test).

Novel object recognition test

Lower intensity exercise improved the cognitive performance of rats with OA in NORT (P = 0.01 *vs.* MIA-control), while higher intensity exercise failed to produce similar benefits (P > 0.99 *vs.* MIA-control).

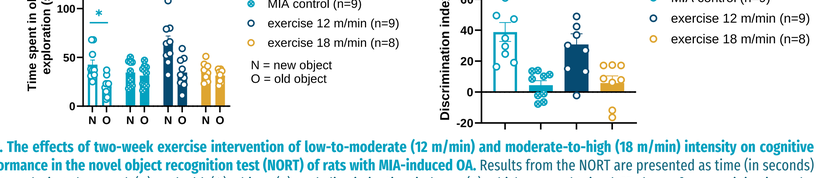


Fig 3. The effects of two-week exercise intervention of low-to-moderate (12 m/min) and moderate-to-high (18 m/min) intensity on cognitive performance in the novel object recognition test (NORT) of rats with MIA-induced OA. Results from the NORT are presented as time (in seconds) spent exploring the novel (N) and old (O) object (A) and discrimination indexes (B) which were obtained 27 days after MIA injection. The differences between time spent in exploring the N and O object was analyzed using two-way ANOVA, with Tukey *post-hoc* test (*P < 0.05, ***P < 0.001 for the comparison between time spent exploring the N *vs.* the O object) and discrimination indexes were analyzed with one-way ANOVA, followed by Tukey *post-hoc* test (###P < 0.001 sham control *vs.* MIA control; **P < 0.01 MIA control *vs.* exercise groups) .

qRT-PCR

Lower intensity exercise reversed the increase in *Ngf* mRNA expression (P = 0.02 *vs.* MIA-control), whereas higher exercise intensity did not attenuate *Ngf* mRNA upregulation (P = 0.82 *vs.* MIA-control).

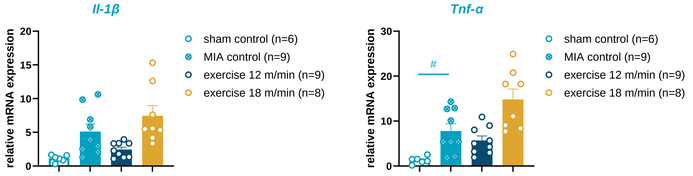


Fig. 4. The effects of two-week exercise intervention of low-to-moderate (12 m/min) and moderate-to-high (18 m/min) intensity on the mRNA expression of *Il-1β*, *Tnf-α* and *Ngf* in knee tissue of rats with MIA-induced OA. The mRNA expression of *Il-1β*, *Tnf-α and Ngf* was determined by qRT-PCR after 28 days of OA induction (#P < 0.05 sham control *vs.* MIA control group; *P < 0.05 MIA control *vs.* exercise groups, one-way ANOVA, followed by a Tukey *post-hoc* test).

Low-to-moderate intensity exercise outperforms its moderate-to-high intensity counterpart!

- ❑ While both exercise intensities effectively mitigated pain-related behavior (with the effects persisting after exercise cessation), low-to-moderate intensity exercise may offer more benefits.
- ❑ It reversed cognitive deficits without detrimental effects on animal well-being.
- ❑ Lower intensity exercise prevented the upregulation of *Ngf* in knee tissue, *a crucial mediator of OA pain.*

References

1. Hunter DJ et Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019 Apr 27;393(10182):1745-1759.
2. Kolasinski SL et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. 2020 Feb;72(2):220-233.
3. Rausch Osthoff AK et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis. 2018 Sep;77(9):1251-1260.
4. Mandolesi L et al. Effects of Physical Exercise on Cognitive Functioning and Wellbeing: Biological and Psychological Benefits. Front Psychol. 2018 Apr 27;9:509.
5. Nastić K et al. The antidepressant drugs vortioxetine and duloxetine differentially and sex-dependently affect animal well-being, cognitive performance, cardiac redox status and histology in a model of osteoarthritis. Biomed Pharmacother. 2023 Oct;166:115360.

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