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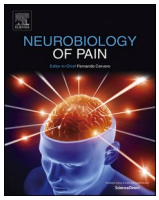

Editorial

Is exercise therapy the first-line treatment for chronic pain?

Chronic pain not only significantly reduces the quality of life of patients, but also imposes a heavy burden on society. Since the opioid crisis in North America is still fresh in our memories and warnings have been issued against the widespread and indiscriminate use of Gabapentinoid (Goodman and Brett, 2019), exercise therapy is attracting attention as an effective, inexpensive, and safe treatment.

In 2017, in the first volume of Neurobiology of Pain, we proposed that chronic pain is a lifestyle-related disease and that chronic pain can be improved by changing inactive lifestyle habits (Senba and Kami, 2017). Patients with chronic pain are more likely to have depression and sleep disturbances (Senba, 2015), and the brain reward system, i.e., DAergic projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), is reduced, resulting in reduced function of NAc (Baliki et al., 2010).

Many articles in this special issue focus on the relationship between exercise and the limbic brain functions. A line of evidence has been accumulated on the relationship between chronic pain and the brain reward system. For example, chronic pain resulted in decreased c-Fos expression in the VTA (Narita et al., 2003) and optogenetic activation of a VTA-NAc pathway significantly improves hyperalgesia in neuropathic pain (NPP) models (Tanaka et al., 2023). Exercise was shown to activate the DA neurons of the VTA (Greenwood et al., 2011), and selective suppression of these DA neurons failed to cause exercise-induced hypoalgesia (EIH), indicating that activation of VTA DA neurons is essential to initiate EIH (Wakaizumi et al., 2016).

We showed that two weeks of voluntary exercise in NPP model mice suppressed pain behavior and activated DA neurons in the VTA (Kami et al., 2018), also showing that neurons in the laterodorsal tegmental nucleus in the midbrain and Orexin neurons in the lateral hypothalamus trigger the activation of VTA DA neurons. In addition to exercise, the activation of VTA DA neurons seems to be induced by enriched environments and positive emotions (Tanaka et al., 2023). The limbic system includes amygdala (Amyg), medial prefrontal cortex (mPFC), ventral hippocampus, in addition to the brain reward system. The limbic system of chronic pain patients is dysfunctional, and exercise therapy and active lifestyle may reduce pain by normalizing the limbic function (Senba and Kami, 2023).

In fact, patients with fibromyalgia (FM) were subjected to 3 weeks of exercise therapy, which resulted in an improvement in motor performance, along with changes in the functional connectivity of each limbic regions (Kan et al., 2023). Moreover, chronic pain patients with an exercise habit showed significant less pain compared to those without an exercise habit, and brain MRI data identified three brain regions (thalamus, Amyg, mPFC) mediating the exercise effect on pain (Wakaizumi et al., 2023). Following 15-week exercise intervention, FM patients reported a reduction of pain intensity, FM severity and depression (Löfgren et al., 2023). A systematic review of intervention studies revealed the effect of exercise on brain function and pain perception/quality of life in adults with either osteoarthritis (OA) or FM (Palmer et al., 2023).

In addition to the brain mechanisms, the roles of immune system and autonomic nervous system in EIH were also emphasized in this special issue. Routine exercise was shown to be beneficial as an intervention to promote an anti-inflammatory immune profile which can subsequently reduce pain (Lesnak et al., 2023). Bossenger et al. (2023) examined the effects of acute isometric exercise on the autonomic nervous system in patients with knee OA or FM, and found that these patients exhibited reduced vagal tone and reduced autonomic modulation in response to exercise, which may contribute to impaired nociceptive processing and EIH in chronic pain patients.

In conclusion, the improvement of the patient's lifestyle by normalizing the function of the brain reward and limbic systems was shown as the main effect of exercise therapy, and other mechanisms that complement it were discussed from multiple perspectives. I am grateful to all the authors contributed to this special issue with their in-depth insights into the various aspects of pain. We hope that these discussions will greatly contribute to the development of future research in this field, and that exercise therapy will play an increasingly important role in the treatment of chronic pain and associated disorders.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Baliki, M.N., Geha, P.Y., Fields, H.L., Apkarian, A.V., 2010. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron 66, 149–160.

Bossenger, N.R., Lewis, G.N., Rice, D.A., Shepherd, D., 2023. The autonomic and nociceptive response to acute exercise is impaired in people with knee osteoarthritis. Neurobiol. Pain. 13, 100118.

Goodman, C.W., Brett, A.S., 2019. Gabapentinoids for pain: potential unintended consequences. Am. Fam. Phys. 100, 672–675.

Greenwood, B.N., Foley, T.E., Le, T.V., Strong, P.V., Loughridge, A.B., Day, H.E., Fleshner, M., 2011. Long-term voluntary wheel running is rewarding and produces plasticity in the mesolimbic reward pathway. Behav. Brain Res. 217, 354–362.

Kami, K., Tajima, F., Senba, E., 2018. Activation of mesolimbic reward system via laterodorsal tegmental nucleus and hypothalamus in exercise-induced hypoalgesia. Sci. Rep. 8, 11540.

https://doi.org/10.1016/j.ynpai.2024.100154

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Kan, S., Fujita, N., Shibata, M., Miki, K., Yukioka, M., Senba, E., 2023. Three weeks of exercise therapy altered brain functional connectivity in fibromyalgia inpatients. Neurobiol. Pain 14, 100132.

Lesnak, J.B., Berardi, G., Sluka, K.A., 2023. Influence of routine exercise on the peripheral immune system to prevent and alleviate pain. Neurobiol. Pain 13, 100126.

Löfgren, M., Sandström, A., Bileviciute-Ljungar, I., Mannerkorpi, K., Gerdle, B., Ernberg, M., Fransson, P., Kosek, E., 2023. The effects of a 15-week physical exercise intervention on pain modulation in fibromyalgia: Increased pain-related processing within the cortico-striatal- occipital networks, but no improvement of exercise-induced hypoalgesia. Neurobiol. Pain 13, 100114.

Narita, M., Ozaki, S., Narita, M., Ise, Y., Yajima, Y., Suzuki, T., 2003. Change in the expression of c-fos in the rat brain following sciatic nerve ligation. Neurosci. Lett. 352, 231–233.

Palmer, K.L., Shivgulam, M.E., Champod, A.S., Wilson, B.C., O'Brien, M.W., Bray, N.W., 2023. Exercise training augments brain function and reduces pain perception in adults with chronic pain: a systematic review of intervention studies. Neurobiol. Pain 13, 100129.

Senba, E., 2015. A key to dissect the triad of insomnia, chronic pain, and depression. Neurosci. Lett. 589, 197–199.

Senba, E., Kami, K., 2017. A new aspect of chronic pain as a lifestyle-related disease. Neurobiol. Pain 1, 6–15.

Senba, E., Kami, K., 2023. Exercise therapy for chronic pain: How does exercise change the limbic brain function? Neurobiol. Pain 14, 100143.

Tanaka, K., Kuzumaki, N., Hamada, Y., Suda, Y., Mori, T., Nagumo, Y., Narita, M., 2023. Elucidation of the mechanisms of exercise-induced hypoalgesia and pain prolongation due to physical stress and the restriction of movement. Neurobiol. Pain 14, 100133.

Wakaizumi, K., Kondo, T., Hamada, Y., Narita, M., Kawabe, R., Narita, H., Watanabe, M., Kato, S., Senba, E., Kobayashi, K., Kuzumaki, N., Yamanaka, A., Morisaki, H., Narita, M., 2016. Involvement of mesolimbic dopaminergic network in neuropathic pain relief by treadmill exercise-a study for specific neural control with Gi-DREADD in mice. Mol. Pain 12. https://doi.org/10.1177/1744806916681567.

Wakaizumi, K., Reckziegel, D., Jabakhanji, R., Apkarian, A.V., Baliki, M.N., 2023. Influence of exercise on pain is associated with resting-state functional connections: a cross-sectional functional brain imaging study. Neurobiol. Pain 13, 100125.

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