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Limbic Brain's Response to Exercise Therapy in Chronic Pain Management

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Description

Chronic pain adversely disrupts the daily lives of patients and continues to impose a burden on modern societies. Currently, there are no effective medications for chronic pain, and people suffer from the side effects of taking large amounts of medication for long periods of time. The opioid crisis in North America is still ongoing. Warnings have been issued against the widespread and indiscriminate use of Gabapentinoid, which is prescribed as an alternative to Opioid. Therefore, in many countries, exercise therapy combined with patient education and Cognitive Behavioral Therapy (CBT), recommended as the first line of treatment for chronic pain, and randomized controlled studies have demonstrated its effectiveness [1].

However, we still do not know the mechanisms how exercise therapy reduces chronic pain. To explore this issue, we focused on the fact that the limbic system of patients with chronic pain is dysfunctional and causes various behavioral disorders. One of the behavioral disorders is that patients are trapped in fear and avoidance thoughts, cannot move their bodies due to fear of pain, and prolonged avoidance of movement and physical inactivity exacerbate pain.

After a series of animal experiments, we found that in a mouse model of neuropathic pain, the function of the brain reward system was reduced and the amygdala was over activated, while two weeks of voluntary exercise on a running disk successfully activated DA neurons in the Ventral Tegmental Area (VTA), i.e., the brain reward system and normalized the activity of the amygdala [2,3]. Naturally, the more the mouse runs, the greater the pain relief effect. Exercise was also found to intensify the projection from the Basal Nucleus (BA) of the amygdala to the Nucleus Accumbens (NAc), which allows for goal-directed and positive behaviors in the face of crises and problems [3]. There are positive neurons and negative neurons in the BA, the former projecting to the NAc and causing positive actions, and the latter projecting to the Central Nucleus of the Amygdala (CeA) and causing negative actions such as freezing. We also observed that exercise almost completely suppresses CeA neurons.

The limbic system consists of the brain reward system, in which DA neurons in the VTA project to the NAc, the amygdala, the medial Prefrontal Cortex (mPFC), and the ventral Hippocampus (vHPC), and is also called the “mesocortico-limbicc system”. In addition to the mPFC, the Orbito Frontal Cortex (OFC) may also function as part of the mesocortico-limbic system. Human studies have shown that pain-inhibitory effects of rewards have been associated with increased OFC activity, and an experimental study has shown that selective activation of the OFC can lead to a reduction in anxio-depressive behaviors induced by neuropathic pain. CBT is known to activate the function of prefrontal cortices, including mPFCs and OFCs.

Our recent review discusses the latest advances in the structure and function of the limbic system, and tries to explain how exercise can help normalize its function, reduce pain and fear and enhance our quality of life [4]. Recently, we also found that exercise activates GABA neurons in vHPC and inhibits projection from vHPC to the amygdala through feedforward inhibition, thereby suppressing contextual fear conditioning [5]. In other words, exercise therapy aims to fundamentally relieve patients from chronic pain by changing their behavior in their daily lives by 1) activating the reward system, 2) activating BA positive neurons, and 3) suppressing fear conditioning for pain [2-4]. This hypothesis was substantiated by a clinical study, in which we demonstrated that 3 weeks of exercise therapy altered the functional connectivity of the limbic system in patients with fibromyalgia, which was associated with improved motor function [6]. Thus, exercise therapy is clearly superior to medication because it is effective, inexpensive, and safe.

This article also considers the brain's function as networks, and proposes a well-balanced exercise prescription considering the adherence and pacing of exercise practice4). In patients with chronic pain, the function of the Default Mode Network (DMN) is reduced because the mind is obsessed with the pain. In order to improve the quality of life of patients with chronic pain, it is important to develop lifestyle habits that activate DMN, suppress Salience Network (SN), and balance DMN and Central Executive Network (CEN).

We conclude that therapies targeting the mesocortico-limbic system, such as exercise therapy and CBT, may become promising tools in the fight against chronic pain.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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