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Exercise and Depression

Jang Won Son

Division of Endocrinology and Metabolism, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon, Korea

Depression is a chronic medical condition that can lead to serious functional impairment, morbidity, and mortality if left untreated [1,2]. Increasing awareness of depression as a significant public health problem has led to greater interest in both the underlying mechanisms and external factors associated with the disease, with therapies developed to address many of the diverse aspects of disease pathology. Accordingly, management of patients with depression often requires a multidisciplinary approach, including a combination of pharmacological and psychological therapies. In addition, regular exercise in the form of structured exercise programs is often encouraged as a means of nonpharmaceutical treatment of depression [3].

Exercise is widely regarded as a major component of a healthy lifestyle, with specific effects seen in terms of brain function and prevention of neurodegenerative diseases. In rodents, running has been shown to improve cognition and synaptic plasticity, reduce depressive behaviors, and enhance hippocampus neurogenesis [4-6]. Peripheral factors generated outside of the central nervous system during exercise are also known to affect neuronal function, including skeletal muscle, an important source of muscle-derived myokines that help to regulate the metabolism of other organs [7].

A recent study by Agudelo et al. [8] provided insights into many of the cellular mechanisms underlying muscle-to-brain communication in a rodent model of depression. In this study, mice overexpressing skeletal muscle-specific peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) were found to be resistant to stress-induced depression by modulation of kynurenine metabolism [8]. These data suggest that PGC-1α produced by skeletal muscle acts as an exercise-mimetic that mediate a form of crosstalk between skeletal muscle and the brain. Similarly, adiponectin, an adipocyte-secreted protein, was shown to act as an important exercise-induced modulator of hippocampal neurogenesis and depression [9].

Collectively, studies in rodent models provide compelling evidence that exercise has the potential to improve brain function. However, it should be noted that that the beneficial effects of exercise on brain function appear highly context-dependent, with outcomes strongly influenced by perceived reward, motivation, exercise duration, and intensity. In essence, the nature of the exercise response is remarkably heterogeneous across different individuals and conditions. In studies where the context was switched from voluntary to forced at higher activity levels, the positive effects of exercise were not reproduced [10]. Therefore, how this stability is maintained remains an intriguing question.

In this issue, Kim et al. [11] evaluate the physiological features of forced (passive) exercise in a specific depression mouse model. The authors exposed mice to 2 hours of restraint daily for 14 days, resulting in a stress-induced depression phenotype in mice. They found that passive exercise on a running wheel rotating at a speed of 9 m per minute for 1 hour daily for 7 days increased hippocampal neurogenesis in normal mice [11]. Similarly, they showed that forced exercise for 1 hour daily for 14 to 21 consecutive days on a running wheel rotating at a speed of 9 m per minute could be implemented without in-

Corresponding author: Jang Won Son
Division of Endocrinology and Metabolism, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 327 Sosa-ro, Wonmi-gu, Bucheon 14647, Korea
Tel: +82-32-340-7040, **Fax:** +82-32-340-2039, **E-mail:** jwsonmd@gmail.com

ducing physiological stress or serum lactate accumulation in a stress-induced depression model [11]. This result is consistent with previous findings showing that forced, low-speed running improves cognition by increased neurogenesis in rodent models [12,13].

An alternative study by Kim et al. [11] sought to identify an effective exercise strategy for a specific-depression model. Unfortunately, this study lacked sufficient details regarding hippocampal neurogenesis and behavior tests during and after passive exercise in a stress-induced depression model. Therefore, it was not possible to determine whether this passive exercise protocol translates into improved depression in a stress-induced depression model. Further elucidation of the mechanisms underlying the effects of exercise strategy on depression will benefit from the addition of more rigorous analysis of behavior, hippocampal neurogenesis, and neurotropin expression in specific-depression models.

Although a clear consensus exists regarding the positive effects of exercise on cognition, memory, and mood disorders in rodent models, these studies are not directly translatable to human brain physiology. Differences in study design make it difficult to directly translate exercise speed, force, duration, and intensity from animal to human models. Various "omics" based approaches combined with novel neuroimaging methods will be necessary to bridge the gap between animal and human studies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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