

# Neural Mechanisms of Exercise: Effects on Gut Microbiota and Depression

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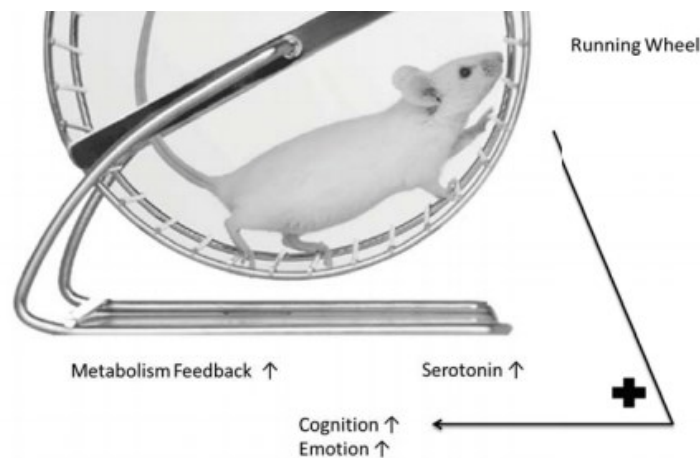
**Abstract:** Microbiota is a set of microorganisms resident in gut ecosystem that reacts to psychological stressful stimuli, and is involved in depressed or anxious status in both animals and human being. Interestingly, a series of studies have shown the effects of physical exercise on gut microbiota dynamics, suggesting that gut microbiota regulation might act as one mediator for the effects of exercise on the brain. Recent studies found that gut microbiota dynamics are also regulated by metabolism changes, such as through physical exercise or diet change. Interestingly, physical exercise modulates different population of gut bacteria in compared to food restriction or rich diet, and alleviates gut syndromes to toxin intake. Gut microbiota could as well contribute to the beneficial effects of exercise on cognition and emotion, either directly through serotonin signaling or indirectly by modulating metabolism and exercise performance.

**Keywords:** Depression, exercise, gut microbiota.

## INTRODUCTION

Microbiota is a set of microorganisms resident in gut ecosystem that reacts to psychological stressful stimuli, and is involved in depressed or anxious status in both animals and human being [1-5]. For instance, maternal separation stress or chronic restraint stress leads to decreased faecal lactobacilli and the altered microbiota composition [6]. These changes were associated with increases in circulating cytokines and the inflammation signaling in the serum, together with the broken integrity of the gastrointestinal (GI) duct [7]. Moreover, germ-free (GF) animals exhibited altered levels of neurochemical transmission in sex-dependent manner [8], and exacerbated hormone secretion to stress stimuli, with anxiety-like behaviors [9]. In addition, the GF animals demonstrated social interaction deficits, which could be normalized through bacterial colonization [10]. It is found that probiotics could antagonize stress/ pathology induced changes in the brain. For example, ingestion of lactic acid bacteria (*Lactobacillus*) acted like “antidepressant” and normalized the stress-induced neurochemical changes [11]. Another probiotic (*Bacteroides fragilis*) was able to restore the GI duct integrity, serum molecular markers, and the abnormal behaviors in the maternal immune activation (MIA) mice [12]. Adult human subjects received fermented milk with probiotics exhibited changed emotion status as well [13]. All these results argued for the importance of gut microbiota in regulating brain function, especially when meeting stress. Physical exercise has been recognized as one important approach to fight against mood disorders. The underlying mechanisms include adult hippocampal neurogenesis, alterations of brain blood perfusion, modulation of neuroinflammation, increased expression of neurotrophic factors in the brain, modulation of synaptic transmission and regulation of neurotransmitters such as serotonin [14-22]. Interestingly, a series of studies have shown the effects of physical exercise on gut microbiota dynamics, suggesting that gut microbiota regulation might act as one mediator for the effects of exercise on the brain. It is known for decades that gut microbiota is implicated in food

metabolism and obesity [23, 24]. Recent studies found that gut microbiota dynamics are also regulated by metabolism changes, such as through physical exercise or diet change [25-28]. Interestingly, physical exercise modulates different population of gut bacteria in compared to food restriction or rich diet [29], and alleviates gut syndromes to toxin intake



**Fig. (1).** Gut-Brain interaction during exercise: Exercise bring neuro-benefits through different mechanisms, such as trophic factors, serotonin signaling and metabolism regulation. Exercise modulates gut microbiota composition. Gut microbiota affect brain functions through nerve feedback, or metabolites release into the circulation.

[30]. It is also noted that regardless of genetic background, exercise could induce gut microbiota composition changes in different lines of animals (e.g. rats with hypertension and obesity) [26], suggesting that exercise-based modulation of gut microbiota might act as therapeutic mechanisms to different diseases. In future studies, it will also be important to identify the exercise-altered gut bacteria species to see if these are the stress-suppressed population. In athletes, the gut microbiota was found to be more diverse in compared to control group, which was also correlated to serum markers of exercise [27]. Notably, gut microbiota organization affects exercise performance as well. For instance, GF mice exhibited less endurance to swimming test, and reduced weight of muscles [31]. Human runners with supplementation of multi-strain probiotics demonstrated increased run time to fatigue in heat [32]. In other practices, probiotics is found to modulate exercise performance through multiple mechanisms, including inflammation, oxidative stress and gut-intestinal integrity [33-36]. Collectively, these results argued the tight relationship between gut microbiota changes and the physical exercise performance (Fig. 1). Therefore the exercise-induced brain benefits might as well be modulated through gut microbiota changes. For instance, serotonin is required for running induced benefits on neurogenesis [16, 17], while gut the major source of serotonin production in the body [37]; GF mice exhibited altered serotonin signaling as well as relevant behaviors [9, 14, 38], suggesting that GF mice might lack the benefits of exercise on neurogenesis. Future studies are required to systemically examine such possibilities. In conclusion, gut microbiota could as well contribute to the beneficial effects of exercise on cognition and emotion, either directly through serotonin signaling or indirectly by modulating metabolism and exercise performance. Employing probiotics therefore provide conjunct therapies for patients under physical exercise training or rehabilitation.

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