

Neural Mechanisms of Exercise: Anti-Depression, Neurogenesis, and Serotonin Signaling

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Abstract: Depression is associated with decreased serotonin metabolism and functioning in the central nervous system, evidenced by both animal models of depression and clinical patient studies. Depression is also accompanied by decreased hippocampal neurogenesis in diverse animal models. Neurogenesis is mainly defined in dentate gyrus of hippocampus as well as subventricular zone. Moreover, hypothalamus, amygdala, olfactory tubercle, and piriform cortex are reported with evidences of adult neurogenesis. Physical exercise is found to modulate adult neurogenesis significantly, and results in mood improvement. The cellular mechanism such as adult neurogenesis upregulation was considered as one major mood regulator following exercise. The recent advances in molecular mechanisms underlying exercise-regulated neurogenesis have widen our understanding in brain plasticity in physiological and pathological conditions, and therefore better management of different psychiatric disorders.

Keywords: Exercise, serotonin, depression, neurogenesis.

INTRODUCTION Depression is associated with decreased serotonin metabolism and functioning in the central nervous system, evidenced by both animal models of depression and clinical patient studies. Promoting serotonergic transmission using serotonin-norepinephrine reuptake inhibitors or monoamine oxidase inhibitors (common antidepressants) leads to improved mood states and potentially the “cure of depression”, suggesting that rescuing the serotonin signaling is critical in depression management [1]. Depression is also accompanied by decreased hippocampal neurogenesis in diverse animal models [1]. Neurogenesis is firstly characterized in rodents in 1960s [2, 3], and mainly defined in dentate gyrus (DG) of hippocampus as well as subventricular zone (SVZ) [4-6]. Moreover, hypothalamus, amygdala, olfactory tubercle, and piriform cortex are reported with evidences of adult neurogenesis [7-9]. The hippocampal neurogenesis is found to be important for spatial learning, as well as emotion state control in both rodents and primates [4, 6, 10]; While the SVZ generated new neurons migrate to olfactory bulb (OB), through rostral migratory stream (RMS), and is involved in olfactory processing, injury repair and defending the viral spreading from the central olfactory pathway [5, 11-14]. Stress hormone (e.g. glucocorticoid) administration in animals could fully mimic the effects of depression on adult hippocampal neurogenesis [15]. Therefore, the trigger stress is responsible for reducing the cells proliferation and neuronal survival. However, this reduction can be reversed by different therapies, such as electroconvulsive therapy, antidepressants, physical exercise, and environment enrichments [16, 17]. Physical exercise is found to modulate adult neurogenesis significantly, and results in mood improvement [18-20]. Interestingly, in recent years it is found that serotonin is one key regulator responsible for exercise-dependent neurogenesis increase, and therefore the “cure of depression”.

PATHOGENESIS OF DEPRESSION

Depression can result from long-term or acute stressful events, pharmacological treatments as well as disease states. Psychological stressors activate the hypothalamic-pituitary-adrenal (HPA) axis, increasing the secretion of glucocorticoids (e.g. cortisol) [21]. Glucocorticoids bind to the glucocorticoid receptors (GR) on neurons and leads to neuronal injury pathways [22, 23]. It is believed that in addition to the monoamine deficiency, brain is suffered from the loss of neurotrophic factors as well. In fact, the expression of brain-derived neurotrophic factor (BDNF) and BDNF-related genes were downregulated in both animal models of depression [24] and post-mortem human brain samples of depression patients [25]. Moreover, chronic but not acute administration of antidepressants increased BDNF levels in the brain, which was temporally correlated to the therapeutic benefits [26, 27]. The suppression of adult neurogenesis is considered as one important pathological mechanism underlying depression in recent years [1, 16, 28]. In addition, immune system activation, inflammation and oxidative stress pathway activations could concomitantly contribute to the pathogenesis of clinical depression [29]. For instance, IL-6 administration to the animals induces depression-like behaviors [30], and the levels of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor- α were reported to increase in depression patients [31]. Interestingly, most pro-inflammatory cytokines suppress hippocampal neurogenesis [32], while anti-inflammation drugs were found to restore adult neurogenesis [33].

ADULT NEUROGENESIS AND DEPRESSION

The neurogenesis-depression hypothesis suggests that the down-regulation of adult neurogenesis contributes to the development of depression, which can then be corrected by antidepressant drugs or therapies [34]. The first evidence of down-regulated neurogenesis in the presence of depression is related to hippocampal atrophy. Brain imaging studies have consistently described hippocampal atrophy or hippocampal volume reduction in unipolar major depression and other diseases associated with affective disorders, such as posttraumatic stress disorder (PTSD) [35, 36]. Endocrine disorders that result in depressive symptoms, such as Cushing's disease, have also shown decreases in brain hippocampal volume [37]. Furthermore, studies on postmortem tissues from depressed subjects showed increases in cell packing density in the hippocampus, as well as decreases in overall hippocampal volume [38], while other studies suggest a reduced volume in both the hippocampus and the amygdala [39]. The stress-induced inhibition of adult neurogenesis has been recognized to be a general phenomenon and occurs independent of species, age and the source of the stress [40]. Numerous studies have shown that adult neurogenesis is down-regulated under both acute and chronic stress conditions [16, 28, 41, 42]. However, hippocampal neurogenesis rates have shown variability between different mouse strains [43, 44]. The widely accepted theory about hippocampal damage during the development of depression focuses on the neurotoxicity of glucocorticoid, which is generated during the over-activation of HPA axis under stress [45]. Removal of circulating adrenal steroids by adrenalectomy increases cell proliferation and adult neurogenesis in rodents [46-48], and increased corticosterone inhibits this process [48, 49]. Patients with depression often display some form of HPA axis activation, and the subtypes of depression most frequently associated with HPA activation are those most likely to be associated with hippocampal volume reductions [50]. The glucocorticoids could exert direct apoptotic effects, reducing cellular resilience and making neurons more vulnerable to the negative impacts of other disadvantageous conditions [51]. Stress-induced decreases in the number of proliferating cells might be the basis for

hippocampal volume reduction, and recent discovery that stress can elevate cell cycle inhibitor suggest a possible mechanism of preventing progenitors from cell cycle re-entering in depression [52]. Given that “diminished” neurogenesis is associated with stressful environments, and has been seen in the development of depression, it would be interesting to see if there is a functional contribution of adult neurogenesis, and whether restoring neurogenesis could cure depression. In the last few years people discovered that antidepressant drugs can enhance dendritic complexity [53, 54] and increase the number of new neurons born in the hippocampus of adult animals in a non-acute, chronic time course [55]. Furthermore, electroconvulsive shock therapy, which has a strong anti-depressive effect and has been clinically adopted as a treatment of depression, has been shown to significantly elevate the neurogenesis in the dentate gyrus of the rodent hippocampus in a dose-dependent manner [56]. This implies a possible relationship between neurogenesis and the antidepressant effect of pharmacological treatment. In some cases, the effects of antidepressants are blocked with ablated neurogenesis [57], indicating that the restoration of functional adult neurogenesis may be the prerequisite for behavioral and affective improvements. Still, it should be noted that neurogenesis is dispensable for antidepressant-like drug effects in some other cases, such as BALB/cj mice [58, 59] (Fig. 1).

EXERCISE AND ADULT NEUROGENESIS: SEROTONIN SIGNALING

The modulating effects of physical exercise, especially voluntary exercise on adult neurogenesis have been well recognized in past decade [19, 20, 60-62]. Different signaling pathways were reported to be involved in the upregulation of hippocampal neurogenesis, such as growth factor signaling (e.g. BDNF, VEGF) [63-65], short peptides (e.g. leptin, adiponectin) [66, 67], and cell cycle regulation (e.g. inhibiting p21) [68]. Very recently, several studies pointed out a new player in exercise-enhanced adult neurogenesis – serotonergic signaling. These findings provided additional evidences underlying the depressioncure effects of exercise-enhanced adult neurogenesis. The first report was made on the brain-specific serotonindeficient mice (tryptophan hydroxylase 2/TPH2 knockout mice). At baseline, the adult neurogenesis is not disrupted; while the Knockout (KO) animals exhibited significantly reduction in upregulation of cell proliferation following running [69], suggesting that serotonin is essential for exercise induced neurogenesis.

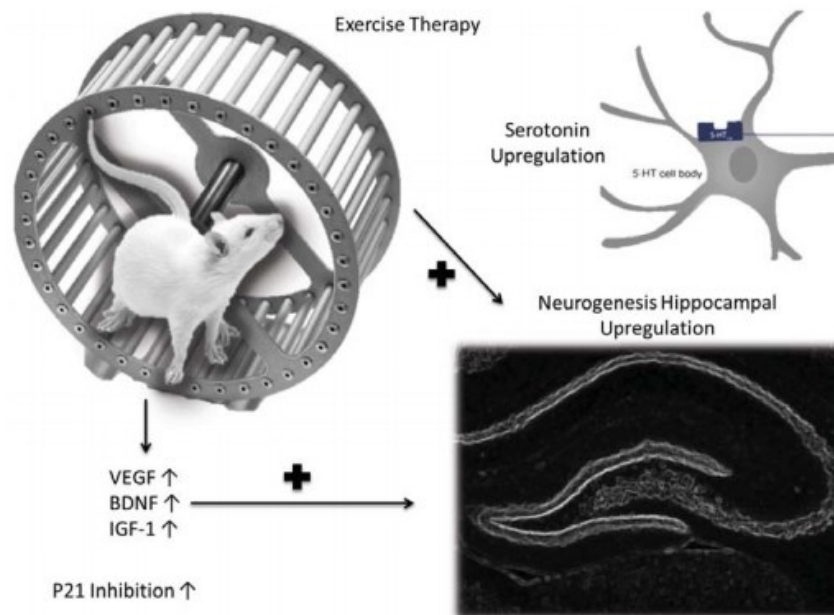


Fig. (1). Exercise induced upregulation of adult neurogenesis is mediated by different molecular pathways, including neurotrophic factor signaling, metabolism-relevant peptides, cell cycle regulation, and serotonin.

It is known that serotonin receptors are expressed well in neurogenic zones and are regulating adult neurogenesis [70, 71]. However, it is unclear how would this affect the running-induced adult neurogenesis. In another study with serotonin receptor type 3A subunit deficit mice, the authors confirmed the involvement of serotonin receptor 3A in regulating the adult neurogenesis under exercise [72]. Similar to TPH2 KO animals, these serotonin receptor type 3A KO mice exhibited normal adult neurogenesis at baseline, but the deficits to increase cell proliferation following physical exercise. Consistently, the antidepressive effect of running is missing in these animals. However, it is found that context-freezing learning is still enhanced following running in the serotonin receptor type 3A KO mice; this might be explained by synaptic plasticity mechanism such as dendritic remodeling [73], or other types of serotonin receptors are involved. These results provided novel targets for depression treatment, such as the serotonin receptor agonists, especially the serotonin receptor 3A agonist. It will be interesting to understand if different subtypes of the serotonin receptors are responsible for differential effects of adult neurogenesis on the hippocampal functions. Indeed, serotonin signaling selectively neural pathways in the hippocampus (e.g. potentiation of TA-CA1 but not SC-CA1 glutamatergic transmission) [74]. Future studies are required to elucidate the role of serotonin in depression-induced-suppression and exercise-induced-enhancement of adult neurogenesis, highlighting the importance of this issue. Current directions point, regardless of inducing effect of neurogenesis, that exercise is an important regulatory source of serotonin, and therefore highly influential on reducing mood symptoms of depression. One may speculate that such a mechanism exercise can replace with the use of specific drugs long-term from a sustained effect.

CONCLUSION

Physical exercise has long been recognized an effective therapy against mood disorders, especially major depression. Cellular mechanisms such as adult neurogenesis upregulation was considered a major mood regulator following exercise. Recent advances in molecular

mechanisms underlying exercise-regulated neurogenesis have widened our understanding in brain plasticity in physiological and pathological conditions, and therefore better management of different psychiatric disorders.

LIST OF ABBREVIATIONS

BDNF = Brain-Derived Neurotrophic Factor

HPA = Hypothalamic-Pituitary-Adrenal

KO = Knockout

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