Behavioral neuroscience of emotion and exercise

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Received: May 21, 2012 / Accepted: July 23, 2012

Abstract The latest neuroscience studies have reported that physical activity and exercise can change the levels of brain monoamines and neurotrophic factors, increase synaptic plasticity and neurogenesis, and alter intracellular signaling proteins and neuronal activity. These studies have considered that physical exercise might be associated with psychological health such as stress reduction, antidepressant/anxiolytic properties, and improvement in mood through morphological and functional alterations of the central nervous system involved in emotion regulation. Although evidence of the neural and behavioral benefits of physical exercise is accumulating, the neural mechanisms behind these beneficial effects and emotion regulation from physical exercise are not clearly understood. This paper discusses how physical activity and exercise regulate emotional functions such as stress responses, mood, and depression or anxiety, focusing on specific areas of the brain involved in emotion regulation.

Keywords: monoaminergic system, hypothalamic-pituitary-adrenal axis, neuroplasticity, depression, anxiety

Introduction

Physical activity and exercise have been shown to be associated not only with improved physical health, but also with life satisfaction, cognitive and memory function, and psychological well-being. The latest neuroscience studies have reported that physical activity can induce morphological and functional alterations in the central nervous system involved in emotion regulation. In addition, there is also increasing clinical evidence that exercise may reduce and prevent the incidence of stress-related psychiatric disorders, especially depression and anxiety. Physical activity could thus be a behavioral strategy to regulate emotion function. However, the neural mechanisms of the beneficial effects of emotion regulation are not clearly understood. This paper discusses how physical activity regulates emotion function, and which exercise regimens are effective in psychological health, focusing in particular on mood disorders such as depression and anxiety.

Emotion-related neural mechanisms

Emotional response usually implies emotional experience (e.g., pleasure, anger, anxiety, and depression) and emotional expression or behavior (e.g., palpitation, arousal, facial pallor, and expressive behaviors), and enhances the survival probability of individuals and species. The brainstem, hypothalamus, and limbic system are considered to be involved in mediating emotional responses. For example, the amygdala in the limbic system is primarily involved in the detection of stimuli that may impact, positively or negatively, the well-being of an organism. The hypothalamus and brainstem are critical for emotional expression and they regulate the integrated stress responses via autonomic and hormonal functions. Furthermore, the hippocampus, which is a limbic structure, has an important primary role in learning and memory, while it is also known to play a role in mood regulation and stress response. Because these emotion-related neural mechanisms usually function on the subconscious level, it is difficult to control the activities of each region consciously. In contrast, physical activity and exercise seem to be simple ways of altering these neural mechanisms to mediate emotion regulation.

Brainstem and exercise

The role of the monoaminergic neuronal systems in the brainstem on emotion regulation has been extensively examined in pleasure, anger, arousal, and stress-related psychiatric disorders such as depression and anxiety. For example, the mesolimbic dopaminergic system from the mesencephalic ventral tegmental area (VTA) to the nucleus accumbens (ACC) could be critical for the expression of pleasurable sensation, motivation, reward, arousal, and addiction. The locus coeruleus (LC) in the pons is a major nucleus of noradrenergic neurons projecting into the amygdala, hippocampus, hypothalamus, and prefrontal cortex, as well as the spinal cord, and mediates stress-related responses such as arousal, attention, and anxiety or depression, as well as autonomic function. Further-

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more, the major source of serotonergic neurons in the central nervous system is the dorsal raphe nucleus (DRN) in the midbrain, which has widespread projections into various brain regions including the amygdala, hippocampus, hypothalamus, basal ganglia, and cortical area\textsuperscript{11,12}). The serotonergic neurons are implicated in antidepressant/anxiolytic properties and the reduction of aggressive behaviors.

Previous studies have indicated that physical activity and exercise mediate activity in the brainstem monoaminergic neuronal systems related to emotional response or mood\textsuperscript{2}). A series of animal studies using a microdialysis technique has shown that central dopamine release and metabolism are altered by acute exercise\textsuperscript{13}). Vagas-Perez et al.\textsuperscript{14}) also reported that the mesolimbic dopamine pathway from the mesencephalic ventral10;32;46 tegmental area (VTA) to the nucleus accumbens (ACC) could be activated by acute wheel running in mice, as shown by c-Fos immuno-histochemical methods. These results suggest that physical activity enhances the activity of dopaminergic neurons and may thereby mediate positive mood, motivation, and the reward system.

Physical activity and exercise have also been shown to affect central and peripheral levels of noradrenaline, and have been associated with brain noradrenergic adaptations in the areas containing the LC and its ascending terminals\textsuperscript{13,15}). Dunn et al.\textsuperscript{15}) reported that exercise training increased noradrenaline levels in the hippocampus, prefrontal cortex, and pons-medulla in rats, and suggested that chronic physical activity may reduce depression and anxiety. In addition, Ohiwa et al.\textsuperscript{16}) showed, in rats, that acute treadmill running enhances the activity of noradrenergic neurons in both A1 and A2 areas of the brainstem in a manner dependent upon running speed. Yanagita et al.\textsuperscript{17}) indicated that physical exercise could activate the LC neurons regardless of the type of exercise (i.e., forced versus spontaneous running) in rats. These results suggest that activation of the LC noradrenaline neurons is involved in detecting exercise itself as a stimulus, or detecting the intensity of the exercise rather than the type of exercise, and may mediate anxiety, arousal, and attention, as well as the activation of autonomic functions.

The effect of physical activity and exercise on the central serotonergic system has also been reported extensively\textsuperscript{2,18-21}). Several studies have shown that acute physical exercise increases the levels of serotonin (5-HT, 5-hydroxytryptamine) and its metabolite in the hippocampus, hypothalamus, and prefrontal cortex\textsuperscript{13,18}). In addition, it is suggested that alterations in the serotonergic system as neural consequences of physical activity may contribute to stress-protective effects. Greenwood et al.\textsuperscript{19,22}) reported that chronic wheel running attenuates serotonin neural activity in the DRN during uncontrollable stress in rats, accompanied by the mitigation of behavioral depression (i.e., learned helplessness), and suggested that increases of 5-HT\textsubscript{1} inhibitory autoreceptor expression in the DRN may contribute to these neural and behavioral responses. On the other hand, Martin et al.\textsuperscript{21}) showed that treadmill-running training amplifies the response of midbrain serotonin metabolism to acute stress (i.e., immobilization).
It is thus reasonable to assume that physical activity and exercise increase stress resistance by producing neuroplasticity in the central serotonergic system.

Moreover, previous studies have suggested that depressive and anxiety disorders respond to physical activity and exercise as well as chronic administration of a selective serotonin reuptake inhibitor (SSRI) in a similar manner. Babay et al. reported that a 4-month course of aerobic exercise, SSRI (sertraline) therapy, or a combination of exercise and SSRI, improved the symptoms of depression in patients with major depressive disorder. Interestingly, the study also showed that after 10 months, i.e., 6 months after the completion of those three treatments, patients in the exercise group had significantly lower relapse rates than those in the medication group. Taken together, physical activity and exercise may reduce the incidence and symptoms of depression or anxiety through activation of the central serotonergic system.

### Hypothalamus and exercise

Physical exercise is known to induce the activation of the hypothalamic-pituitary-adrenal (HPA) axis that is initiated by the activation of corticotropin-releasing factor (CRF) neurons in the hypothalamic paraventricular nucleus (PVN) in a manner that is dependent on exercise intensity and duration. CRF neurons in the PVN also project into extrahypothalamic brain regions such as the LC, DRN, amygdala, and bed nucleus of the stria terminalis, which are regions involved in mood, emotion, and stress responses.

It is thus possible that physical exercise is one stressor that activates CRF neurons and the HPA axis, which could, in turn, regulate autonomic and hormonal responses, as well as psychological alterations. Timofeeva et al. reported that acute treadmill running leads to strong expression of CRF mRNA in the parvocellular part of the PVN in rats. Soya et al. showed that only supra-lactate threshold treadmill running activates the various hypothalamic regions, including the parvocellular part of the PVN in rats, and increases plasma adrenocorticotropic hormone (ACTH), which is indicative of activation of the HPA axis. In addition, Yanagita et al. reported that the activation of CRF neurons in the PVN during spontaneous running is low compared with that during forced running in rats, even though the amount of exercise is equivalent. These results suggest that CRF neurons and the HPA axis may be activated depending on the type, duration, and intensity of physical activity and exercise.

Hyperactivity of the HPA axis is often observed in association with and even prior to the onset of major depression. Repeated stress and HPA axis hyperactivation are suggested to be important risk factors for the development of depression. Activation of the HPA axis results in the culminating secretion of adrenal glucocorticoids into the circulatory system, which normally acts to maintain bodily equilibrium in response to an acute stressor. Almost half of patients with depression show hypersecretion of glucocorticoids throughout the day, due to hyperactivation of the HPA axis by impairment in the ability of the hippocampus to control glucocorticoid negative feedback. Kawashima et al. reported that 4-week endurance treadmill training in rats alters PVN CRF bio-synthetic activity and reduces ACTH release in response to acute running. Dishman et al. showed that chronic wheel running attenuates the increases of plasma ACTH resulting from acute cage-switch stress (cage exchange) in rats. These results suggest that the HPA axis system may be influenced by physical activity and that chronic exercise may affect activation of the HPA axis to a given stressor. It is thus possible to assume that physical activity and exercise improve psychiatric disorders, such as depression and anxiety, as well as autonomic and hormonal responses, by altering the activation of CRF neurons and the HPA axis.

### Plasticity in the hippocampus and exercise

It is well known that the hippocampus has important primary roles in learning and memory. Several studies have indicated the effects of physical activity and exercise on hippocampal-dependent learning and memory processes. On the other hand, the hippocampus is also involved in general cognition, mood regulation, and response to stress. It has been shown that repeated stress and HPA axis hyperactivation can lead to neuronal atrophy and loss in several brain regions, including the hippocampus, and that the decreased hippocampal volume may be involved in mental illnesses such as major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and Alzheimer’s Disease. Physical exercise can also enhance the expression of brain-derived neurotrophic factor (BDNF) in the dentate gyrus, which is involved in general cognition, mood regulation, and maintenance, and long-term potentiation. In addition, it has been shown that increased BDNF levels and neurogenesis in the hippocampus could be caused by chronic antidepressants as well as physical exercise, and that these hippocampal alterations may be initiated by the activation of monoaminergic neurons (i.e.,

Van Praag et al. have shown that voluntary exercise increases cell proliferation in the dentate gyrus in mice, and that the enriched environment enhances the survival of the newly-formed neurons. Yuede et al. reported that chronic voluntary and forced exercise increased hippocampal volume in an animal model of Alzheimer’s Disease. Physical exercise can also enhance the expression of brain-derived neurotrophic factor (BDNF) in the dentate gyrus, which is involved in neuronal growth, maintenance, and long-term potentiation. In addition, it has been shown that increased BDNF levels and neurogenesis in the hippocampus could be caused by chronic antidepressants as well as physical exercise, and that these hippocampal alterations may be initiated by the activation of monoaminergic neurons (i.e.,

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noradrenaline and serotonin). Taken together, physical activity and exercise can induce changes in hippocampal neural plasticity, including increased neurogenesis, long-term potentiation, and enhanced expression of BDNF, and thereby may improve stress-related mood disorders such as depression, as well as learning and memory function.

Exercise regimens and emotional function

Several studies have reported that physical activity and exercise have beneficial effects on mood, stress responses, and anxiety or depression disorders. These previous studies have examined the positive effects on psychological well-being, using various characteristics of an exercise program (e.g., duration, intensity, frequency, and type of exercise). Which exercise regimens are more effective in psychological health? Unfortunately, few general concepts for the optimal regimens of physical activity for psychological health or the central nervous system involved in emotion regulation have been developed. Several studies have suggested that the effects of physical activity and exercise on mood, anxiety, and depression may be differentially mediated depending on the forms of exercise, including intensity, duration, and type of exercise (e.g., voluntary versus forced exercise, and type of exercise). In addition, the beneficial effects of exercise may also be affected by a given subject's characteristics (e.g., age, sex, race, and severity of disorder) and environment (e.g., stress and social interaction). These results suggest that physical activity and exercise, which could be a normally beneficial experience, are not always effective in psychological health. Therefore, establishment of optimal exercise conditions for clinical use is a critical issue that requires further research.

References

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