Exercise and Depression; From Physiology overview

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Abstract

Background: Major depressive disorder (MDD) is a debilitating neuropsychiatric disease characterized by persistent bad mood, anhedonia, decreased interest, reduced energy, cognitive impairment, and sleep disorders. With the rising stress of modern life and work, the number of individuals suffering from mental illness is fast increasing. Indeed, those with a medical condition such as diabetes mellitus, stroke, cardiovascular disease, and cancer are more likely to experience depression than the general population and the risk of depression is multiplied several times higher in many of these patient categories. Exercise is physical activity that is organized, repeated, and purposeful with the goal of maintaining or enhancing one or more aspects of physical fitness. Interestingly, numerous epidemiological studies have shown that sedentary habits or lower levels of physical activity (PA) are linked to a higher risk of mental health problems. The main physiological and biochemical mechanisms through which exercise alleviates depression are yet to be elucidated. Therefore, greater investigations are required into the processes behind the antidepressant benefits of exercise. The relationship between exercise and inflammation has recently been clarified by the identification of myokines, or cytokines produced and released by skeletal muscle. A myokine called IL-6 was the first to be identified; it acts like a hormone and has impacts on other organs. Although IL-6 is regarded as a pro-inflammatory cytokine, research also shows that IL-6 produces an increase in anti-inflammatory cytokines like IL-10 and decreases the production of other pro-inflammatory cytokines like TNF
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Keywords: Exercise, Depression

Introduction

Major depressive disorder (MDD) is a debilitating neuropsychiatric disease characterised by persistent bad mood, anhedonia, decreased interest, reduced energy, cognitive impairment, and sleep disorders. With the rising stress of modern life and work, the number of individuals suffering from mental illness is fast increasing **(1)**.

Depression is a major cause of disability, with high morbidity and mortality. Indeed, those with a medical condition such as diabetes mellitus, stroke, cardiovascular disease, and cancer are more likely to experience depression than the general population and the risk of depression is multiplied several times higher in many of these patient categories. Moreover, around 800,000 people die by suicide each year, suggesting that depression is a major risk factor for suicide **(2)**.

Prevalence:

According to the World Health Organization, 350 million people worldwide are currently suffering from depression. By 2030, depression is proposed to be in the top three of all diseases with the highest burden according to the Global Burden of disease project. It is the most common psychiatric disorder and occurs across all ages in all people, ignoring social backgrounds, with a high rate of recurrence and suicide **(3).**

The pathogenesis of depression is highly complex and not entirely understood, but various causative factors have been reported and several theories have been suggested, such as neuroinflammation, monoamine deficiency, neuroendocrine mechanisms, oxidative stress, and the neuroplasticity hypothesis **(3).**

The monoamine hypothesis of depression was the earliest theory to emerge, and it is the most common hypothesis of major depressive disorder (MDD) due to its simplicity. It's the idea that monoamine neurotransmitters, such as norepinephrine (NE), serotonin and dopamine (DA) are decreased in depression. This theory is supported by the fact that antidepressant drugs restore neurotransmitter levels to normal **(4).**

A euphoric mood is induced in the brain by the indole neurotransmitter 5-HT. There are two different catecholamines. DA is known as the happiness hormone, but NE is known as an excitatory neurotransmitter that alerts individuals by triggering a fight or flight response. Therefore, a shortage of these neurotransmitters leads to apathy and depression **(5)**.

However, the monoamine hypothesis is inadequate to elucidate the pathophysiology of MDD as it fails to explain the latency of response to antidepressant drugs. Although monoamine levels increase within some hours due to inhibition of reuptake or metabolism, therapeutic effects on depressive symptoms develop only after several weeks. Moreover, many patients do not improve even when the medications have significant pharmacologic effects **(6).**

Thus, there is a pressing need to further investigate the pathophysiology of depression and search for novel targets as traditional antidepressants have multiple side effects leading to poor adherence and function slowly, with a third of patients failing to respond, indicating that other factors may be involved in depression pathogenesis **(1)**.

More recently, there has been a paradigm shift from the monoamine deficiency hypothesis as the main cause of depression to a more comprehensive view that considers the neuroplasticity hypothesis and changes in the immune and endocrine systems as fundamental causal factors in the pathophysiology of depression **(7).**

Surprisingly, the topic of neuroinflammation has recently come to light in a majority of textbooks of psychiatry and neuroscience instead of limiting inflammation's role to the field of immunology and infection because the brain was thought to be an immune-privileged organ and hence generally untouched by immunological alterations in the periphery. The revelation that the immune system might significantly alter emotional state regardless the somatic changes caused by an acute illness resulted in a significant change in the situation. As the field of psychoneuroimmunology developed, it was later shown that proinflammatory cytokines were critical in the development of psychological symptoms **(7)**.

Recent data point to neuroinflammation as a critical player in the pathology of depression. A biological connection between depressed moods and inflammation has received a lot of evidence in recent decades. Pro-inflammatory cytokines, particularly TNF- and IL-6, have been reported to increase in depression. Consistent with this, inducing inflammation in study subjects has also been found to produce depression, according to studies. For example, elevated IL-2, IL-6, and TNF- following INF-therapy for Hepatitis C infection or certain types of cancer results in impaired cognition. Furthermore, a profound neuroinflammatory response brought on by immune system activation stimulated by the injection of pro-inflammatory cytokines, the injection of lipopolysaccharide (LPS), or the induction of a bacterial infection is accompanied by depressive-like behaviors like anhedonia or behavioral despair (**8)**.

There is a positive loop between depression and inflammation in which long-term stress and the accompanying production of pro-inflammatory cytokines lead to chronic neuroinflammation, which in turn

leads to depression. The clinical link between depression and inflammatory illnesses is analogous to the reciprocal association between depression and inflammation. Autoimmune illnesses are more common in depressed people, and inflammatory diseases patients are more likely to experience depression. Furthermore, anti-inflammatory medicines have been successfully used as antidepressant adjuncts **(9).**

Cytokines are small proteins that have the ability to either promote or inhibit inflammation. They influence how cells work and interact. Specialized cytokines come in a variety of families and perform various tasks. Although immune cells, such as the CNS's microglia, produce the majority of cytokines, other cells such as astrocytes, monocytes, macrophages, and lymphocytes can also do so **(10)**.

The brain's main immune cells, known as microglia, come in two different phenotypic varieties. In a healthy state, microglia perform non-immune tasks such as removing dead neurons, removing abnormal synapses during neurodevelopment, and keeping an eye on synaptic modulation. Additionally, the microglial cells are responsible for policing the microenvironment and eradicating invasive infections **(7)**.

Microglia activation under pathological conditions results in the production of a significant variety of inflammatory mediators such as tumor necrosis factor (TNF), C-reactive protein, and interleukin-6 (IL-6). Activated astrocytes and microglia can produce more reactive oxygen species (ROS), which can lead to oxidative stress in the central nervous system (CNS) and neurodegeneration. Studies have shown that depressed patients with increased inflammatory cytokines exhibit resistance to treatment **(11)**.

Miller et al. (12) reported that numerous neurotransmitter systems in the brain are affected by inflammation, including the serotonin, dopamine, and glutamate pathways, which may have an impact on neurocircuits that control behavior, particularly those behaviors associated with reduced motivation (anhedonia), avoidance, and alarm (anxiety), which are symptoms of a number of neuropsychiatric disorders, including depression **(12)**.

Parallel evidence demonstrates that oxidative stress and accumulation of inflammatory mediators and cytokines induce indoleamine 2,3 dioxygenase (IDO) activation which in turn trigger tryptophan degradation and quinolinic acid (QUIN) production so prevent tryptophan from entering the, serotonin (5-HT) synthesis pathway **(13)**.

Moreover, (QUIN) stimulates NMDA receptors and encourages glutamate release; this effect may result in CNS excitotoxicity and deterioration of neurotrophic support **(12)**.

According to **Caspersen et al. (14)** exercise is physical activity that is organized, repeated, and purposeful with the goal of maintaining or enhancing one or more aspects of physical fitness.

Classification of exercise:

Exercise may be categorized in a variety of ways, including:

1) **Aerobic exercise**

In order to provide your body with oxygen-rich blood, aerobic exercise entails physical activity that elevates your breathing and heart rate. Exercise that is aerobic such as, cycling, running and swimming helps to build heart muscle, enhances lung function, and promotes circulation and healthy blood flow throughout the body **(Xiao, 2020)**. Fascinatingly, numerous studies have shown that aerobic exercise has a strong antidepressant impact and is both simple to engage in and beneficial to one's health **(15)**.

2) **Anaerobic exercise**

The (American College of Sports Medicine) ACSM defines anaerobic exercise as vigorous physical activity that lasts for a short time and is powered by the energy reserves of the contracting muscles, rather than by the inhalation of oxygen. Sprinting, high-intensity interval training (HIIT), and power lifting are examples

of anaerobic exercise. Resistance exercise is a form of exercise intended to increase muscular strength and endurance. Resistance training not only slows down muscle aging, boosts metabolism, and significantly lowers age-related fractures and falls, but it also it Improves Mental Health **(15)**.

3) Mind-body exercise

Multimodal exercise, known as "mind-body exercise" (MBE), emphasizes slow physical motions, proper breathing techniques, mental concentration, and full-body stretching and relaxation such as yoga.
Considering that MBE involves gradual, low-impact motions that range from mild to moderate in intensity, it is suited for fragile populations, especially those who have low exercise intolerance and suffer from cognitive impairment **(16)**.

Exercise and mental health:

Interestingly**,** numerous epidemiological studies have shown that sedentary habits or lower levels of physical activity (PA) are linked to a higher risk of mental health problems **(17)**.
The American College of Sports and Exercise advises performing resistance and aerobic activities on the majority of days of the week to promote health. The scientific community has been more interested in research on the effects of various forms of physical activity (aerobic and resistance) on mental health. Fresh evidence has recently come to light that suggests that engaging in physical activity is good for one's health, regardless of age, and may effectively maintain brain health and cognitive function in both healthy and diseased states, even preventing cognitive decline and neurodegenerative disorders **(18)**.
With a number of studies demonstrating that exercise is beneficial in reducing depressive symptoms and improving physiological systems like the cardiorespiratory system and cognitive function, exercise has recently attracted attention as a low-cost and simple therapy for depression. However, the inclusion of exercise as a crucial part of treatment and prevention of depression is inconsistent, which may be due to a lack of knowledge, skepticism about the available data, or even a refusal to accept it **(19)**.

The explanatory mechanisms of exercise in prevention and treatment of depression

The main physiological and biochemical mechanisms through which exercise alleviates depression are yet to be elucidated. Therefore, greater investigations are required into the processes behind the antidepressant benefits of exercise **(20).**

Exercise and neuroinflammation

Inflammation and immunity are intricately correlated with exercise **(21)**. **Gleeson (22)** demonstrated that regular, moderate exercise lowers the intensity of systemic inflammation, whereas sustained high-intensity training can raise systemic inflammation and the risk of infection. According to several studies, brief changes in cytokine levels in the muscles and blood before and after exercise are likely significant elements contributing to the positive effects of physical activity on health **(23)**.
Although the exact processes underlying this advantageous impact are unknown, different possible mechanisms have been found. Exercise lowers the expression of Toll-like receptors on the surface of monocytes, which have been linked to controlling systemic inflammation **(22)**. It also promotes the release of substances that have immunomodulatory effects such as adrenaline, cortisol, growth hormone, and prolactin **(23)**.
The relationship between exercise and inflammation has recently been clarified by the identification of myokines, or cytokines produced and released by skeletal muscle. A myokine called IL-6 was the first to be identified; it acts like a hormone and has impacts on other organs. Although IL-6 is regarded as a pro-inflammatory cytokine, research also shows that IL-6 produces an increase in anti-inflammatory cytokines like IL-10 and decreases the production of other pro-inflammatory cytokines like TNF **(24)**.

Interestingly, in adults, investigations using self-reported measures of physical activity have demonstrated that physically active individuals have CRP concentrations 19–35% lower than less active individuals. Even though the majority of studies show that exercise reduces inflammation in both adults and children, the relationship between exercise and reduced inflammation depends on a number of variables, including the type, frequency, and duration of exercise, any underlying medical conditions, and the initial levels of inflammation. Therefore, further research is necessary to provide more conclusive findings, especially in individuals who are depressed **(25)**.

Exercise and Neuroplasticity

Exercise's antidepressant benefits are linked to the adult hippocampus's enhanced neurogenesis, synaptic development, and plasticity, which successfully stimulate neurogenesis in the hippocampal dentate gyrus (DG) and foster hippocampal growth. In addition to improving brain nerve processing efficiency and delaying the decline of cognitive function, exercise has a positive impact on maintaining hippocampal volume and white matter volume integrity. Exercise can rebuild brain structure, activate nearby brain regions, and encourage adaptive behavioral changes **(15)**.

Vaynman et al. (26) offered further direct proof that the cognitive benefits of exercise are really mediated by and reliant upon the function of BDNF. The association between exercise, BDNF, and depression symptoms has been studied in parallel investigations. It has been demonstrated that exercise increases BDNF in unmedicated patients with MDD and older individuals with remitted depression **(27)**.

As an endocrine organ, skeletal muscle is well acknowledged. Various physiologically active chemicals, referred to as myokines, such as BDNF, are produced and secreted by contracted skeletal muscles. As a result, one of the most potent elements that promote neurogenesis may be the interaction between skeletal muscle and the neural system via BDNF (**28)**.

Exercise and HPA axis homeostasis

The association between exercise and HPA activity is complicated because it is impacted by the length, kind, intensity, and chronicity of exercise **(25)**.

Surprisingly, diverse results of changes in cortisol following exercise training in MDD were recorded. Considerable cortisol reductions were shown in studies that looked at morning cortisol following an overnight fast and 24 hours of urine excretion. On the other hand, investigations that examined baseline cortisol found non-significant variations in cortisol levels **(29)**.

Zheng et al. (30) reported that in addition to reducing anhedonia and the impairment of spatial cognition in stressed rats, voluntary wheel running also reversed the rise in blood corticosterone levels and the decline of glucocorticoid receptor (GR) mRNA in the hippocampus region. According to animal research, swimming for four weeks lowered blood corticosterone levels and depressed behaviors in rats exposed to high amounts of glucocorticoids during pregnancy **(31)**.

Hill et al. (32) are in favor of the idea that moderate to intense exercise will cause increases in circulating cortisol levels. Low-intensity exercise, however, does not raise cortisol levels. On the other hand, **Archer et al. (33**) suggest that continuous exercise lowers the stress response, but acute high-intensity exercise raises cortisol levels.

But more crucially, there is a contradiction. An "exercise-glucocorticoid paradox" has been mentioned by a number of authors. Exercise therefore activates the hypothalamic-pituitary-adrenal (HPA) axis and raises

cortisol levels, while being ultimately favorable for cognition, mood, and the brain. **Chen et al. (34)** proposed preliminary solutions that may account for this paradox. First, chronic exercise buffers, but chronic stress intensifies the HPA axis response to new stress. Second, expression of mineralocorticoid and glucocorticoid receptors is downregulated by chronic stress but upregulated by exercise.

Furthermore, these intermittent cortisol elevations have anti-inflammatory effects **(35)**. Additionally, **Archer et al. (33)** reported that exercise increases atrial natriuretic peptide (ANP), a peptide hormone that has been demonstrated to suppress the HPA system by lowering adrenocorticotrophic hormone (ACTH), corticotropin-releasing hormone (CRH), and cortisol, a further pertinent component that is correlated with exercise's anxiolytic effects.

Exercise and oxidative stress

There is evidence that moderate aerobic exercise boosts endogenous antioxidant defense, enhances endothelial nitric oxide synthase (eNOS) expression and activity, which is related to a decrease in ROS production, increases the production of superoxide dismutase, glutathione peroxidase, and glutathione reductase, and limits the action of NADH oxidase **(20).**

Parallel evidence demonstrated by **da Silva et al. (3**6**)** showed that an aquatic low-intensity aerobic exercise program can help cure depression by lowering anxiety and reducing oxidative stress.

On the other hand, It Was reported that regular exercise training activates the body's endogenous antioxidant system and protects it from harmful oxidative damage while acute exercise increases reactive oxygen and nitrogen species and oxidative stress. This seems paradoxical. However, chronic exercise is thought to cause widespread adaptation involving the brain, liver, and skeletal muscle and resistance to the effects of exercise by up-regulation of endogenous antioxidant defenses and enhanced antioxidant/oxidative damage-repairing enzyme activity **(37)**.

Exercise and neurotransmitters

Exercise's potential to alter monoamine communication and modulate their function may be the cause of its antidepressant benefits **(25)**. According to **Lin & Kuo (38)** chronic moderate exercise has been shown to activate the monoamine systems (DA, NE, and 5-HT) without causing central fatigue.

Exercise-induced brain 5-HT release occurs as a result of elevated plasma levels of free fatty acids in long-term exercise, which in turn compete with tryptophan (TRP) for albumin binding in plasma. Consequently, a larger fraction of free TRP penetrates the blood-brain barrier resulting, in enhanced cerebral serotonin production. Moreover, exercise -induced suppression of pro-inflammatory cytokines results in a reduction of serotonin uptake by transporters, which raises the amount of serotonin in the nerve terminal **(39).**

Fascinatingly, the majority of research indicates that exercise raises dopamine levels in several brain areas. These effects may result from exercise capacity to undo abnormalities in dopaminergic transmission brought on by inflammation, in addition to its ability to modulate activation of tyrosine hydroxylase by calcium and calmodulin **(40)**.

Additionally, many lines of research point to the possibility that PA modifies the noradrenergic system both directly and indirectly to lessen depressive symptoms in those who are inflammatory. Within minutes, PA stimulates the sympathetic nervous system, modulating the release of the adrenal hormone adrenaline in a way depending on activity **(40)**.

Conflicts of Interest: The authors declare no conflict of interest.

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