Exercise Prevents Mental Illness

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Abstract. Multiple current studies show that neuroinflammation may contribute to mental illness such as depression, anxiety, and mood disorder. Chronic inflammation in peripheral tissues is indicated by the increase of inflammatory marker like cytokine IL-6, TNF-α, and IL-1β. Pro-inflammatory cytokine in peripheral tissues can reach brain tissues and activate microglia and it causes neuroinflammation. Psychological stress may led peripheral and central inflammation. Activated microglia will produce pro-inflammatory cytokine, ROS, RNS, and tryptophan catabolizes. This neuroinflammation can promote metabolism changes of any neurotransmitter, such as serotonin, dopamine, and glutamate that will influence neurocircuit in the brain including basal ganglia and anterior cingulated cortex. It leads to mental illness. Exercise give contribution to reduce tissue inflammation. When muscle is contracting in an exercise, muscle will produce the secretion of cytokine like IL-6, IL-1ra, and IL-10. It will react as anti-inflammation and influence macrophage, T cell, monosit, protein Toll-Like Receptor (TLR), and then reduce neuroinflammation, characterised by the decrease of pro-inflammatory cytokine and prevent the activation of microglia in the brain. The objective of the present study is to review scientific articles in the literature related to the contribution of exercise to prevent and ease mental illness.

1. Introduction
In developing countries the number of mental illnesses such as anxiety, depression, mood disorders, schizophrenia, including neurodegenerative diseases reported continues to increase. Various studies have been conducted to determine the cause of this mental illness. In the last decade, many studies have shown that neuroinflammation responsible for this disease. Microglia in the brain plays an important role in neuroinflammation. Activated microglia will cause neuroinflammation. Cytokines contained in peripheral tissues can activate microglia. Psychological stress can also activate microglia.

It is known in sports, muscle contraction can issue multiple cytokines. The first known cytokine is interleukin 6 (IL-6). In contrast to IL-6 released by macrophages, IL-6 is released by muscles is anti-inflammatory. Today has been known that muscles are not only secrete IL-6, but also secrete cytokines such as IL-10 and IL-1 receptor antagonist (ra). Therefore cytokines released by muscles called the myokin. This article will discuss how exercise can prevent or alleviate mental illness.
2. Discussion

2.1. Microglia

Microglia are cells found in the brain that function in the homeostatic processes in the central nervous system (CNS). Microglia are considered the resident immune cells of the central nervous system. Microglia are involved in the process of formation, maintenance, injuries, and improvements in CNS [1]. They actually macrophages in the brain that serves as the brain's immune cells and regulate innate immune responses [2]. As well as macrophages, microglia also divided into two phenotypes, namely rest and activated [3]. In contrast to macrophages, microglia in the resting state to the visible presence of branching (ramified appearance). In this resting state, microglia are involved in neurogenesis [4], neuroprotective [5], and plays an important role in synaptic pruning [6]. If microglia in the activated state, the microglia would draw its branches so that the shape amoeboid-phagocytic [7].

Microglia activated in response to brain injury and immunostimulation [8]. Many opinions were expressed activated microglia can be both beneficial and detrimental. Under normal circumstances, activated microglia have a phagocytosis function for cellular debris in cell death, including damaged cells and foreign objects [3]. Microglia also secrete nerve growth factors, neurotrophins, and other neurotropic factors [9]. In pathology, activated microglia release cytotoxic substances which play a role in the neuroinflammation process [10]. Systemic Inflammation is one of the cause’s neuroinflammation [11].

2.2. Neuroinflammation

Today the causes of mental disorders lead to neuroinflammation [12]. Chronically activated microglia may trigger neuroinflammation. Systemic inflammation may activate microglia. Microglia will release substances that are cytotoxic such as pro-inflammatory cytokines such as IL-6, Tumor Necrosis Factor-α (TNF-α), Interferon-γ (IFN-γ), IL-1β, radical oxygen species (ROS), radical nitrogen species (RNS) [13]. Activated microglia also increase the synthesis of tryptophan catabolizes (TRYCATs) after activation of indoleamine 2, 3-dioxygenase (IDO) by cytokines pro-inflames [13].

Various studies in animals and humans suggest that pro-inflammatory cytokine with various tracks including p38 MAPK affects various neurotransmitters like monoamines, serotonin, dopamine, and glutamate [14]. These cytokines affect the synthesis, spending, and reuptake of various neurotransmitters. Cytokines will also activate kynurenine which not only reduces tryptophan, a precursor of serotonin, but also produce metabolites that actively influence the regulation of dopamine and glutamate. Through its effect on neurotransmitters, cytokines will affect neurosirkuit in the brain including the basal ganglia and anterior cingulate cortex, which will cause significant changes in motor activity, motivation and anxiety [15].

Neuroinflammation causing pro-apoptotic neuronal pathways with increased expression of cysteine-aspartic proteases (caspasases) and lower anti-apoptotic and neurotropic molecules, such as Bcl-2 and BAG-1 (Bcl-2 related athanogen) [16]. Neuroinflammation will be accompanied by suppression of neurogenesis and reduced neurotropic molecule such as brain-derived neurotropic factor (BDNF) [17]. Neuroinflammation also cause neurodegeneration through neurotoxic effects of cytokines and TRYCATs, damage caused by ROS, DNA damage, pathological apoptosis, and necrosis of neuron [16].

2.3. Systemic inflammation and neuroinflammation

Chronic systemic inflammation can cause neuroinflammation. Systemic inflammation is characterized by increasing pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, IFN-γ [17]. These pro-inflammatory cytokine can reach the CNS and activate microglia that can change behavior. There are several ways of cytokines in peripheral inflammation may reach the brain. Among them is through an area that leaked blood-brain barrier, active transport through storable cytokine-specific transport molecules on endothelial brain, activation of endothelial cells and stimulate the release of second
messengers such as prostaglandins and nitric oxide, the transmission through afferent nerves fibers such as the vague nerve, entry into the brain parenchyma via peripherally activated monocytes [18]. These various circumstances cause systemic inflammation such as obesity, chronic pulmonary disease, rheumatoid arthritis, autoimmune diseases such as systemic lupus erimatosus (SLE) and multiple sclerosis, irritable bowel syndrome, and infectious diseases such as HIV reported as psychiatric disorders comorbidities [19].

Ascending neural pathways, function in conveying the body's internal state to the brain [20]. Research on mice showed inflammation and infections that change behavior might be caused by a system viscerosensory (bottom-up) [21]. The viscerosensory system may be a signal of metabolic, gastrointestinal, cardiovascular status, infection and inflammation, and chronic inflammation which can lead to anxiety disorders and depression [21]. Viscerosensory signal due to inflammation was detected in the dorsal vagal complex, and the ventrolateral medulla of the caudal medulla. Ventrolateral medulla influenced by signals from the dorsal vagal complex and spine lamina 1, and modulate the function of the lungs and cardiovascular [22].

2.4. Stress and neuroinflammation
Psychological stress can cause changes in physiology, immune system, and behavior in humans and animals that may affect the quality of life. Chronic stress may lead to hypothalamus-pituitary-adrenal (HPA) axis “fatigue” and glucocorticoid resistance [23]. The transcription of I kappa B alpha (IκB) to block the NF-κB activation which induced by glucocorticoid stimulation, is diminished with the blunted HPA axis and glucocorticoid-resistance. Glucocorticoid resistance and blunted HPA axis causes transcriptional fingerprint on peripheral monocytes characterized by increased expression of pro-inflammatory genes, particularly those related to the control path [24]. Therefore, the inflammation related pathways are activated, and they in turn activate the genes responsible for proinflammatory cytokine production [24]. As a result of HPA axis “fatigue,” glucocorticoid-resistance, and inflammation-related transcription pathways activation cause the proinflammatory cytokines to increase further, such as IL-6, IL-1β and TNF-α.

Chronic and repetitive stress will activate the HPA axis and the SNS, because a release catecholamine’s into immune organ. Because peripheral immune has a receptors for norepinephrine, the stimulation of these receptors influence on the development, inflammatory phenotype, and the ability to migrate from the peripheral immune cells [25]. Improved cycle of these myeloid cells in the bone marrow, resulting in changes in the peripheral monocytes into immature and more inflammation [26].

Recent evidence shows that revealed that trafficking of monocytes to the brain promoted the establishment of anxiety-like behaviors following prolonged stress exposure [21]. The evidence is quite surprising, because monocytes moving to the brain without any tissue abnormalities or injury to the tissue. Monocytes trafficking occurs even though there is no damage to the blood brain barrier. Monocytes trafficking is important because the accumulation of monocytes in the brain can cause neuroinflammation and behavioral disorders [23]. Thus the psychological stress can increase inflammation of the tissues and can induce neuroinflammation.

2.5. Exercise and neuroinflammation
It is known that muscle contractions when exercise release a cytokines. Cytokines issued by the muscle is IL-6, IL-8, IL-15, BDNF, LIF, FGF21 and Follistatin-like-1 [27]. IL-6 is a cytokine which first successful identification and the first issued by the muscles during exercise. During exercise is not followed by an increase of TNF-α and IL-1β, but there was an increase of IL-1ra, IL-10, and sTNF-R [28].

IL-6 is the most widely researched myokine. Unlike IL-6 signaling in macrophages that dependent on the activation NFκB pathway, expression of IL-6 intra-muscular governed by a network of the signaling cascade, including calcineurin / NFAT pathway [29], JNK / AP-1 [30] and glycogen / p38
MAPK pathway [29]. An increase of IL-1ra, IL-10, and sTNF-R leads to the stronger presumption that IL-6 is released by muscles as an anti-inflammatory nature. Research conducted by Fischer showed that the duration or longer exercise as the most important thing in an increase in IL-6-induced muscle contraction [31].

In adipose tissue, IL-6 will be led to an increase in fat oxidation and lipolysis [32]. Exercise restrict the movement of peripheral blood mononuclear cells (PBMCs) into the adipose tissue in the same way as reducing the displacement PBMCs toward bronchial epithelial cells infected with the virus [33]. Exercise can decrease lower the Toll like Receptors (TLRs) [34]. TLRs are molecules that are important for inflammation [35]. Temporary increase in inflammatory monocytes occurred after intensive exercise, followed by a rapid decline during convalescence, but regular exercise can reduce the proportion of inflammatory monocytes in the circulation [36].

Cells CD14 + CD25 + regulatory T (Treg) in particular, shows the gene encoding fork head/winged helix transcription factor (Foxp3) and suppress the immune response through contact-dependent mechanism. Exercise significantly led to an increase in Treg cells [37]. Animal studies have shown some evidence that exercise may alter the phenotype of macrophages, which may change the nature of pro-inflammatory macrophages (M1) into anti-inflammatory macrophages (M2) [38]. So it becomes clear that the exercise has anti-inflammatory effects. Thus, to decrease proinflammatory cytokines. A decrease of proinflammatory stone would prevent the activation of microglia, thus preventing neuroinflammation.

Exercise can relieve psychological stress caused by the problems of life [39]. Exercise can increase antioxidants in the body, DNA repair and protein-degrading enzymes, the resulting in decreases in the incidence of oxidative stress-related diseases [40]. Exercise can also improve mood. Thus, exercise can prevent the effects caused by psychological stress. Exercise can prevent monocyte trafficking to the brain. Exercise prevent glucocorticoid resistance, and prevents activation of inflammatory pathways. Exercise boosts BDNF that essential in reducing depression and anxiety [41].

3. Conclusion

Exercise have anti-inflammatory effects. Exercise can help prevent and reduce inflammation both Systemic inflammation and neuroinflammation. With Neuroinflammation averted the mental and behavioral disorders can be prevented.

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