Review Article

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Regulatory role of cytokines on etiology of depression in animal models: their biological mechanisms and clinical implication with physical exercise

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It has been known that chronic psychological or physical stress elicits depressive behaviors (learned helplessness, anhedonia, anxiety, etc.) and also activates to release proinflammatory cytokines in the brain. Especially, postmenopausal women under stress condition exacerbates neuroimmune systems and mood disorder. Repeated restraint stress in the ovariectomized female rats poses an immune challenge which was capable of inducing depressive-like behaviors, promoting exaggerated corticosterone responses and changing the proinflammatory cytokine expression such as interleukin (IL)-1β in the brain. Also, anti-inflammatory cytokines including IL-4 are known to regulate inflammation caused by immune response or stress challenge. Furthermore, some studies reported that physical activity can reduce stress hormones and improve personal immunity. Physical exercise has been shown to be associated with decreased symptoms of depression and anxiety, and with improved physical health, immunological function, and psychological well-being. This paper aims to discuss an overview of how stress shapes neuroimmune response and diverse roles of cytokines in animals models, acting on depressive-like behavioral changes; some beneficial aspects of exercise on stress-related disorders are addressed.

Keywords: Stress, Physical exercise, Neuroinflammation

INTRODUCTION

"Stress" is a commonly used word, and it is often used with different meanings. Stress is a global disease that places a significant burden on human health. An inflammatory pathway process is developed by imbalanced release of proinflammatory cytokines and anti-inflammatory cytokines in response to stress (Köhler et al., 2017). Especially, proinflammatory cytokines and neuroinflammatory responses are important not only in inflammation but also in neuroprotection and neurogenesis (Bluthé et al., 2002). Repeated stress and the subsequent release of proinflammatory cytokines lead to depressive like responses (Colpo et al., 2018). However, several studies reported that anti-inflammatory cytokines could suppress the synthesis of interleukin-1 family, tumor-necrosis factors (TNFs), and other cytokines in peripheral immune and non-immune cells (Lee et al., 2016). The accurate roles of anti-inflammatory cytokines in the regulation of stress response are still controversial.

Some studies reported that the menopausal women experience difficulty in coping with stressful situations (Callan et al., 2018; Park et al., 2015). Following menopause, women experienced mood disorder that is found related to change of the synthesis, release, and reuptake of some receptors for serotonin or dopamine (Shepherd, 2001). Treatment of 17β-estradiol (E_2) replacement exhibits anti-inflammatory effects in the central nervous system (CNS) (Brown et al., 2010). Recent study indicated imbalance be-

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tween anti-inflammatory cytokine (interleukin [IL]-4) and proinflammatory cytokine (IL-1β) in ovariectomized (OVX) and stressed female rats (Park et al., 2020). However, the different regulatory functions of cytokines and the effect on behavioral changes and monoamine levels in animal models of depression are currently under investigation.

Physical activities including jogging, walking, swimming, and dancing have been proved to reduce stress, anxiety and depression (Smith and Merwin, 2021). Exercise has also been found to reduce symptoms such as social problem and self-esteem (Smith and Merwin, 2021). Many epidemiological studies have demonstrated that lower amounts of physical activity are related with greater risk of poor mental health (Argenyi et al., 2022). This review is aimed at discussing the literature on rodent models of stress-induced depression and exercise interventions. We pay special attention to the effect of stress-induced neuroinflamation, with the capacity of exercise to correct biological processes and aberrant behavior associated with stress.

THE ROLE OF ANTI-INFLAMMATORY CYTOKINES IN RESPONSE TO STRESS

Recent evidence suggests that neuroinflammation plays a crucial role in etiology of psychiatric disorders such as depression and anxiety. Neuronflammation involves a combination of psychological, neuroendocrine, and neural systems resulting in changes of neurotransmitters, the hypothalamus-pituitary-adrenal axis, and impaired neuroplasticity, and structural and functional brain changes leading to cognition and emotional behavior. Cytokines can be divided into proinflammatory cytokines such as IL-1β, IL-6, interferon (IFN)-γ, and TNF-α which activate inflammation. In contrast, anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 inhibit inflammation (Abbas et al., 1996). Cytokines interact with each other to keep the balance between proinflammatory and anti-inflammatory cytokines.

Stress induces neuroinflammation, demonstrated by altered production of neuropeptides and inflammatory cytokines in the CNS. Such modulation in the CNS affects endocrine and immune systems followed by behavioral changes (Black, 2002; Park et al., 2015). Immobilization (IMO) is a severe stressor that triggers both physiological and behavioral responses. It has been demonstrated that IMO stress affects neuroimmune systems followed by alterations of physiology and behavior. IMO is a severe stressor that triggers both physiological and behavioral responses. IL-4, an anti-inflammatory cytokine, is known to regulate inflammation caused by immune challenge. Recent study reported the effect of IMO on modulation of IL-4 expression in the brain (Lee et al., 2016).

It was demonstrated that IL-4 was produced by noradrenergic neurons in the locus coeruleus (LC) of the brain and release of IL-4 was reduced in response to IMO. It was observed that IMO groups were more anxious than nontreated groups. Acute IMO (2 hr/day, once) stimulated secretion of plasma corticosterone and tyrosine hydroxylase (TH) in the LC whereas these increments were diminished in exposure to chronic stress (2 hr/day, 21 consecutive days). Glucocorticoid receptor, TH, and IL-4-expressing cells were localized in identical neurons of the LC, indicating that hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary (SAM) axis was involved in IL-4 secretion in the stress response.

Change of central and peripheral IL-4 concentration was associated with suppressing depressive behaviors (Bluthé et al., 2002; Park et al., 2015) and IL-$4^{-/-}$ mice exhibited more anxious behavior compared to wild type (Moon et al., 2015). It has been reported that corticosterone had a suppressive effect on IL-4 protein production and signaling in *in vitro* and *in vivo* studies (Bluthé et al., 2002; Park et al., 2015; So et al., 2002). Also, acute stress or lipopolysaccharide has been shown to stimulate release of norepinephrine (NE) or to increase TH messenger ribonucleic acid (mRNA) level and TH activity (Dronjak et al., 2004). Since TH is a rate-determining enzyme of NE synthesis, change of TH protein was not detected right after exposure of acute stress (Ong et al., 2011). Accordingly, it was concluded that stress-induced decline of IL-4 concentration from LC neurons may be related to anxiety-like behavior and an inverse relationship exists between IL-4 secretion and HPA/SAM-axes activation.

THE DIFFERENTIAL EFFECTS OF CYTOKINES ON STRESS RESPONSES IN A MENOPAUSE ANIMAL MODEL

Menopause is a risk factor of anxiety and depression. Also, psychoneurological symptoms are shown in almost all women in the perimenopausal period. Ovarian hormones regulate cognitive and mood function (Azizi-Malekabadi et al., 2015; Lozza-Fiacco et al., 2022; Schaedel et al., 2021; Shors and Leuner, 2003). 17β-estradiol (E_2) replacement exhibits anti-inflammatory properties in the CNS (Brown et al., 2010). Some studies reported that mood disorders are related to change of neuroimmune systems (Lozza-Fiacco et al., 2022; Schaedel et al., 2021). Also, psychological stress is related with proinflammatory cytokines in the brain such as IL-6, IL-1β, and TNF-α (Buchanan et al., 2008). However, roles of cy-

tokines on stress responses are unknown in a menopause animal model.

It was shown that repeated stress modulates behavioral changes or the balance of pro- and anti-inflammatory cytokines in OVX rats (Park et al., 2020). SD female rats were randomly divided into four groups: the naïve normal (NOR) group, a surgically OVX group, the only stressed (ST) group, and the OVX and IMO stressed groups (OVX+ST). They were performed a battery of tests such as the forced swimming test, the sucrose intake, and social exploration. The corticosterone was assessed in the serum, and also, two representative cytokines (IL-1β and IL-4) were examined in different brain regions after all the behavior sessions for all the experimental groups. The OVX+ST group showed more immobility time in forced swimming test than the OVX group or the ST group. Also, the OVX+ST group tended to have a decreased active social exploration and sucrose solution intake compared to the OVX group or ST group. The serum concentration of corticosterone of the OVX+ST group was higher than the OVX group or ST group and also the level of corticosterone in OVX+ST was markedly increased compared to the NOR group. In the brain, the number of IL-1β immunoreactive neurons of the OVX+ST group was increased compared to the NOR group. The OVX+ST group tended to have an increase in IL-1β-positive neurons compared to the OVX or ST group. However, the number of IL-4 immunoreactive neurons of the OVX+ST group was markedly decreased compared with the NOR group. Also, the IL-4-positive neurons in the OVX+ST group was significantly decreased when compared to the ST group. These results prove that ovariectomy and stress combine to increase the depressive-like behaviors and neuroinflammatory responses. These studies indicate that ovariectomy and stress combine to increase the depressive-like behaviors and neuroinflammatory responses. Together, these data show neuroinflammation as a potential contributor to depressive-like symptoms during menopausal transition.

PREVENTIVE EFFECT OF ANTI-INFLAMMATORY CYTOKINES ON DEPRESSIVE-LIKE BEHAVIOR AND CENTRAL NEUROTRANSMITTER ALTERATIONS

Cytokines in the CNS have been implicated in the evolution of several neurophysiological states, including depressive disorders. The systemic administration of proinflammatory cytokines such as IL-1β and TNF-α activates HPA axis (Maes, 1999; Park et al., 2015; Raison et al., 2006). Most of evidence supports a role of cytokines, especially IL-1, IL-6, TNF-α, and IFN-γ in the pathophysiology of depression and anxiety.

It has been known that cytokines interact with each other to keep the balance between proinflammatory and anti-inflammatory cytokine. If neuroinflammation is involved in etiology of depression, it can be assumed that anti-neuroinflammation drugs might have an effect on depressive behaviors. We have tested this idea and have shown that intracerebral injection of IL-4 markedly decreased IL-1β-induced anhedonic responses and increased social exploration and total activity. Treatment of IL-4 blocked IL-1β-induced increase in prostaglandin E_2 (PGE_2) and corticosterone levels. Also, IL-4 reduced IL-1β-induced 5-HT levels by inhibiting tryptophan hydroxylase mRNA and activating serotonin transporter in the hippocampus, and levels of NE were increased by activating TH mRNA expression. IL-4 may locally contribute to the regulation of noradrenergic and serotonergic neurotransmission and may inhibit IL-1β-induced behavioral and immunological changes. Also, IL-4 modulates IL-1β-induced depressive behavior by inhibiting IL-1β-induced central glial activation and neurotransmitter alterations. IL-4 reduced central and systemic mediatory inflammatory activation, as well as reversing the IL-1β-induced alterations in neurotransmitter levels. Centrally injected IL-1β can cause depressive behaviors (Bluthé et al., 2000; Park et al., 2015). However, IL-4 suppresses the activation of various immune regulating cells, including neutrophils, monocytes, and macrophages, by limiting the production of proinflammatory cytokines (Park et al., 2015; Standiford et al., 1990; te Velde et al., 1990; Wertheim et al., 1993), and it decreases production of PGE_2. (Niiro et al., 1997). Exposure of murine peritoneal macrophages to murine IL-4 before stimulation with IL-1β induced production of PGE_2 (Bluthé et al., 2002).

The activation of the central immune system or exposure to repeated stress can disrupt balance of anti-/proinflammatory cytokines. The acute administration of IL-1β can be a reliable inflammatory preclinical model of depressive-like behavior that is sensitive to antidepressant treatment that may be useful to test potential new antidepressant drugs. Moreover, the cross talk between these systems, mediated by IL-4, may become a target for novel antidepressant therapies.

THE ROLE OF PHYSICAL EXERCISE ON STRESS-RELATED DISEASES

Stress is major public health problem throughout the world and

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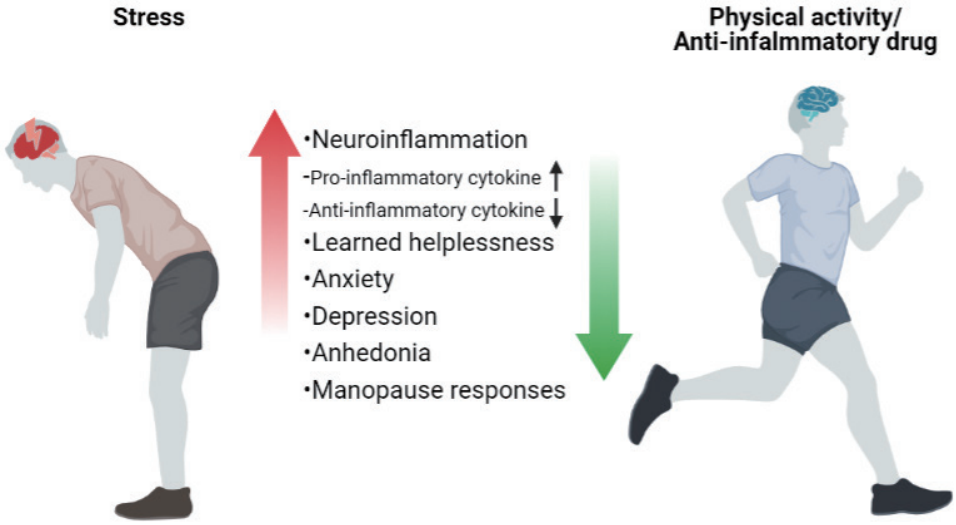

Fig. 1. Schematic diagram summarizing the main conclusion.

is characterized by lowered mood, loss of pleasure, fatigue, and imbalance of neuro-immune system. Smith and Merwin (2021) suggests that physical exercise training is beneficial for mental health outcomes. Long-term exercise helps mental health via neurophysiological mechanisms, or exercise is one of the most factors for cultivating behavioral mechanisms of change. Recent evidence proves that in addition to modifying cardiovascular system, neuroendocrine, and muscular system both acute and chronic exercise have immune system modifying properties like an overall whole-body anti-inflammatory effect (Gleeson et al., 2011). Also, emerging evidence suggests that exercise may be as effective as drug therapy and more effective than another behavioral treatment for mood disorder (Carek et al., 2011; Gujral et al., 2017).

Clinical study reported that many patients suffering from depression frequently display activation of the HPA axis resulting in elevated cortisol levels. One main behavioral change of this condition is anhedonia. In laboratory experiment, there is evidence that physical exercise training can be used as a rehabilitative intervention for treatment of depressive disorders treatment (Sigwalt et al., 2011). The exercise training consisted of swimming (1 hr/day, 5 day/wk) for 3 weeks, with an overload of 5% of the rat body weight. Rats were injected with either dexamethasone or saline or fluoxetine. Rats showed the decrease of blood corticosterone level, reduced adrenal weight (HPA disruption), preference for sucrose consumption and increased depressive-like behavior increased IL-10 and total brain-derived neurotrophic factor and a severe loss of body mass characterized the dexamethasone-treated animals. However, the swim training protected anhedonia state, following the same profile as fluoxetine, and from the dexamethasone-induced impaired neurochemistry. The swimming exercise could protect from the neurophysiological changes induced by the long-term administration of dexamethasone. The physical exercise could be a helpful tool in preventing and treating depressive disorders.

CONCLUSION

Main conclusion of this study is summarized in Fig. 1. The activation of the central immune system or exposure to repeated stress can disrupt balance of anti-/ proinflammatory cytokines. It was concluded that stress-induced decline of IL-4 concentration from LC neurons may be related to anxiety-like behavior and an inverse relationship exists between IL-4 secretion and HPA/SAM-axes activation. The cross talk between these systems, mediated by IL-4, may become a target for novel antidepressant therapies. The physical exercise could be a helpful tool in preventing and treating depressive disorders.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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