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Original Article

Valine Consumption and Endurance Exercise Modified the Inflammation in Rat Model of Anxiety/Depression.

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Abstract

Background: Depression and anxiety are disabling conditions with side effects on cognition, quality of life, memory, and mood. Anxiety is a dysregulated mood condition that could disturb cognition. The present study aimed to evaluate the effect of dietary interventions and endurance training in managing anxiety and depressive symptoms.

Methods: In this study, 30 rats were divided into five groups: Normal group, anxiety/ depression group, rat model of anxiety/depression who consumed valine 3.0 µmol/500 µl intraperitoneal injection once/day for eight weeks, rat model of anxiety/depression who conducted endurance training (32 m/min for 45 minutes/session, six days a week for eight weeks), and rat model of anxiety/depression who conducted endurance training (75% $VO2_{max}$) and consumed valine (3.0 µmol/500 µl). The level of anxiety/depression was evaluated by behavior open field tests and relative expression assay of the genes related to the inflammation.

Results: Findings indicated that the expression level of the NF-κB and TNFα significantly increased in the anxiety/depression group. Moreover, the endurance training and consumed valine improved the NF-κB and TNFα expression in the brain of the rat model of anxiety/depression. In addition, endurance training and consuming valine decreased the anxiety/depression level.

Conclusion: Endurance training and consuming valine reduced the brain's inflammation level and improved the anxiety/depression level.

Keywords: Anxiety, Depression Valine , Endurance training, Brain

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Introduction

Psychiatric problems in both industrialized and developing countries have had a significant economic and social impact on healthcare systems (1, 2). The coronavirus pandemic could boost the risk of anxiety and depression because depression is a common mood disorder, which could lead to a rise in cerebrovascular disorders, heart diseases, gastrointestinal diseases, and the disruption of microbiota in the colon (3-5). The pathogenesis of depression is still unknown, but an artificial intelligence survey found some signaling pathways, including neuroinflammation, neurotransmitter function, phosphatidylinositol signaling system, gap junction, muscle contraction, insulin signaling pathway, and dopaminergic synapse, may be involved (5, 6).

The inflammation pathway could modulate behavior, the mucosal immune system, and emotion (7). Hence, managing or halting the inflammation might be essential for healthy brain function (8). Based on the evidence, depression and anxiety might be induced by cytokine storm and cytokine release syndrome (9). Furthermore, comprehensive studies have indicated that anxiety and depression could distribute sensory/motor neurons and increase brain inflammation (10). However, the mechanistic and molecular pathway is not elucidated.

The hippocampal area in depression is less than in healthy persons, according to Darren W.Roddy *et al.* Furthermore, they have found a link between the severity of depression and the size of the hippocampus (11). Hence, the hippocampus might play a decisive role in anxiety and depression.

No effective therapy strategy is available to stop the progression of depression. Of the therapies for depression, only 60% showed improvement in symptoms (12). As a result, an effective and safe treatment could shed light on how to reduce this illness and improve the gastrointestinal environment. In addition, epidemiological research suggests that environmental factors may play a significant role in the development of depression (13). Thus, the present study aimed to evaluate the effect of dietary interventions and endurance training in managing anxiety and depressive symptoms (14).

In addition, it was well-known that the production of neurotransmitters could be hampered without adequate physical activity and nutrition (15). Growing evidence demonstrated that regular exercise could improve inflammation agents and cytokine release syndrome (16, 17). Non-pharmacological interventions such as exercise effectively treat anxiety and depression (18). Mental disorders might be reduced by increased physical

exercise, probably due to their favorable impacts on psychological well-being, coping mechanisms, and self-perceptions of one's physical appearance (19).

An exciting aspect of depression treatment is that producing neurotransmitters by aromatic amino acids like phenylalanine, tyrosine, and tryptophan might be practical (20, 21). Evidence suggests that the blood-brain barrier (BBB) competes with valine for the transport of aromatic amino acids, which could lead to reduced neurotransmitter concentrations in aromatic amino acids and a delay in serotonin production, as well as a suppression of central tiredness. It is not apparent how valine amino acid concentrations affect depression, even though this is a common finding (22).

The study aimed to evaluate the significant hub genes in brain rats with depression-like behaviors. Moreover, we revealed that the hub genes involved in inflammation could improve with endurance training and Valine /Isovaline supplementation.

Materials and Methods

Animal Study

Male rats aged seven weeks were furnished and maintained in the animal facility. Rats were kept under conventional conditions of 24±3°C temperature, 55 to 60% humidity, 12-hour light and dark cycles, and ad libitum access to food and drink. In addition, all animals were provided with a regular diet. Before beginning the research, rats were acclimated for one week. In this study, the rats were distributed into five groups: Normal group, anxiety/depression group (An/Dep), rat model of anxiety/depression who consumed valine (Val) (3.0 μmol/500 μl intraperitoneal injection once a day for eight weeks), rat model of anxiety/depression who conducted endurance training (Exercise) (32 m/min for 45 minutes each session, six days a week for eight weeks), and rat model of anxiety/depression who conducted endurance training and consumed valine (Ex+Val). The infusion of xylazine (10 mg/kg body weight per animal) and ketamine (80 mg/kg body weight per mouse) were used to euthanize rats.

Inducing Depression

As stated previously, we separated rats with depression into four groups. Rats were treated with fixation, electric tail, and foot shocks for 1 second with ten repetitions (0.5 mA intensity) and food deprivation, followed by 14 days. (23, 24).

Rat behavioral tests

Open field test

Rest periods and locomotor activity were assessed. The open field space was split into 16 squares measuring 40×40×40 cm. Each mouse was positioned within the core area and observed for one-hour periods. Distance moved (cm), duration time (sec), and Rest times (sec) were computed and scored (25, 26).

Valine complement and food intake

Rats had unrestricted access to regular food and running water. In addition, 3.0 μmol/500 μl of valine was administered intraperitoneally once every day for two months (25, 27).

Exercise protocol

On a motorized treadmill, endurance training (EX) was executed. On the treadmill, the intensity was moderate to high for two months (6 days a week). After that, the workout and running pace length gradually increased to 75% VO2 max (32 m/min) for 45 minutes. Additionally, the slope of the treadmill was deemed to be 0% (28, 29).

Quantitative real-time PCR (qRT-PCR)

The TRIzol reagent isolated total RNA from the hippocampal area and ileum tissue (Sigma, USA). cDNA synthesis was performed using 1 g of total RNA and a cDNA synthesis kit according to the manufacturer's instructions (TaKaRa, Japan). qRT-PCR was performed with CYBR Green (TaKaRa, Japan) and Corbet rotor gene 6000 (Qiagen, Australia). The detection of gene expression was assessed using the $2^{-\Delta\Delta CT}$ technique. The expression levels of glyceraldehyde-3-phosphate dehydrogenase (Gapdh) were used to compute the relative expression of genes.

Statistical Analysis

Using GraphPad Prism, statistical analysis was performed (Version 9; GraphPad Software). Distribution was normalized using the Shapiro-Wilk test, and variables were normally distributed. Due to numerous comparisons, the data were analyzed using a one-

way analysis of variance (ANOVA) with Tukey's post hoc test. At *P.value<0.05*, differences were judged statistically significant. In addition, data were presented as the mean±SD.

Result

This study indicated that the total movement rat model of anxiety/depression was reduced compared with the Normal group (Figure 1). Moreover, the endurance training increased the total movement compared with the An/Dep group. In addition, consuming valine enhanced the total movement compared with the An/Dep group. furthermore, the endurance training and consuming valine (Ex+Val) significantly elevated the total movement compared with the other group.

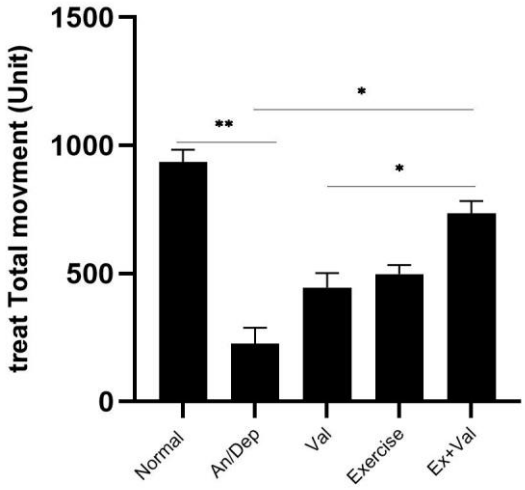

Figure 1. Estimated total distance movement (Unit) via open field test. (mean ±SD; n = 6)

The results revealed that the expression level of the NF-κB and Tnfα in the anxiety/depression group was amplified compared with the control group in the hippocampus (Figure 2). Also, endurance training and valine consumption diminished the relative expression of the level of the NF-κB and Tnfα in the hippocampus (Figure 2). On the other hand, endurance training along with valine consumption decreased the expression level of the NF-κB and Tnfα compared with the other groups (Figure 2).

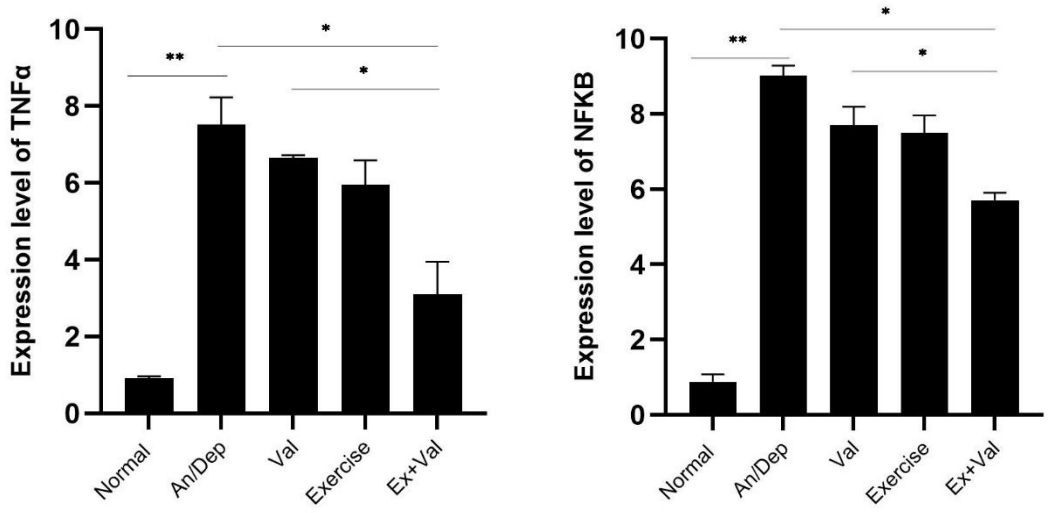

Figure 2. Expression level of the Tnfα and NF-κB. (mean ±SD; n = 6)

Discussion

In this study, we indicated that the inflammation agents such as NF-κB and Tnfα significantly increased in the rat model of anxiety/depression hippocampus. Moreover, we found that endurance training along with valine consumption regulated the expression level of the NF-κB and Tnfα compared with the other groups. Literature review showed that several molecular mechanisms, such as Toll-Like receptor, Cytokine-Cytokine, IL-17 pathway, and TNF signaling pathway involved in the pathomechanism of anxiety/depression (30). In addition, emerging data suggested that receptors of the advanced glycation end product are elevated in neurodegenerative diseases compared to samples from normal patients (31). These results from earlier investigations confirmed that inflammation is a neuropathologic change facilitator (31). A separate investigation determined that increased inflammation such as NF-κB and Tnfα might induce depression condition [56]. These findings showed that the Toll-Like receptor, Cytokine-Cytokine, IL-17 pathway, and TNF signaling pathway may play a crucial role in anxiety/depression. These signalings have been recognized as one of the prospective treatment methods for depression (32). Since proliferation-differentiation and cell cycle programming are essential for body homeostasis, Cytokine-Cytokine and TNF signaling pathways may be useful in determining the cell destiny of many organs (33). Therefore, Cytokine-Cytokine and TNF signaling pathways were altered in the hippocampus regions of mice with depression. In the present study, we demonstrated that the expression level of the mRNAs involved the inflammation signaling

pathway. Based on our data, we found that the expression level of the NF-κB and Tnfα significantly increased in the depression condition. Also, we established that receiving valine could improve the expression of the NF-κB and Tnfα in the depression condition. Several studies have indicated that consumption of the valine has an advantageous effect and can impact molecular processes. This natural supplement can be alternative and complementary medicine in preventing and treating the symptoms of a disease in conjunction with a prescription drug. Based on these findings, valine may be a safe and useful adjunct in treating several neurological and psychiatric illnesses. Evidence has demonstrated that valine, leucine, and isoleucine consumption altered the involved metabolism and mitochondrial biogenesis gene expression (29).

Moreover, DeyangYu *et al.* revealed valine could mediate metabolic health and regulate the FGF21. Based on these results, branched-chain amino acids could improve energy expenditure and induce Ucp1 (27). Notably, our study revealed that endurance exercise improved the expression of NF-κB and Tnfα. Immense evidence has indicated that endurance exercise is considered non-pharmacological interference. Based on the epidemiology studies, endurance exercise might regulate inflammation, antioxidant balance, subtractive lipid-peroxidation, and oxidative stress status (16, 17). Although the particular pathomechanism involved in inflammation has not been fully understood, artificial intelligence analysis and text mining emphasized that high oxidative stress, apoptosis, and inflammation increased depression risk (18). Paolucci and colleagues indicated that moderated intensity interval training decreased the concentration of the Tnfα and interleukin-1 beta (IL-1β), C-reactive protein (CRP), and interleukin-6 (IL-6). Moreover, they found that 6 weeks of moderated intensity interval training modified the student's mental health (34). In another study, exercise significantly decreased the concentration of the interleukin-1β (IL-1β), interleukin-6 (IL-6), Tnfα, and interferon-γ (IFN-γ) of patients involved in the major depressive disorder. Based on these data, physical activity could have the antidepressant medications (35)

Conclusion

According to biological analysis approaches, we could conclude that synchronizing valine consumption and endurance exercise could have a synergetic effect on the

inflammation level. Hence, endurance training and consuming valine reduced the brain's inflammation level and improved the anxiety/depression level.

Competing interests

There is no competing of interest to disclose.

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