Depressive Symptoms, Exercise, and Brain-Derived Neurotrophic Factor in Fibromyalgia Syndrome: A Mini Review

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Abstract: Fibromyalgia syndrome is a chronic widespread pain condition. Other symptoms often can be found, such as fatigue, lack of sleep, irritable bowel syndrome, and mood disturbance. In addition, depression is a clinically relevant symptom that commonly found in fibromyalgia syndrome patients. Brain-derived neurotrophic factor has been known to play a role in fibromyalgia syndrome patients. Additionally, brain derived neurotrophic factor is related to depression. However, the role of this neurotrophin and depression in fibromyalgia syndrome patients needs to be elucidated. Exercise is one of recommended treatment modalities for fibromyalgia syndrome patients which may influence the level of brain-derived neurotrophic factor. Thus, this review summarize the available data on the correlation of brain-derived neurotrophic factor with depression in fibromyalgia syndrome patients and the knowledge about influences of exercise on brain-derived neurotrophic factor levels.

Keyword: Fibromyalgia syndrome depression, exercise, bdnf.

1. INTRODUCTION

Fibromyalgia syndrome (FMS) is a debilitating disease which has many symptoms, such as chronic widespread pain, fatigue, sleep disorder, mood disturbances and irritable bowel syndrome [1]. Prevalence of FMS is 2-4% in adult population [2-4]. Regarding definition, American Colleague of Rheumatology (ACR) has published definition of FMS in 1990 [5] and 2010 [6]. In addition to chronic widespread pain, fatigue, waking unfreshed, and cognitive symptoms, as well as general psychosomatic symptoms are included in the latter definition.

Until now, the aetiology and pathophysiology of FMS still need to be elucidated. Some proposals related to aetiology are including familial and environmental factors [7, 8]. Meanwhile, mechanisms related to pathophysiology aberration in FMS are including serotonin disturbance [9] and HPA-axis perturbations [10]. However, in this review we focus on recent finding regarding to the role of brain-derived neurotrophic factor (BDNF) in FMS patients and possible influences of exercise treatment to the level of BDNF and gives possible benefits to FMS patients.

2. DEPRESSION IN FMS PATIENTS

Depression as one of clinical relevant symptom is commonly found in FMS patients. The prevalence of depression is higher in FMS population (20-60%) as compared to general population (26%) in clinical samples from the US [11-13] and Europe [14-16].

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Study related to FMS and depression has been shown that depression in FMS patients correlated with activity-related discomfort, subjective work quality, as well as regularity of meals [17]. Another report demonstrated that current depression in FMS patients is inversely associated with age, illness duration and predictive of sustained pain throughout treatment [18] and low esteem [14]. Additionally, current major depression in FMS patients is also negatively associated with physical functioning [13], functional disability [19], and satisfaction with social support [20]. However, it still needs to be studied further regarding its association with income and education attainment [21].

Another study in 2007 [22] showed that prevalence of depression in FMS patients is in the range of 20-80%. This data supported by a Canadian survey which demonstrated that 22% of FMS population had current major depression [21]. This depression is associated with younger age, sex (female gender), being unmarried, food insecurity, number of chronic conditions, and limitations in activities [21]. Furthermore, 22% of FMS population in a cross sectional study have depressive mood symptom [23].

Depressed FMS patients tend to experience a general decline in pain intensity and depression as compared to non-depressed patients in one year study [24]. The author also reported that self-efficacy was a significant predictor of changes in both pain and depression for depressed participants, but not in the group of non-depressed patients. Comparing with osteoarthritis, male FMS patients have higher depression, lower self-efficacy and lower well-being [25].

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3. BDNF IN FMS PATIENTS

Although no report could show correlation of BDNF and intensity of pain in FMS patients, it is undoubtedly that BDNF plays a role in FMS, because BDNF has been known to be altered in FMS patients, including in plasma [26], serum [27, 23] and cerebrospinal fluid [28]. Several hypotheses regarding higher level of BDNF in FMS patients which is related to pain symptom, are including the role of BDNF in pain (see review, [29]). However, the role of BDNF in depression of FMS patients still needs to be elucidated, because only one study could show the correlation of BDNF with depression [23]. This difference could be caused by several factors, including sources of BDNF and different assessment tools to measured depression.

4. DEPRESSION AND BDNF

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration [30]. Due to those symptoms, clinically and biologically it is a heterogenous disease. The prevalence of depression is higher in women (10-30%) as compared to men (7-15%) in their life time [31].

BDNF plays a role in the brain by promoting neurogenesis, cell survival and death, neuronal maturation, and synaptic plasticity [32-34]. Additionally, it plays a role in long-term plasticity and psychiatric pathophysiology, including depression [35, 36], as it is suggested that depression is related to neuronal atrophy and neuronal cell loss, especially in the hippocampus and cerebral cortex.

In humans, low level of BDNF has been shown in several type of diseases, such as bipolar disorder, manic, and depressed patients [37, 38]. The hypothesis that depression correlates with BDNF is based on the findings of decreased of level of BDNF in both peripheral and central [27], but the treatment of antidepressant could increase its level both in animal [39-41) and human studies [35, 42, 43].

There are several areas of the brain which are related to depression, including hippocampus, prefrontal cortex, nucleus accumbens, and amygdala (see review, [44]). The level of BDNF level in peripheral could reflect its level in the brain [45], although it is complicated, since besides neuron, other tissues/cells can also produce BDNF, such as endothelial cells, submandibular glands, and pituitary gland [46, 47].

However, the level of BDNF itself does not correlate with severity of depressive symptom [45], since the author found out the level of peripheral BDNF in early remission (1-6 months) is comparable to those of currently depressed patients.

5. PHYSICAL EXERCISE AND BDNF

Many studies compel benefit of exercise to human health. One of benefits is related to the reduction of depression. One of mechanisms is related to neuronal growths (Figure **1**). BDNF is one of principal growth factors that mediate the effect of exercise on the brain [46]. The role of exercise in increasing the level of BDNF is similar as the role of antidepressant in depressive patients or animal model. Besides controlling the signalling cascades and gene expression, such as the transcription factor cyclic

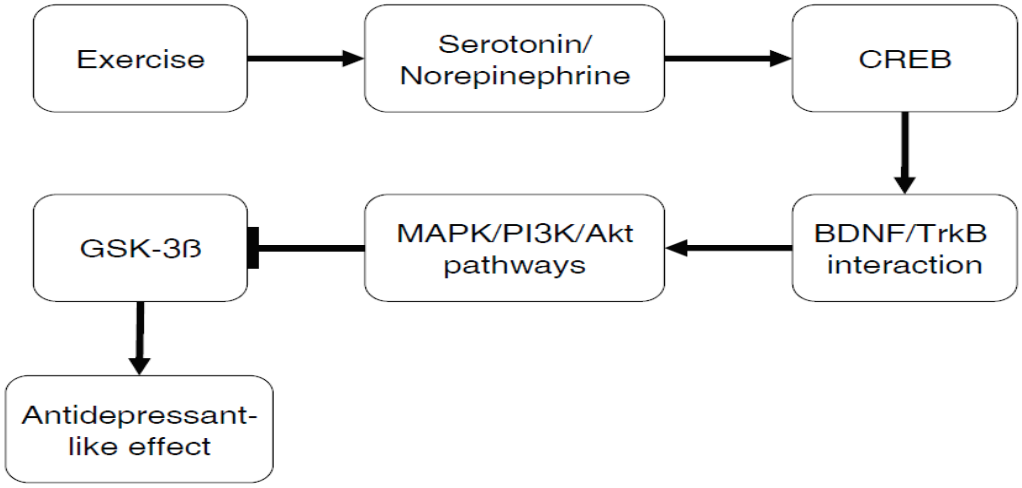

Figure 1: Interaction of Exercise and BDNF in producing antidepressant-like effect.

AMP/Ca^{2+}-response element-binding protein (CREB) [9, 47], exercise activates the mitogen-activated protein kinase (MAPK) and phosphotidylinositol-3 kinase (PI3K)/Akt signalling pathways, which plays a role in promoting neuronal survival and synaptic plasticity [48, 49]. Additionally, treadmill exercise reverses stress-induced changes in the hippocampus of the rats [50]. Synaptic plasticity is regulated by critical modulators such as BDNF and CREB. In addition, the interaction of BDNF and TrkB activates MAPK and PI3K/AKt signalling pathways, which is also involved in functional role related to neuronal survival and synaptic plasticity as aforementioned. Activation of PI3K/Akt pathways inhibit glycogen synthase kinase-3ß (GSK-3ß) activity which leads to produce antidepressant-like effects in the forced-swimming test in rodents [50-52].

6. EXERCISE AND DEPRESSION

The evidence of benefit of exercise to depression has been reported in some studies. In MDD, a tightly controlled study show that aerobic exercise which is consistent with public health recommendation is effective to treat mild to moderate severity of MDD patients [53]. Similar effects was also seen in the study by Knapen *et al.* [54] and concluded that the effect of exercise may be comparable to antidepressant medication and psychotherapy for mild to moderate depressive patients. The latter author assumed that exercise training can produce positive side effects on depression associated physical diseases and cognitive decline. These results are in line with recent review that there is evidence for the treatment of depression, three times per week supervised aerobic exercise at moderate intensity for a minimum of nine weeks [55].

7. INTERRELATION OF BDNF, EXERCISE, AND DEPRESSION IN FMS PATIENTS

In FMS patients, it has been known that BDNF is increased [23, 26-28] and has correlation with depressive symptom of FMS patients [23]. Furthermore, exercise has been shown to have positive effect on the pain [56, 57] and depressive symptom [57] in FMS patients. As BDNF mediates pain [60] and depression [42-45], and BDNF itself can be altered by exercise [59, 60], therefore we hypothesized that BDNF may plays a role in mediating the effect of exercise on pain and depressive symptom in FMS patients. However, further studies are needed to elucidate this mechanism.

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