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Optimizing the Exercise Prescription for Depression: The Search for Biomarkers of Response

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Abstract

There is growing support for the efficacy of exercise interventions for the treatment of individuals who present with mild-to-moderate depression. The variability in treatment response across studies and individuals suggests that the efficacy of exercise for depression will be most optimal when prescribed to individuals who are most prone to respond. The present article reviews contemporary theoretical accounts and recent empirical data pointing to neuroinflammatory states and neurotrophin production as possible biomarkers of the antidepressant response to exercise. The larger exercise and depression literatures provide justification for elevated levels of pro-inflammatory cytokines and deficits in BDNF production as putative matching variables. Although there is some empirical support for these hypotheses, it is clear that this research warrants replication and extension. We offer a few suggestions for future research in this emerging area.

Keywords

Depression; Major Depressive Disorder; Exercise; Treatment; Moderators; Biomarkers

Introduction

While there are a variety of antidepressant medications available for treatment of depression there are no reliable methods to determine which antidepressant treatment will be effective for which patients. Toups and Trivedi [1] discussed the need to identify characteristics for antidepressant medication matching as only a little over a third of patients seeking antidepressant medication treatment achieve remission with their first two treatment steps, and nearly a third of all patients only achieve minimal or no improvement on any given antidepressant medication [2,3]. Therefore, the road to recovery for patients is often long, as

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months can be spent trying a series of medications, and still, many may never recover through medication.

Several randomized controlled trials have supported the efficacy of exercise interventions to alleviate symptoms of mild-to-moderate depression to a degree comparable to other evidence-based treatments, including medications and cognitive behavior therapy [4,5]. Additionally, there is some—however limited—evidence suggesting that exercise may be useful for treating patients with “treatment-resistant” depression [6]. As a single-modality or adjunctive to standard medication treatment or psychotherapy, exercise interventions appear to be most efficacious when the prescription is moderate-to-vigorous-intensity aerobic activity performed 3 to 5 days per week for a length of 6 to 12 months [7–9]. In addition, trials that include follow-up assessments up to 12-months indicate that the benefits of exercise may outlast those observed with medication treatments [7].

Similar to medication interventions, exercise interventions have their limitations. For certain people exercise does not alleviate their depression. Indeed, exercise interventions also exhibit a fairly high non-response and non-remission rates. In a well-controlled study comparing four doses of exercise, only the highest dose of exercise, one that meets the public health recommendations for physical activity performed 5 times per week, achieved the response and remission rates similar to a multistep medication intervention of approximately 60% [10]. All other doses, including one that met the public health recommendations for physical activity performed 3 times per week, only achieved response and remission rates ranging from about 20-30% [10].

Another challenge to exercise interventions is that exercise prescriptions for depressed individuals are marked by meaningful non-compliance rates [11,12], thus possibly reducing their effectiveness. A major exercise treatment dissemination trial conducted in the United Kingdom assigned depressed adults to clinician-recommended exercise or standard care alone and showed that patients prescribed exercise exhibited poor rates of adherence to their recommendations with most participants only attaining small deviations from their pre-treatment sedentary patterns [13]. Due to the patients’ noncompliance tendencies there were no differences in depressive symptoms between the treatment groups at post-treatment and 4-month follow-up.

Without understanding for whom exercise is most effective, exercise interventions may become another step along the long road to establishing an alternative or complimentary effective antidepressant treatment. In this paper, we review recent theoretical accounts and empirical research pointing to neuroinflammatory state and neurotrophin production (brain-derived neurotrophic factor; BDNF) as possible biomarkers of the response to exercise in the treatment of depression. Aiding the goal to personalize the exercise prescription for depression, we suggest a few useful avenues for future research in this emerging area.

Inflammatory Markers

Recent research suggests that depressed patients have elevated levels of pro-inflammatory cytokines, with the most reliably observed elevations in Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-alpha) [14,15]. Since adipose tissue is a key source of cytokines

and is often associated with depression [16,17], it is important to note the observed IL-6 elevations appear to be specific to the state of depression rather than the high levels of body mass index across many study samples [18]. Along with the elevated levels of pro-inflammatory cytokines among depressed individuals, several studies show lower than average levels of anti-inflammatory cytokines such as Interleukin-10 (IL-10) [19] and a lack of correlation between IL-10 and IL-6 that typically is present [20], suggesting there is a dysregulation of the inflammatory system among depressed patients (see Hiles, et al 2012 for a meta-analysis showing large amounts of variability of IL-10 levels between depressed and non-depressed [21]). Moreover, there are several findings suggesting that administration of Interferon-alpha (IFN-alpha; increases IL-6 and TNF-alpha signaling) induces, along with depressed mood and what is sometimes referred to as “sickness behavior” [22–24], pathophysiological states similar to those found in medically healthy depressed patients such as disruption of neurotransmitter metabolism [25] and alternations in brain circuitry related to information processing [26] (see Raison et al. 2006 for a review of these data [27]). Together, these findings provide support for the hypothesis that inflammatory deregulation is implicated in the maintenance and etiology of depression, thus highlighting a promising target for clinical intervention.

Exercise has emerged as an effective strategy to target inflammatory deregulation [28–30] (see Eyre, Papps, & Baune, 2013 for an excellent review of the neuroimmunological effects of physical exercise in depression [31,32]). For example, acting as a stressor, acute bouts of exercise result in the release of the pro-inflammatory cytokine IL-6 from muscles. This release of IL-6, in turn, activates the synthesis of anti-inflammatory cytokines such as IL-10 and inhibits release of pro-inflammatory cytokines such as TNF-alpha [29], suggesting that exercise promotes, in this way, an anti-inflammatory environment. Similarly, when occurring chronically, exercise (training) reduces the production of pro-inflammatory cytokines such as IL-6 and TNF-alpha [33,34] and increases the production of the anti-inflammatory cytokine IL-10 [35]. Interestingly, there is also some initial research suggesting that exercise may, in addition to reducing the neuroinflammatory state, buffer the risk this state confers for depression. Specifically, Rethorst and colleagues found that the relation between IL-6 and depression symptom severity was moderated by the level of participation in moderate-intensity physical activity, such the relation was positive and significant among those who were not active but not significant among those who were active [36]. No inferences with respect to the specificity of this exercise-inflammation-depression relation could be made because the authors only measured and modeled IL-6.

The rationale for prescribing exercise as an intervention for depression specifically for those who exhibit elevations in pro-inflammatory cytokines is further supported by the observation that these individuals may be less likely to respond to other established interventions. Indeed, high levels of TNF-alpha are associated with non-response to selective serotonin reuptake inhibitors (SSRIs) [37,38]. Initial support for this possible matching strategy comes from a recent study (TREAD) evaluating the efficacy of a 12-week exercise program to augment antidepressant treatment for non-responders to SSRIs. In this study, 126 sedentary men and women who remained on a stable dose of SSRI treatment were randomized to either a low (4 kcal per kg per week [KKW]) or high (16 KKW) dose exercise prescription and completed supervised as well as home-based exercise sessions to

fulfill the prescription [39]. Seventy-three of these participants provided blood samples at baseline and immediately following the 12-week interventions that were analyzed for IL-6, and TNF-alpha, IFN-gamma, IL-1beta. Of these inflammatory markers, only TNF-alpha level at baseline was associated with the rate of decrease in depression severity over the course of treatment, such that the improvements were greater among those with high levels relative to those with low levels of TNF-alpha [40]. This relation was not dose-dependent. In its early phases, this research requires replication and extension. It will be particularly important to demonstrate that the relation between depressive symptom severity improvement and levels of TNF-alpha (or other cytokines) at presentation is specific to exercise. Studies comparing the efficacy of different single modality (e.g., cognitive behavior therapy, antidepressant treatment, exercise) and or combination interventions that involve assessment of cytokines at baseline are required to achieve this aim.

BDNF

BDNF is a member of the neurotrophins, a family of structurally related proteins that promote neuronal differentiation and survival during development [41,42], and has been implicated in the development of and recovery from depression [43]. Indeed, depressed patients have lower peripheral BDNF concentrations relative to their non-depressed counterparts [44,45] and these BDNF levels appear to normalize with successful antidepressant treatment [46]. Importantly, when BDNF is administered into the hippocampus of rats or peripherally, antidepressant effects are observed that are equivalent to those when rats are administered antidepressant medications [47,48].

In human and non-human animal studies, acute bouts and training programs of aerobic exercise have generally shown to increase the synthesis, release, and expression of BDNF as well as other relevant growth factors [31,49–52]. Interestingly, though, in the two clinical trials of exercise for depression that included assessment of BDNF [53,54], pre- to post-treatment increases in serum BDNF levels were only observed in one trial [54]. The study with the positive findings, which compared electroconvulsive therapy and aerobic exercise training to its combination in 60 adults with major depressive disorder, did not, however, observe a correlation between changes in serum BDNF levels and symptom improvement [54]. The other study [53], which comprised another secondary analysis of the TREAD study described earlier, did not observe a change in resting serum BDNF from pre- to post-treatment, but found that BDNF levels at presentation predicted the response to treatment, such that patients with higher levels of BDNF showed greater reductions in depression symptom severity relative to patients with lower levels of BDNF. Clearly, these initial findings from the exercise literature do not support the hypotheses that the antidepressant effects of exercise are mediated by increases in BDNF and that exercise therapy may be best targeted to individuals who exhibit reduced BDNF production.

Given the available data for testing these hypotheses is scant, it is premature to draw firm conclusions. Here, it is important to consider literature pointing to a number of likely moderators (e.g., stressors, gene polymorphisms) of the BDNF-depression relation [55], perhaps suggesting that modeling peripheral levels of BDNF for predicting and/or accounting for the antidepressant response to exercise is too simplistic (and may yield

misleading results) and requires that one takes into account interactions with such factors. Among other factors, the BDNF val66met polymorphism may be particularly relevant to identifying individuals for whom the neuroprotective responses to exercise are critical to achieving remission from depression. The BDNF val66met polymorphism is the result of a missense mutation in the gene that codes for BDNF, producing a valine (VAL) to methionine (MET) substitution. This substitution results in modifications to the trafficking and packaging of pro-BDNF, reducing activity-dependent secretion of mature BDNF from the neurons [56,57] and significantly decreases the available BDNF protein, ultimately resulting in lower than average levels of serum BDNF [56]. Initial evidence suggesting that the exercise may confer stronger antidepressant effects for MET carriers comes from a small-scale study that assessed physical activity, BDNF genotype and depression symptom severity in 82 adolescent girls [58]. In this study, physical activity levels interacted with the BDNF polymorphism to predict depression symptom severity, such that physical activity was associated with lower depression scores among MET carriers, while physical activity and depression scores were not related among girls who were homozygous for the VAL allele. These data comport well with an earlier report that had shown that increases in positive affect following an exercise bout were greater among MET carriers relative to those homozygous for the VAL allele [59]. As research may build upon these extant studies, it seems prudent that the assessment of peripheral BDNF levels is complemented by BDNF genotyping as well as measurement of other variables that influence these relationships.

Conclusion

Exercise has shown promise for the treatment of depression, although like other interventions, its efficacy will be most optimal when prescribed to individuals who are most prone to respond. In this paper, we have reviewed a select literature pointing to some potential targets for treatment matching. It is clear from the review that this research is in the early phases and that studying the relation between exercise and neuroinflammatory markers and neurotrophins is complicated, especially considering that these putative biomarkers and their relation with exercise are influenced by other person and environmental factors. The next step forward will require integrating the study of these biomarkers and related variables, also paying careful attention to their interplay [60,61]. Addressing the concern about the potential transportability of exercise interventions for depression, research in this area will benefit from expanding the focus on symptom improvement (i.e., efficacy) to adherence and other factors related to the adoption of an exercise intervention.

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depression. While all three groups of patients exhibited increases in BDNF levels and decreases in depressive symptoms, the combination of treatments resulted in the greater decreases in symptoms. Interestingly, BDNF levels and depressive symptoms were unrelated. [PubMed: 25073431]

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Highlights

1. Exercise has shown effects for depression that rival those of other established interventions
2. Exercise can target several neuroinflammatory mediators of depression pathology
3. Exercise may be effective in increasing BDNF production in genetically at-risk groups
4. Exercise may help correct an inflammatory imbalance among depressed individuals