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Interleukin-6 and depressive symptom severity in response to physical exercise

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ABSTRACT

Elevated IL-6 has been implicated in depression. The anti-inflammatory effects of exercise may be associated with its clinical efficacy for depression. We determined if serum IL-6 levels were altered by 12 weeks of physical exercise, and if IL-6 levels were associated with baseline depression severity and change in depression severity in response to exercise. Data from 116 adults (42.7 ± 11.5y) with mild-to-moderate depression (Patient Health Questionnaire > 9) who participated in the physical exercise arm of the Regassa RCT (www.regassa.se) were analyzed. Participants were requested to complete three 60-min exercise sessions weekly for 12 weeks. Blood samples were provided at baseline and post-intervention following an overnight fast and were analyzed for serum levels of IL-6 using ELISA. IL-6 values were logarithm-transformed. Higher baseline serum IL-6 levels were significantly associated with reduced depression severity after exercise. Reduced IL-6 levels following exercise were significantly associated with parallel reductions in depression severity. These findings are consistent with a previously reported association between reduced serum IL-1β levels and reduced depression severity following 12 weeks of physical exercise in 105 depressed adults. Findings support associations between IL-6, depressive symptoms, and exercise response, and provide support for the plausible involvement of IL-6 in the antidepressive effect of exercise.

1. Introduction

Depression is a major public health burden for which successful treatment remains limited (Chisholm et al., 2016; Vigo et al., 2016). Thus, there is continued interest in alternative and complementary treatment strategies for depression. The antidepressive effects of exercise, an inexpensive and accessible potential adjuvant therapy, are well-established and comparable to other empirically-supported treatments in mild-to-moderate depression (Cooney et al., 2013). Physical exercise training significantly improves the severity of depressive symptoms among healthy adults (Conn, 2010), patients with a chronic illness (Herring et al., 2012), and clinically depressed patients (Schuch et al., 2016b), and reduces other associated signs and symptoms of depressive disorders (Herring et al., 2011). Exercise has fewer negative side effects than antidepressant medication, and may also reduce metabolic abnormalities overrepresented among persons with depression (Vancampfort et al., 2015).

Though exercise has shown promise as an adjuvant therapy against depression, the mechanisms underlying the positive effects of exercise remain understudied. Alterations in levels of several neurotransmitters and neurotrophic peptides have been implicated as plausible mechanisms of the antidepressive effects of exercise, including serotonin (5-HT), noradrenaline, galanin, and brain-derived neurotrophic factor (Erickson et al., 2011; Greenwood and Fleshner, 2011; Sciolino et al., 2012; Strohle et al., 2010). Other related mechanisms include changes in brain anatomy (e.g., alterations in hippocampal volume) and serum oxidative stress markers (e.g., GPX) (Schuch et al., 2016a).

Inflammation is another factor that putatively links exercise to improvement in depression. Increased inflammation resulting from peripheral immune activation, partly due to increased total body and

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visceral adiposity, can produce sickness behavior with symptoms consistent with depression (Dantzer and Kelley, 2007). Elevated serum or plasma levels of interleukin-6 (IL-6), IL1β, tumor necrosis factor α (TNFα) are the most consistently replicated inflammation-related findings in depression (Dowlati et al., 2010; Miller et al., 2009). Indeed, Shelton and colleagues recently reported significant differences in IL-6 between patients with Major Depressive Disorder (MDD) and controls after adjusting for BMI (Shelton et al., 2015). Elevated IL-6 levels were also found in cerebrospinal fluid of patients with depression, and in the frontal cortex of a rat model with depression-like behavior (Lindqvist et al., 2009; Wei et al., 2016). More recently, a meta-analysis of 82 studies showed elevated peripheral levels of cytokines, including IL-6, among patients with Major Depressive Disorder compared to healthy controls (Kohler et al., 2017). Inflammatory processes may also indirectly affect the pathophysiology of depression by influencing neurotransmitter systems (Schwarcz et al., 2012). For example, pro-inflammatory cytokines upregulate tryptophan metabolism in the kynurenine pathway generating functional ligands (e.g, kynurenic acid and quinolinic acid) which affect NMDA and α7 nicotinic receptors to also influence dopamine signaling (Schwarcz et al., 2012). Activation of the kynurenine pathway has been implicated in depressive symptoms (Schwarcz et al., 2012).

Exercise influences pro-inflammatory factors (Eyre and Baune, 2012; Eyre et al., 2013; Petersen and Pedersen, 2005), having the potential to alter the number and function of immune cells (Walsh et al., 2011a). Several inflammatory markers are reduced following increased physical activity and reduced energy intake (Petersen and Pedersen, 2005). Moreover, the protective effect of exercise on chronic inflammation-induced sickness behavior may be partly attributed to the anti-inflammatory effect of regular exercise, mediated by reduced visceral adiposity and/or via increases in anti-inflammatory cytokines including IL-1 receptor antagonist and IL-10 (Walsh et al., 2011a). Recent animal research supported that the kynurenine pathway can be impacted by exercise-induced skeletal muscle kynurenine aminotransferases which may protect against stress-induced depressive behavior (Agudelo et al., 2014).

Importantly, recent evidence has suggested that the anti-inflammatory effects of exercise may be associated with clinical efficacy for depression (Eyre et al., 2014). For example, change in IL-1β and higher baseline levels of TNFα were associated with larger improvements in depressive symptoms following 12 weeks of aerobic exercise among 105 depressed patients (Rethorst et al., 2013). However, exercise dose was not significantly associated with change in cytokine levels, likely due to the low exercise dose used in the study. Similarly, a recent review reported no significant acute or chronic changes in any inflammatory marker following exercise training in people with MDD, based on in total 5 studies (Schuch et al., 2016a). Nonetheless, among the limited available studies, significant associations have been reported between inflammatory markers, depressive symptoms, and exercise response (Schuch et al., 2016a).

Thus, the aims of the present study were to examine: 1) baseline associations between IL-6 levels and depressive symptom severity; 2) the change in IL-6 levels in response to a 12-week exercise intervention; 3) if baseline IL-6 levels influence the change in depressive symptoms by exercise; 4) if baseline depressive symptom levels influence the change in IL-6 levels by exercise; and, 5) the association between changes in depressive symptoms and IL-6 levels. This was examined in 116 adults with a baseline diagnosis of mild-to-moderate depression derived from a Swedish randomized controlled trial (RCT) of interventions against depression, the Regassa project (Hallgren et al., 2015).

2. Methods

2.1. Participants

Study participants were recruited from the RCT Regassa (www.regassa.se), which evaluated the relative effectiveness of three interventions for depression (Hallgren et al., 2015), including physical exercise, internet-based cognitive behavioral therapy, and treatment as usual (TAU). The study was performed at primary care facilities located in six county councils in Sweden between the years 2011 and 2013. The study protocol has been previously described in detail by Hallgren et al. (2015). In brief, each intervention lasted 12 weeks with assessments of depression severity at baseline (pre-treatment) and post-treatment (3 months after baseline). An ethical review board at the Karolinska Institutet approved the study (Dnr 2010/1779-31/4), and all participants provided informed consent prior to participation.

Patients, 18–64 years old, who scored >9 on the Patient Health Questionnaire (PHQ-9) were invited to participate in the trial. The PHQ-9 is a valid instrument for diagnosing depressive disorders and scores above nine have a reported sensitivity and specificity of 88% for major depression (Kroenke et al., 2001), though recent meta-analytic evidence has somewhat questioned its specificity (Mitchell et al., 2016). The complete MINI (Sheehan et al., 1998) was performed to confirm diagnoses and identify psychiatric exclusion characteristics. The exclusion criteria were: severe somatic illness, a primary alcohol or drug use disorder, or a psychiatric diagnosis that required specialist treatment (such as psychosis).

Patients in the physical exercise group were randomized to one of three conditions: 'light exercise', which consisted of yoga classes (or similar) with a focus on gentle stretching and controlled breathing; 'moderate exercise', an intermediate-level aerobics class; and 'vigorous exercise', a higher intensity aerobics/strength-training and balance class. Patients were requested to participate in three 60-min exercise classes per week for 12 weeks. As previously reported (Helgadóttir et al., 2016), heart rate (HR) within each session was monitored using pulse watches, and average session HR significantly differed between conditions (light: ~54% of estimated maximum heart HR (MHR, calculated as 220 minus age); moderate: ~70% MHR; vigorous: ~76% MHR). The exercise sessions were undertaken at 'Friskis och Svettis' a modern fitness center with multiple locations throughout Sweden. Adherence was monitored through weekly face-to-face meetings with a qualified personal trainer and patients who failed to attend this meeting were contacted by the trainer with a telephone call and encouraged to continue the exercise intervention.

Physical activity level was scored using a self-reported questionnaire (GIHAv score) (range 0–152) (Ekblom-Bak et al., 2011), where a score of ≥21 is equivalent to the minimum physical activity level recommended for general health by the American College of Sports Medicine (ACSM) and the World Health Organization, while scores ≥42 are equivalent to the activity level recommended by the ACSM and WHO to achieve additional health benefits in adults. Though some evidence suggests limitations of self-report measures of physical activity among people with mental illness (Soundy et al., 2014), the GIHAv has been validated in a separate (unpublished) study in which it corroborated objectively-measured moderate-to-vigorous and vigorous physical activity (Hallgren et al., 2016b).

Severity of depression was assessed at baseline and post-treatment using the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), a 10-item scale designed to be sensitive to changes in depressive symptoms following treatment. Higher scores indicate more severe depression; each item yields a score ranging from 0 to 6. Ten symptoms are rated: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts. Total scores range between 0 and 60.