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Exercise affects symptom severity but not biological measures in depression and somatization – Results on IL-6, neopterin, tryptophan, kynurenine and 5-HIAA

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ABSTRACT

Exercise leads to symptom reduction in affective disorders and functional somatic syndromes. Biological hypotheses of underlying mechanisms include serotonergic and immunological pathways. We aimed to investigate biological features in persons with major depression and somatoform syndromes, and to analyze effects of short-term graded exercise on these parameters. Baseline values for depressive and somatoform symptoms, tryptophan, kynurenine, 5-hydroxyindoleacetic acid, neopterin and interleukin-6 were compared with those after one week of increased and one week of reduced physical activity. Thirty-eight persons with major depression, 27 persons with a minimum of 6–8 somatoform symptoms, and 48 healthy controls participated in the study. Depressive and somatoform symptoms were reduced after the active week, and an interaction pointed towards group-specific reduction of psychopathology. Participants with major depression had lower levels of kynurenine compared to controls, with intermediate concentrations in somatoform patients. There were no systematic associations of symptom improvement with biological changes. A possible limitation of the design is that a control condition with low physical activity, but no placebo condition was included. People with multiple somatoform symptoms and major depression benefit from a short and low-graded exercise intervention. These effects do not seem to be mediated by changes in serotonergic and inflammatory parameters.

1. Introduction

Depressive disorders are a major cause of morbidity worldwide (WHO, 2001) with a lifetime prevalence of 3–16.9% (Andrade et al., 2003; Kessler et al., 2003) and a high impact on productivity and health care cost (Donohue and Pincus, 2007). In regard of the high rate of persons suffering from depression being untreated (Wittchen and Pittrow, 2002), there is considerable interest on low-graded self-help treatments. As avoidance of physical activity, or physical inactivity, has been proposed as a risk factor in the psychopathology of affective (Paffenbarger et al., 1994) as well as somatoform disorders (Looper and Kirmayer, 2002; Witthoft and Hiller, 2010), an extensive body of research targeted exercise interventions. Symptom reducing effects of regular graded exercise in major depression have been repeatedly demonstrated (Brosse et al., 2002; Craft and Perna, 2004; Stathopoulou et al., 2006; Cohen and Shamus, 2009; Deslandes et al., 2009). Previous studies showed that even relatively short periods of exercise (10 days, (Dimeo et al., 2001)) can be beneficial. There is less research in the effects of exercise in somatoform spectrum disorders, and the few published studies point toward symptom reduction (Kornreich, 2006; Nickel et al., 2006). More widely, 'functional somatic syndromes', medical conditions associated with somatoform disorders such as chronic pain, fibromyalgia and chronic fatigue syndrome have been targeted for exercise interventions. Again, effects on the psychopathology are positive (Edmonds et al., 2004; Liddle et al., 2004; Henningsen et al., 2007; Busch et al., 2008). Mechanisms underlying the effects of exercise on depressive psychopathology remain largely unexplained (Craft and Perna, 2004; Wipfli et al., 2009). Hypothesized pathways of action can be broadly sorted into two categories: psychological (for example distraction from negative cognitions, enhancement of self-esteem) and biological theories (Lawlor and Hopker, 2001; Stathopoulou et al., 2006; Wipfli et al., 2009).

A number of biological parameters connected to the pathophysiology of major depression are presumably involved in the beneficial effects of exercise on psychiatric disorders. Evidence strongly suggests involvement of monoaminergic, especially serotonergic mechanisms

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in depressive disorders (Coppen, 1969; Lapin and Oxenkrug, 1969; for an overview, see Hasler et al., 2004). It is hypothesized that exercise may provide a function similar to that of antidepressant drugs by making more serotonin available via increased production and altered receptor efficiency (Broocks et al., 2001; Wipfli et al., 2009). Previous studies show changes in the (central and peripheral) tryptophan metabolism, such as increased serotonin (5-HT) synthesis after exercise in animals (Dey et al., 1992; Dishman et al., 2006) and humans (Wipfli et al., 2009) as well as increased concentrations of free tryptophan and its main metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Chaouloff, 1997). In addition, immunological changes, mainly chronic inflammatory processes are considered relevant in affective disorders (for example, Maes et al., 1990, 1994, 1995 for an overview, see Dinan, 2009). Exercise influences inflammatory processes (Steinacker et al., 2004; Zaldivar et al., 2006; Edwards et al., 2007; Gleeson, 2007; Nielsen and Pedersen, 2008) which seem to be important in the mediation of antidepressant mechanisms (Hallberg et al., 2010). Inflammatory and serotonin-related changes are connected (Weiss et al., 1999; Myint and Kim, 2003). Catabolization of tryptophan along the kynurenine pathway occurs through the enzyme indoleamine-2,3-dioxygenase (IDO), and the production of IDO is upregulated by proinflammatory cytokines (Myint and Kim, 2003; Wichers and Maes, 2004; Maes et al., 2011).

The aims of this study were to examine effects of short-termed, moderate exercise on depression and somatoform disorders, and to assess the role of depression-related biological parameters in the mechanism underlying the symptom-reducing effects of graded exercise. We analyzed concentrations of tryptophan, kynurenine, 5-HIAA, neopterin and IL-6. We focused on tryptophan as the precursor of serotonin, and its metabolization along the kynurenine pathway, and into 5-HIAA as the main metabolite on the other hand (indicating serotonergic activity), thus assessing for different paths of the tryptophan metabolism. Neopterin is induced by IFN-γ; it is a sensitive marker for the detection of cellular activation (Huber et al., 1984; Weiss et al., 1999, Schröcksnadel et al., 2006). Due to concomitant induction by IFN-γ, neopterin concentrations and TRP degradation (KYN/TRP ratio) are closely associated (Schröcksnadel et al., 2006). IL-6 is a proinflammatory cytokine and considered a relevant marker in major depression (Dowlati et al., 2010). IL-6 has also been associated with exercise effects (Nielsen and Pedersen, 2008). For an overview on tryptophan metabolism and the interactions with proinflammatory cytokines, see Fig. 1.

We hypothesized (i) that participants show significant decrease in depressive and somatoform symptoms after exercise compared to a control condition, (ii) differences in biological parameters between the patient groups and the healthy controls, such as heightened inflammatory parameters in persons with major depressive disorder, with the same parameters possibly lowered in persons with multiple somatoform symptoms, (iii) "normalizing" effects of exercise on biological parameters.

2. Methods

2.1. Subjects

Participants were 38 persons with present DSM-IV major depressive disorder (MDD) (mean age 32.08+12.25, 60.5% females), 27 persons with somatization syndrome (see below; Somatoform Symptom Index SSI-8, (Escobar et al., 1989; Rief et al., 1996)); (mean age 33.81+14.29, 74.1% females), and 48 healthy controls (mean age 36.44+13.28, 66.7% females). Gender ratio approximately reflects the sex distribution in somatoform spectrum disorders in the general population (Escobar et al., 1989; Gureje et al., 1997; Rief et al., 2001a). Exclusion criteria were current delusional disorders, alcohol or substance abuse or dependence, persistent medical illnesses that could affect immune status (autoimmune diseases, severe chronic viral infection), ongoing psychotherapy, medical illnesses or injuries in the last two weeks and medication with opiates. Diagnosis of major depression was an exclusion criterion for the SSI-8 group. Participants in this group had to report at least 6 (men) or 8 (women) persistent and medically unexplained bodily symptoms. This is a less restrictive definition for multiple somatoform symptoms than the DSM-IV diagnosis of somatization disorder (Escobar et al., 1989; Rief et al., 1996; Rief and Hiller, 1999), and a study by Rief and Hiller (1999) demonstrated that this criterion differentiates sufficiently between persons with somatoform syndromes and clinical controls. Participants of the depression group had to fulfill criteria for major depression and were only included if they had a maximum of 3 persistent medically unexplained bodily symptoms. Of the 38 persons in the major depression group, 4 of them presented with one persistent somatoform symptom (10%). We also excluded control participants when they had current or past mental disorders. Fig. 2 shows a flow chart of the selection process.

Of 458 persons screened through a telephone interview, 172 participated in a diagnostic session. 44 of them did not fulfill the inclusion criteria or were not interested to participate further. Thirteen subjects had withdrawn due to acute illness, lack of interest and other reasons. Two persons were excluded because of too many missing variables. 113 persons were included in the data analysis. Participants (target age range: 18–65 years) were recruited via advertisements, leaflets in pharmacies and waiting rooms of doctors, press releases in local papers and postings in public buildings in and around the two survey centers Marburg and Munich (Germany).

2.2. Design and procedure

We compared baseline values of psychometric (depressive symptoms, somatoform symptoms in the last 7 days) and biological parameters (interleukin-6, neopterin, tryptophan, kynurenine, 5-hydroxyindoleacetic acid) with those after two physical activity conditions.

Suitable candidates attended a diagnostic session after a screening interview by telephone. The investigator explained the procedures in detail and participants gave written informed consent. The ethics committee of the 'Deutsche Gesellschaft fuer Psychologie' (DGPs) approved the protocol of the study. Subjects received a compensation of 100€ (approximately $140). DSM-IV Major depression diagnosis, SSI-8 criteria and comorbid axis-I disorders were confirmed with the German version of the Structured Clinical Interview for DSM-IV (SCID) (Wittchen et al., 1997) and the participants answered a set of questionnaires. If reported symptoms lacked known physical causes, the category "medically unexplained" applied (Kirmayer et al., 2004). Discussion on uncertainty about categorization relied on medical findings—if necessary, we collected additional clinical information from participants' general practitioner. The results reported here were part of a larger study on biological and psychological aspects of depression and somatization. For the present purpose, we used three of six assessment points over three months. The examiner drew the blood samples (see below), and participants filled in questionnaires.

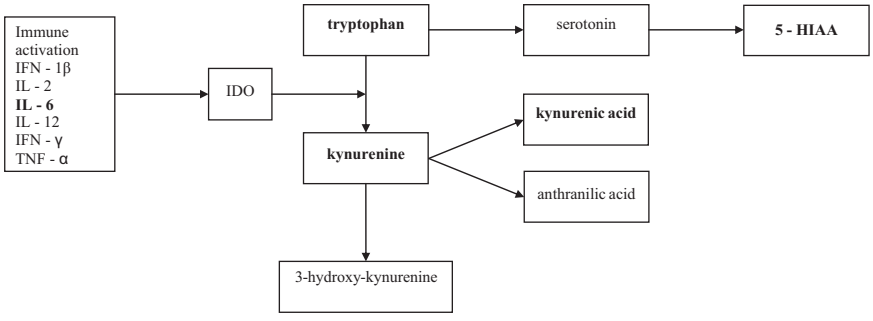

Fig. 1. Tryptophan catabolism and metabolism (simplified). Based on (Myint and Kim, 2003; Pilger, 2005; Wichers et al., 2005). Parameters of further relevance in this study are highlighted in bold letters. 5-HIAA=5-hydroxyindoleacetic acid; IDO=indoleamine 2, 3-dioxygenase