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Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis

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ABSTRACT

Background: Clinical studies have suggested beneficial effects of exercise on cognitive function in ageing adults and neurodegenerative diseases such as dementia. Recent work indicates the same for progressive multiple sclerosis (MS), an inflammatory and degenerative disease of the central nervous system (CNS). The biological pathways associated with these effects are however not well understood.
Objective: In this randomized controlled study, we explored serum levels of the myokine Irisin, the neurotrophin brain-derived neurotrophic factor (BDNF) and Interleukin-6 (IL-6) during acute endurance exercise and over the course of a 9-weeks endurance exercise training period in n = 42 patients with progressive MS.
Results: We detected a significant increase of BDNF levels in progressive MS patients after 30 min of bicycling ($p < 0.001$). However, there were no significant changes for baseline levels after 22 sessions of training. No significant effects of acute or prolonged exercise could be found for Irisin or Interleukin-6.
Conclusion: Our results indicate that BDNF is strongly induced during acute exercise even in patients with progressive MS and advanced physical disability. Long-term effects of exercise programs on biological parameters (Irisin, BDNF, IL-6) were much less pronounced. Given the hypothesis-driven selection of a limited set of biological markers in this pilot study, future studies should use unbiased approaches in larger samples to obtain a comprehensive picture of the networks involved in exercise effects on neurological diseases.

1. Introduction

It is becoming increasingly clear that neurodegenerative processes play an important role in the pathogenesis and progression of multiple sclerosis (MS) (Trapp and Nave, 2008; Frischer et al., 2009). Anti-inflammatory or immunomodulatory treatments have limited effects on neurodegeneration and clinical disability during the progressive phase of the disease (Molyneux et al., 2000; Mullard, 2011). Therefore, novel neuroprotective therapeutical approaches are required (Mullard, 2011; Fox et al., 2012). Similarly, no effective treatments are available for cognitive dysfunction (Comi, 2010; Amato et al., 2013; Benedict and Zivadinov, 2011), which is correlated with neurodegeneration and grey matter atrophy (Rinaldi et al., 2010) and is a common symptom in MS (Rao et al., 1991; Amato et al., 2006).

The neuroprotective and -regenerative potential of exercise has been demonstrated in numerous animal studies f.e. by inducing neurogenesis in the hippocampus, an important brain structure for learning and memory (van Praag et al., 2002; van Praag et al., 2005; Cotman et al., 2007). These findings are concordant with clinical findings in neurodegenerative diseases such as Parkinson's disease (Petzinger et al., 2013) or Alzheimer's disease (de Andrade et al., 2013), where aerobic exercise can ameliorate symptoms and delay disease progression. Moreover, exercise is known to improve neurocognitive function of older adults (Smith et al., 2010).

In MS, meta-analyses have provided evidence for beneficial effects of exercise on well-being, walking ability, fatigue and depression

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(Kuspinar et al., 2012; Pearson et al., 2015; Heine et al., 2015; Dalgas et al., 2014; Latimer-Cheung et al., 2013). Moreover, cross-sectional data indicate that cardiorespiratory fitness is associated with grey matter volume and white matter tract integrity (Prakash et al., 2010; Motl et al., 2015). We have recently reported in a small randomized controlled trial, that 9 weeks of standardized endurance exercise in a cohort of progressive MS patients (n = 47, Expanded Disability Status Scale (EDSS) 4–6) improved several domains of cognitive function as well as fitness, walking ability, depressive symptoms and fatigue (Briken et al., 2014). Therefore, exercise training might impact on brain function and neuroplasticity in MS. The underlying biological mechanisms, however, are not yet understood and biomarkers to reliably quantify these are still missing (Fischer et al., 2011; Heesen et al., 2012). A possible candidate which is upregulated during exercise in humans in the peripheral blood is brain-derived neurotrophic factor (BDNF) (Knaepen et al., 2010; Cotman and Berchtold, 2002). BDNF is a member of the neurotrophin family, which plays an important role for synaptic plasticity, neuronal survival and differentiation and mediates the beneficial effects of exercise in the central nervous system (CNS) in animal models (Leal et al., 2014; Benarroch, 2015; Vaynman et al., 2004). While the relevance of peripheral BDNF for processes in the CNS remains unknown, several studies have reported associations between exercise, circulating BDNF levels, hippocampal volume and cognitive function in the general population (Smith et al., 2010; Erickson et al., 2011; Erickson et al., 2010).

A relatively novel myokine which is known to be induced by exercise training is Irisin (Boström et al., 2012). Elevated Irisin plasma levels were found during exercise in mice and humans and are induced by increased expression of PPARγ-coactivator-1-α (PGC1-α), a regulator of mitochondrial biogenesis. PGC1-α is an inducer of Fibronectin type III domain-containing protein 5 (FNDC5) expression, a single-pass membrane spanning protein. Upon physical activity, the ectodomain of FNDC5 - termed Irisin - is shed and released into the bloodstream. Interestingly, FNDC5 was recently shown to mediate beneficial CNS effects of endurance exercise by upregulating BDNF expression in the hippocampus in an animal model (Wrann et al., 2013).

A pleiotropic cytokine which is also substantially upregulated during acute exercise in muscle tissue is Interleukin 6 (IL-6) (Pedersen and Febbraio, 2012). Anti-inflammatory effects of muscle-derived IL-6 have been hypothesised (Pedersen, 2011; Benatti and Pedersen, 2014). However, studies including MS patients have shown inconsistent changes of IL-6 serum levels during or after a period of frequent exercise (Schulz et al., 2004; Bansi et al., 2013).

We have previously shown that acute moderate exercise induces BDNF serum concentrations not only in healthy subjects (Szuhany et al., 2015), but as also in MS patients (Gold et al., 2003). For the most part, studies on the acute effects of exercise on biological markers have to date focused on patient groups during the early stages of MS with limited disability.

The aim of this study was to investigate if endurance exercise changes the acute and long-term serum levels of Irisin, BDNF and IL-6 in progressive MS patients and if these levels are associated with the observed changes in the clinical outcomes. Based on the current knowledge, we expected an induction of Irisin, BDNF and IL-6 in serum after acute exercise and possibly also elevated resting state levels and increased responsivity after the training interval of 9 weeks (Szuhany et al., 2015).

2. Material and methods

2.1. Study design

Patients with primary or secondary progressive MS (PPMS/SPMS) (Polman et al., 2011; Lublin and Reingold, 1996) and moderate disability (EDSS 4–6) were included in a randomized controlled trial (RCT). A detailed description of the study rationale and design of the RCT were published previously (Briken et al., 2014). Patients with medical contraindications for exercise therapy (such as cardiovascular or major orthopedic disease), severe developmental, psychiatric, or neurological disorders other than MS were excluded. We also excluded patients who had started immunomodulatory therapy within the last 6 months, had undergone steroid therapy within the last 4 weeks or suffered from documented relapses within the last 12 months. Patients were randomized to one of four study arms: Waitlist-control group or one of three arms of different exercise training modalities (arm ergometry, rowing and bicycle ergometry). The training programs were tailored to the individual level of fitness of the participants, as determined by a bicycle ergometry performance test at baseline (increase of 12.5 W/min until exhaustion, average duration 10–20 min, average performance approx. 100 W). The training program consisted of 2–3 sessions of standardized endurance training per week as interval training with stepwise progression in intensity and duration over a time of 9 weeks. Bicycle ergometry was performed again at the end of the training period to determine aerobic fitness parameters.

2.2. Standardized bicycle ergometry performance test

Participants started cycling at 25 W and resistance was steadily increased with an incline of 12.5 W/min. VO_2 and heart rate were measured continuously and maximum power was recorded. Lactate was measured every two minutes. Depending on their physical condition, for some patients (n = 14) an easier protocol was applied starting at 8 W with an incremental increase of 8 W/min.

2.3. Measurement of Irisin, BDNF and IL-6 levels in serum

Blood samples for determination of Irisin, BDNF and IL-6 were drawn during the bicycle ergometry performance tests at resting state, directly after and 30 min after termination of the ergometry performance test. After the 9 weeks of intervention (arm ergometry, rowing, bicycle ergometry or waitlist-control) all procedures were repeated. In total, we obtained 6 serum samples for each participant, 3 samples before (pre) and 3 samples after (post) 9 weeks of intervention. Blood samples were collected in standard tubes (S-Monovette 4.9 ml Z-Gel, Sarstedt, Nümbrecht, Germany, with no protease inhibitors added), aliquoted and stored at −80 °C until assayed.

Chemicals of analytical grade were purchased from Merck (Darmstadt, Germany). Irisin levels were determined according to manufacturer's instructions using a commercially available ELISA (Phoenix Pharmaceuticals Inc., Burlingame, USA) with a detection limit of 1 ng/ml, a detection range from 0.3–200 ng/ml and no cross-reactivity observed (Huh et al., 2012). Each 140 μl of serum were diluted with sample buffer and BDNF was quantified by a modified ELISA (Promega, Madison, WI, USA). The assay has a detection limit of 1 pg/ml and shows <3% cross-reactivity with other related neurotrophic factors (NGF, NT-3 and NT-4), in detail described by Hellweg et al. (2003) and Ziegenhorn et al. (2007). The plasma concentration of IL-6 was determined using commercially available ELISA kits (Quantikine ELISA Kit, R&D Systems, Minneapolis, USA) according to the manufacturer's instructions. This IL-6 ELISA has a reported detection limit of 0.7 pg/ml, an assay range of 3.1–300 pg/ml and <0.5% cross-reactivity observed with available related molecules. For determination of the acute effects of exercise on serum levels, we compared Irisin, BDNF and IL-6 at the three time points during ergometry (resting state, directly after, 30 min after performance test). For long-term changes we compared resting state serum levels from pre and post 9 weeks of training in comparison to the serum levels of the control group. Additionally, we studied ergometry effects (resting state, directly after, 30 min after performance test) after 9 weeks of regular training in comparison to the response in the control group.