Neuroscience and Biobehavioral Reviews 61 (2016) 1–11

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Neurobiological effects of exercise on major depressive disorder: A systematic review

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ARTICLE INFO

Article history:
Received 21 September 2015
Received in revised form 2 November 2015
Accepted 23 November 2015
Available online 2 December 2015

Keywords:
Depression
Exercise
Inflammation
Hormones
Neurotrophines
Neuroplasticity
Neuronal activity
Oxidative stress

ABSTRACT

Exercise displays promise as an efficacious treatment for people with depression. However, no systematic review has evaluated the neurobiological effects of exercise among people with major depressive disorder (MDD). The aim of this article was to systematically review the acute and chronic biological responses to exercise in people with MDD. Two authors conducted searches using Medline (PubMed), EMBASE and PsycINFO. From the searches, twenty studies were included within the review, representing 1353 people with MDD. The results demonstrate that a single bout of exercise increases atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), copepetin and growth hormone among people with MDD. Exercise also potentially promotes long-term adaptations of copeptin, thiobarbituric acid reactive species (TBARS) and total mean frequency (TMF). However, there is limited evidence that exercise promotes adaptations on neurogenesis, inflammation biomarkers and brain structure. Associations between depressive symptoms improvement and hippocampus volume and IL-1β were found. Nevertheless, the paucity of studies and limitations presented within, precludes a more definitive conclusion of the underlying neurobiological explanation for the antidepressant effect of exercise in people with MDD. Further trials should utilize appropriate assessments of neurobiological markers in order to build upon the results of our review and further clarify the potential mechanisms associated with the antidepressant effects of exercise.

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http://dx.doi.org/10.1016/j.neubiorev.2015.11.012
0149-7634/

1. Background

Major depressive disorder (MDD) is a relatively common condition and a leading cause of years lived with disability across the world (Ferrari et al., 2013). Several models have been proposed to explain the etiology of MDD, with one original hypothesis being attributed to "chemical imbalance in the brain" (Schildkraut, 1965). More recently, emerging evidence has demonstrated that MDD has a more complex etiology, involving other neurobiological mechanisms such as neurotrophins, oxidative stress, inflammation, and changes in brain structure and activation (Belmaker and Agam, 2008; Furtado and Katzman, 2015; Rive et al., 2013).

In summary, several studies have shown that Patients with MDD present with: (1) decreased levels peripheral (plasma and serum) brain-derived neurothrophic factor (BDNF) levels, a marker of neurogenesis (Brunoni et al., 2008); (2) increased levels of peripheral (plasma and serum) pro-inflammatory markers, such as interleukin (IL)-6 (Dowlati et al., 2010; Valkanova et al., 2013); (3) increased serum oxidative stress markers, such as superoxide dismutase (SOD) and decreased antioxidant enzymes, such as glutathione peroxidase (GPX) (Lopresti et al., 2014), and (4) changes in brain anatomy (e.g., decrease in the hippocampus volume) and activity of some cortical structures (e.g., abnormally reduced activity in lateral prefrontal cortices during explicit voluntary control of emotional experiences) (Hamilton et al., 2012; Soares and Mann, 1997; Steffens and Krishnan, 1998). Taken together, these results clearly suggest that the etiology of MDD is complex and multifaceted, involving numerous interlined neurobiological systems (Song and Wang, 2011).

Physical exercise has been shown to be an efficacious treatment for MDD, with effect sizes ranging from small (−0.4) to very large (−1.4) (Cooney et al., 2013; Craft and Landers, 1998; Daley, 2008; Danielsson et al., 2013; Josefsson et al., 2014; Krogh et al., 2011a; Rethorst et al., 2009; Silveira et al., 2013; Stathopoulou et al., 2006). Indeed, a number of studies have previously demonstrated that exercise may offer comparable benefits to antidepressant medication in those with depression (Blumenthal et al., 1999, 2007). Moreover, exercise is efficacious for outpatients (Dunn et al., 2005; Park and Yu, 2015) and inpatients (Schuch et al., 2015). Despite its efficacy, the mediators or mechanisms underlying the antidepressant effects of exercise in MDD are unclear, speculative and predominantly derived from animal studies or findings from studies conducted in people without MDD (Eyre and Baune, 2012b; Fuqua and Rogol, 2013; Knaepen et al., 2010; Pedersen and Hoffman-Goetz, 2000; Radak et al., 2001, 2008a, 2008b; Scheewe et al., 2013).

It is essential that underlying mechanisms through which exercise exerts its antidepressant effects are better understood, since this will enable more optimal targeted interventions to be developed. Current hypotheses for the antidepressant effect of exercise include both acute (transient responses that occur during or immediately after the exercise bout) and chronic responses (adaptive changes following a training period of two or more consecutive exercise bouts) that influence several systems such as neuroendocrine, neurogenesis, oxidative stress, auto-immune and cortical structural changes (Eyre and Baune, 2012b; Fuqua and Rogol, 2013; Knaepen et al., 2010; Pedersen and Hoffman-Goetz, 2000; Radak et al., 2001, 2008a, 2008b; Scheewe et al., 2013). It is important that acute and chronic responses are considered separately due to the fact that the responses to exercise may be different, and even opposite directions. For example, acute exercise increases some pro-inflammatory and oxidants, while chronic responses to exercise over several weeks appears to decrease pro-inflammatory and oxidant markers (Pedersen and Hoffman-Goetz, 2000; Radak et al., 2001, 2008a, 2008b).

Research considering the neurobiological response to exercise among people with MDD is equivocal. Given the rising burden of MDD and the promise of exercise as an intervention, there is an urgent need to consider the plausible mechanisms underlying the antidepressant response elicited from exercise. To our knowledge, no systematic review has addressed this gap and reviewed studies conducted in humans with MDD. Given the aforementioned, the aim of the present study was to systematically review studies that have evaluated acute and chronic biomarker responses to exercise across five current biological hypotheses proposed to explain MDD etiology including neuroendocrine, neurogenesis, oxidative stress, inflammation and cortical thickness and activity. The present study provides a comprehensive review of the main pathways proposed to explain the antidepressant effects of exercise in subjects with MDD.

2. Methods

The present systematic review was conducted according to the PRISMA (Moher et al., 2009) statement.