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Review Article

Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: A scoping review

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ABSTRACT

Background: Fatigue is one of the most common and most disabling symptoms of multiple sclerosis (MS). It is a multidimensional and complex symptom with multifaceted origins, involving both central and peripheral fatigue mechanisms. Exercise has proven to be safe for people with MS, with cumulating evidence supporting significant reductions in fatigue. However, the potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in MS remain elusive.
Objectives: The objectives were, in PwMS (1) to update the knowledge on the pathophysiology underlying primary and secondary fatigue, and (2) to discuss potential pathophysiological pathways that can explain the positive effects of exercise on MS fatigue.
Methods: A comprehensive literature search of six databases (PubMed, Embase, Cochrane Library, PEDro, CINAHL and SPORTDiscus) was performed. To be included, the study had to 1) enroll participants with definite MS according to defined criteria, 2) assess explicit pathophysiological mechanisms related to MS fatigue, 3) be available in English, Danish or French, and 4) had undergone peer-review.
Results: A total of 234 studies fulfilled the inclusion criteria. Primary MS fatigue mainly originated from a dysfunction of central nervous system neuronal circuits secondary to increased inflammation, reduced glucose metabolism, brain atrophy and diffuse demyelination and axonal lesions. Secondary MS fatigue was linked with sleep disturbances, depression, cognitive impairments, and deconditioning. Cardiovascular, immunologic, neuroendocrine, and neurotrophic changes associated with exercise may alleviate primary MS fatigue while exercise may improve secondary MS fatigue through symptomatic improvement of deconditioning, sleep disorders, and depression.
Conclusions: >30 primary and secondary pathophysiological fatigue pathways were identified underlining the multidimensionality and complexity of MS fatigue. Though the underlying key cellular and molecular cascades still have to be fully elucidated, exercise holds the potential to alleviate MS fatigue, through both primary and secondary fatigue pathways.

Contents

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1. Introduction

Multiple sclerosis (MS) fatigue can be defined as 'a lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual and desired activities' [1]. Fatigue is one of the most common and most disabling symptoms of MS [2], and previous studies report that 70–90% of persons with multiple sclerosis (PwMS) experience fatigue [3–5]. Also, 55% of all PwMS describe MS fatigue as one of their worst symptoms, which demonstrates the significant negative effect of MS fatigue on the mental health and general health status [6].

Fatigue is a multidimensional and complex symptom with multifaceted origins and, hence, the exact etiology of MS fatigue remains unclear. However, both central and peripheral fatigue mechanisms have been proposed to be involved [7]. Moreover, MS fatigue is termed "primary fatigue" when it is directly related to the disease mechanisms of MS, while fatigue caused by non-disease-specific factors is termed "secondary fatigue" [8]. Primary fatigue may arise from centrally mediated processes that are specific to MS, such as inflammation, demyelination or axonal loss, whereas secondary fatigue may be the consequence of sleep problems, pain, medication use, deconditioning, depression or psychological functioning [7,8]. Furthermore, the terminology and assessment of fatigue is intricate since the term fatigue may be used as a reference to subjective sensations while fatigability normally refers to objective changes in performance [9]. This implies that fatigue is measured by self-report scales measuring perceptions of fatigue whereas fatigability is measured by quantification of decline in fatiguing aspects of continuous performance or before and after prolonged performance [9]. The multidimensional nature, assessment and definition of the symptom complicate the management of MS fatigue and, consequently, positive effects of therapies for fatigue management have often failed to appear. Previous reviews on the topic have investigated the effect of various types of fatigue management interventions including exercise therapy, education, psychological interventions and medication [8,10–14]. Findings have been heterogeneous, but in general rehabilitation interventions appear to have stronger and more profound positive effects on MS fatigue compared to pharmacological and psychological interventions [11,13,15]. In addition, beneficial "side effects" are often seen following rehabilitation interventions, as compared to many medical treatments associated with negative side effects such as headache, anxiety, nausea, insomnia and dizziness [14].

One of the promising rehabilitation interventions targeting MS fatigue is exercise therapy. Despite a longstanding concern towards the application of exercise [16], exercise therapy has proven to be safe for PwMS, with cumulating evidence supporting significant reductions of fatigue among PwMS [13,17]. Moreover, a recent Cochrane review concluded that several exercise modalities (endurance, mixed, or 'other' training) were moderately effective in reducing self-reported fatigue without increasing the risk of relapses [17]. However, a substantial heterogeneity was found implying that there are important methodological issues/limitations to consider when assessing the effectiveness of exercise for the treatment of MS fatigue (e.g. non-fatigued study population, subjective fatigue questionnaires, and fatigue often being a secondary outcome measure). Also, supporting the notion that exercise is associated with a significant reduction in MS fatigue, is the results from a previous meta-analysis showing a significant reduction in fatigue among persons with MS [13]. Furthermore, exercise therapy (e.g. aerobic training) may have beneficial "side effects" in terms of improved cardiorespiratory fitness, which is regarded as a crucial health indicator for PwMS [15], and which has previously been associated with better walking performance [18], improved cognitive processing speed [19], and a possible prophylactic influence on the structural decline of brain tissue in PwMS [20]. Nonetheless, the potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in MS remain elusive and, to the best of our knowledge, no previous study has tried to synthesize the existing information on this topic in a scoping review. Such a review may assist and optimize future original studies as well as healthcare professionals in using a pathophysiologic approach when designing therapeutic exercise interventions aimed at reducing MS fatigue.

Consequently, the objectives of the present review were, in PwMS, (1) to update the knowledge on the pathophysiology underlying primary and secondary fatigue, and (2) to discuss potential pathophysiological pathways that can explain the significant positive effects of exercise on MS fatigue.

2. Methods

2.1. Study selection

The study is based on a comprehensive literature search of six databases (PubMed, Embase, Cochrane Library, PEDro, CINAHL and SPORTDiscus), that was conducted to retrieve studies assessing MS fatigue published before August 19th, 2016. Relevant reviews covering the topic were also included. A broad search methodology was used in order to include all relevant studies describing MS fatigue pathophysiology. For the exact MeSH search terms used in the various databases, see

Table 1
Detailed list of retrieved articles and applied search terms in six different databases.

Database	Articles retrieved	Search terms (e.g. MeSH)
PubMed	881	"Multiple sclerosis" AND "fatigue"
Embase	4630	
Cochrane Library	105	
CINAHL	465	
SPORTDiscus	124	
PEDro	122	Abstract and title: "Multiple sclerosis fatigue".