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Review article

Effects of exercise in experimental autoimmune encephalomyelitis (an animal model of multiple sclerosis)

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ABSTRACT

Exercise training has improved many outcomes in "clinical" research involving persons with multiple sclerosis (MS), but there is limited understanding of the underlying "basic" pathophysiological mechanisms. The animal model of MS, experimental autoimmune encephalomyelitis (EAE), seems ideal for examining the effects of exercise training on MS-disease pathophysiology. EAE is an autoimmune T-helper cell-mediated disease characterized by T-cell and monocyte infiltration and inflammation in the CNS. To that end, this paper briefly describes common models of EAE, reviews existing research on exercise and EAE, and then identifies future research directions for understanding the consequences of exercise training using EAE.

Contents

1. Introduction

Multiple sclerosis (MS) is an immune-mediated neurological disease with an estimated prevalence of 1 per 1000 adults in the U.S. (Page et al., 1993; Mayr et al., 2003). This neurological disease typically begins with periods of inflammation within the central nervous system (CNS) that results in axonal demyelination and transection. Such an expression is consistent with the relapsing–remitting course of MS (Mäurer and Rieckmann, 2000). There are further neurodegenerative processes presumably resulting from insufficient neurotrophic support that results in axonal and neuronal loss (Frohman et al., 2006). The damage and its location within the CNS can result in walking and cognitive dysfunction, symptoms such as fatigue, pain, and depression, and reduced quality of life (QOL) and participation in activities of daily living (Lublin, 2005).[1]

There is an abundance of research from clinical trials demonstrating the beneficial effects of physical activity and exercise training on outcomes in persons with MS (Motl and Pilutti, 2012). For example, our laboratory has demonstrated that exercise training has improved walking mobility (Snook and Motl, 2009), depression (Ensari et al., 2013), fatigue (Pilutti et al., 2014), and QOL (Motl and Gosney, 2008) based on meta-analyses of clinical trials including persons with MS. This research provides evidence for "clinical" benefits of exercise training, but does not widen our understanding of exercise training effects on

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[1] Multiple sclerosis (MS); central nervous system (CNS); experimental autoimmune encephalomyelitis (EAE); quality of life (QOL); T-helper (Th); Theiler's Murine Encephalomyelitis (TMEV); antigen presenting cells (APCs); proteolipid protein (PLP); myelin basic protein (MBP); myelin oligodendrocyte protein (MOG); complete Freund's adjuvant (CFA); chronic relapsing EAE (CR-EAE); guinea pig spinal cord tissue (GPSC); days post-induction (dpi); spontaneous inhibitory postsynaptic currents (sIPSCs); brain-derived neurotrophic factor (BDNF); tumor necrosis factor-α (TNF-α); nerve growth factor (NGF); glial cell line-derived neurotrophic factor (GDNF).

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the "basic" pathophysiology of MS. For example, exercise training seemingly exerts beneficial effects in MS through immunomodulation and regulation of neurotrophic factors that reduce axo-neuronal degeneration and promote neuroprotection, respectively, in MS (Castellano and White, 2008). Indeed, exercise training and physical activity have increased expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), in the hippocampus of mice and rats (Cotman and Berchtold, 2002; Gibbons et al., in press), and insulin-like growth factor-1 (IGF-1) in the brain of rats (Carro et al., 2000). Hippocampal neurogenesis, in particular, is a commonly documented effect of exercise in the rodent brain (Cotman et al., 2007; Gibbons et al., in press) and exercise has further been associated with neuroprotective effects by increasing gene expression that promotes synaptic plasticity (Cotman et al., 2007). Exercise training, both acute and chronic, and physical activity may further influence the number and function of many cells of the innate immune system including neutrophils, monocytes, and natural killer (NK) cells (Walsh et al., 2011). There is additional evidence that lymphocytosis occurs during and after exercise, with effects on numbers of both T and B cells and alterations in pro and anti-inflammatory cytokine balance (Walsh et al., 2011). However, effects of exercise training and physical activity on the peripheral immune system for protection against infections and disease seem to be highly dependent on parameters such as volume and intensity (Pedersen and Hoffman-Goetz, 2000; Terra et al., 2012). Such hypotheses and observations could be examined using an animal model of MS and thereby provide a basic science or preclinical understanding of exercise training effects on MS disease pathophysiology.

The most common animal model for examining the mechanisms of action for treatment effects on MS pathophysiology is experimental autoimmune encephalomyelitis (EAE). EAE is a T-helper (Th) cell-mediated autoimmune disease characterized by T-cell and monocyte infiltration in the CNS associated with local inflammation (Robinson et al., 2014). The autoimmune molecular targets identified have been proteins expressed by myelin-producing oligodendrocytes in the CNS, resulting in primary demyelination of axonal tracks, impaired axonal conduction in the CNS, and progressive hind-limb paralysis (Robinson et al., 2014). The EAE model has been extremely useful for studying disease pathogenesis and potential therapeutic interventions (Robinson et al., 2014). Indeed, variations of the EAE model that produce different patterns of clinical MS presentation are often used in preclinical research for identifying the benefits and dissecting the mechanisms of new therapeutic interventions for subsequent translation into human clinical trials of MS (Steinman and Zamvil, 2006). This model would further be beneficial for dissecting the possible mechanisms of exercise training effects in MS.

Researchers have speculated that exercise training exerts its consequences through pathophysiological mechanisms within the CNS (Heesen et al., 2006; White and Castellano, 2008; Motl and Pilutti, 2012) and this can be most readily studied through research involving EAE. To that end, the purpose of this paper is to generate a case for EAE as a model for understanding the possible pathophysiological mechanisms of exercise training and physical activity effects in humans with MS. We briefly describe common models of EAE that might be considered for such research, review existing research on exercise and EAE, and lastly identify future research directions for understanding the benefits of exercise training using EAE.

2. Common models of EAE

Over the past 60 years, researchers have developed different animal models for understanding mechanisms and targets of therapeutic interventions in MS (Denic et al., 2011; Simmons et al., 2013). These include the autoimmune EAE model, virally induced models such as Theiler's Murine Encephalomyelitis (TMEV) infection, and toxin-induced models of demyelination (Denic et al., 2011). To date, EAE is the most extensively studied murine model of MS as many of the pathologies observed in the CNS of mice resemble those observed in the CNS of persons with MS (McCarthy et al., 2012). The classic EAE model focuses on the role of CD4 + T cells as a major effector cell and explains the strong correlation of MS susceptibility to MHC class II alleles (Simmons et al., 2013). Mice are most commonly used in EAE due to the availability of transgenic and knockout mice for mechanistic studies (Robinson et al., 2014). There are many pathophysiologic forms of EAE in mice with different patterns of clinical presentation depending on the animal species and strain, priming protein or peptide, and route of immunization (Gold et al., 2006). These different models have been used to study disease development and specific histopathological characteristics with relevance to MS, and to dissect mechanisms of potential therapeutic interventions (Steinman and Zamvil, 2006; McCarthy et al., 2012).

Two routes of immunization are widely used for inducing EAE in mice: active induction by immunization with myelin antigens and passive induction by adoptive transfer of pre-activated myelin-specific T cells into naïve mice (McCarthy et al., 2012). Peripheral immunization of mice with myelin antigen in active EAE results in breakdown of peripheral immune tolerance and further activation of myelin antigen-specific T cells in secondary lymphoid organs. After initial activation, these T cells differentiate into effector T cells and leave the secondary lymphoid organs. Effector T cells express integrins (Yednock et al., 1992) that allow the cells to cross the blood–brain barrier and are reactivated by antigen presenting cells (APCs) presenting myelin antigens in the CNS (Kawakami et al., 2004). This activation enables the effector T cells to express pro-inflammatory cytokines such as IFN-γ that locally damage the surrounding nervous tissue (Lees et al., 2008). Chemokines are produced by T cells, leading to recruitment of nonspecific effector cells (i.e., monocytes, macrophages, and neutrophils) into the CNS (Kroenke et al., 2008). Together, these inflammatory cells are responsible for destruction of the myelin-sheathed surrounding axons and lesion formation. The adoptive transfer of activated, myelin-specific Th cells from immunized donors into naïve syngeneic receptors can directly induce the 'effector phase' of EAE (Raine et al., 1984; Zamvil et al., 1985; Cross and Raine, 1990). The clinical features of passive EAE are identical to those of active EAE; yet passive EAE induction is a more direct way of establishing T cell effector function in the CNS.

There is variation in the specific strains of mice and encephalitogenic peptides capable of eliciting EAE. EAE is often actively and passively induced in the SJL mouse through immunization with CNS homogenate, proteolipid protein (PLP), myelin basic protein (MBP), encephalitogenic epitopes of PLP ($PLP_{139–151}$, $PLP_{178–191}$), myelin oligodendrocyte protein ($MOG_{92–106}$), or $MBP_{84–104}$, in a suspension with complete Freund's adjuvant (CFA) (Robinson et al., 2014). The disease follows a predictable course, with initial symptoms appearing 10–15 days post-induction, followed by ascending hind limb and tail paralysis that progresses to the fore limbs with accompanying weight loss. The disease in SJL mice is characterized by a relapsing–remitting course of paralysis. In C57BL/6 mice, $MOG_{35–55}$ is an encephalitogen that presents in the clinical form of a chronic progressive disease course in both active and passive EAE induction. This is characterized by sustained priming antigen-specific T cell responses. The description of clinical disability, or of disease course as relapsing–remitting or chronic progressive, is based on a standard, 6-point clinical grading scale; Grade 0 = asymptomatic; Grade 1 = decreased tail tone or weak tail only; Grade 2 = hind limb weakness (paraparesis); Grade 3 = hind limb paralysis (paraplegia) and/or urinary incontinence; Grade 4 = weakness of front limbs with paresis or paraplegia (quadriparesis) and/or atonic bladder; and Grade 5 = paralysis of all (4) limbs (paraplegia) and/or quadriplegic with reduced mental alertness and/or increased respiratory effort and/or moribund (Miller and Karpus, 2007; McCarthy et al., 2012). The onset and progression of clinical disability in models of relapsing–remitting and chronic progressive EAE are the result of inflammation and demyelination mainly manifesting in the spinal cord and brain (Simmons et al.,