Altered signaling for mitochondrial and myofibrillar biogenesis in skeletal muscles of patients with multiple sclerosis

DOMINIQUE HANSEN, INEZ WENS, FRANK VANDENABEELE, KENNETH VERBOVEN, and BERT O. EIJNDE

DIEPENBEEK AND HASSELT, BELGIUM

Patients with multiple sclerosis (pwMS) experience muscle weakness and lowered muscle oxidative capacity. To explore the etiology for the development of such muscle phenotype we studied skeletal muscle adenosine monophosphate (AMP)-activated protein kinase phosphorylation (phospho-AMPKα, governing mitochondrial biogenesis) and mammalian target of rapamycin phosphorylation (phospho-mTOR, governing myofibrillar biogenesis) in pwMS. After assessment of body composition, muscle strength, exercise tolerance, and muscle fiber type, muscle phospho-AMPKα and phospho-mTOR were assessed in 14 pwMS and 10 healthy controls (part 1). Next, an endurance exercise bout was executed by 9 pwMS and 7 healthy subjects, with assessment of changes in muscle phospho-AMPKα and phospho-mTOR (part 2). Increased basal muscle phospho-AMPKα and phospho-mTOR were present in MS ($P < 0.01$) and independently related to MS. Correlations between muscle phospho-AMPKα or phospho-mTOR and whole-body fat mass, peak oxygen uptake, and expanded disability status scale ($P < 0.05$) were found. After endurance exercise muscle phospho-AMPKα and phospho-mTOR remained increased in pwMS ($P < 0.01$). Muscle signaling cascades for mitochondrial and myofibrillar biogenesis are altered in MS and related to the impairment and disability level. These findings indicate a link between muscle signaling cascades and the level of disability and impairment, and thus may open a new area for the development of novel therapies for peripheral muscle impairment in MS. (Translational Research 2015;166:70–79)

Abbreviations: AMPK = AMP-activated protein kinase; BMI = body mass index; CSA = cross-sectional area; HR = heart rate; pwMS = patients with multiple sclerosis; MS = multiple sclerosis; mTOR = mammalian target of rapamycin; RER = respiratory gas exchange ratio; VO_{2peak} = peak oxygen uptake; W_{max} = cycling power output

INTRODUCTION

Multiple sclerosis (MS) is associated with peripheral muscle alterations such as muscle weakness and lowered muscle oxidative capacity.[1-3] In accordance, a smaller type 1 and 2 skeletal muscle fiber diameter, lower succinate dehydrogenase activity, delayed phosphocreatine resynthesis after isometric exercise, blunted intramuscular metabolic responses during isometric exercise, and complex-1 deficiency in skeletal muscle mitochondria are present in patients with multiple sclerosis (pwMS).[4-9] These data collectively indicate significantly disturbed

From the REVAL—Rehabilitation Research Center, BIOMED—Biomedical Research Center, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium.

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Reprint requests: Dominique Hansen, Faculty of Medicine and Life Sciences, Hasselt University, Agoralaan, Building A, 3590 Diepenbeek, Belgium; e-mail: Dominique.hansen@uhasselt.be.

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AT A GLANCE COMMENTARY

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Background

The etiology for the commonly observed peripheral muscle impairment in patients with multiple sclerosis (pwMS) remains uncertain. We studied skeletal muscle AMP-activated protein kinase phosphorylation (phospho-AMPKα, governing mitochondrial biogenesis) and mammalian target of rapamycin phosphorylation (phospho-mTOR, governing myofibrillar biogenesis). Increased basal muscle phospho-AMPKα and phospho-mTOR were present in MS and correlations with disability level were found. After endurance exercise muscle phospho-AMPKα and phospho-mTOR remained increased in pwMS. Muscle signaling cascades for mitochondrial and myofibrillar biogenesis are altered in MS and related to the disability level.

Translational Significance

A link between muscle signaling cascades and the level of disability and impairment is present. This may open a new area for the development of novel therapies for peripheral muscle impairment in MS.

skeletal muscle cell biochemistry and composition in pwMS.

Although inactivity, which is associated with pwMS,[10] could contribute to muscle weakness and lowered endurance exercise tolerance, it remains unknown whether the previously mentioned biochemical skeletal muscle cell and fiber abnormalities are also related to disturbed molecular signaling pathways.

Two "master switches" (skeletal muscle kinases) are known to mediate muscle biochemistry and composition in humans: AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR).[11,12] AMPK is a serine-threonine (Ser/Thr) kinase, which is activated during repetitive muscle contractions, hypoxemia, ischemia, oxidative stress, metabolic poisoning, and nutrient deprivation.[11] Such AMPK activation in skeletal muscle cells enhances mitochondrial biogenesis through phosphorylation of peroxisome proliferator–activated receptor-γ coactivator 1α and thereby increases skeletal muscle oxidative capacity.[11] mTOR is a Ser/Thr kinase, which is activated by heavy-load muscular contractions, anabolic hormones (insulin-like growth factor-1, insulin), and high amino acid availability.[12] Activation of mTOR leads to myofibrillar biogenesis and thereby lean tissue mass gain.[12]

Examining skeletal muscle AMPKα phosphorylation (phospho-AMPKα) and mTOR phosphorylation (phospho-mTOR) in pwMS might provide important clues to the etiology of disturbed skeletal muscle biochemistry and composition and would be promising to improve treatments for peripheral muscular impairment in MS. In the present study, we examined basal skeletal muscle phospho-AMPKα and phospho-mTOR in pwMS and hypothesized that significant anomalies in phospho-AMPKα or phospho-mTOR are present in skeletal muscle cells of pwMS.

To counteract muscle wasting and lowered muscle oxidative capacity pwMS participate in exercise therapy interventions.[13] The demonstration of altered skeletal muscle AMPK or mTOR master switch pathways in MS could enhance the level of evidence of peripheral muscle involvement and might have important consequences for treatment strategies. However, changes in skeletal muscle phospho-AMPKα and phospho-mTOR to acute exercise in pwMS are presently unknown. In healthy subjects, acute endurance exercise significantly alters muscle phospho-AMPKα and phospho-mTOR.[14-21] These changes are instrumental to mitochondrial and myofibrillar biogenesis. To optimize the selection of training modalities and to induce significant beneficial changes in muscle phenotype of pwMS, the biochemical responses of skeletal muscle cells to acute exercise should be studied. In the second part of the present study, we studied the effect of acute endurance exercise on skeletal muscle phospho-AMPKα and phospho-mTOR in pwMS. We hypothesized that disturbed changes in muscle phospho-AMPKα or phospho-mTOR are present in pwMS after exercise.

MATERIALS AND METHODS

Study design. This study was part of a large study examining the impact of exercise training on MS (executed from March 2013 to June 2013). This was a combination of a cross-sectional study (part 1) and a prospective observational study (part 2) (Fig 1). Basal skeletal muscle phospho-AMPKα and phospho-mTOR were studied in Caucasian pwMS and healthy subjects in part 1, and the impact of acute endurance exercise on phospho-AMPKα and phospho-mTOR was examined in a subsample of subjects in part 2. After expanded disability status scale (EDSS) determination[22] and screening of medication intake, body weight and height were measured from which body mass index (BMI) was calculated. Next a dual x-ray absorptiometry scan was executed to analyze body composition, a dynamometry test was executed in pwMS to determine which leg was the weakest, and a