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Preliminary evidence of a blunted anti-inflammatory response to exhaustive exercise in fibromyalgia

Britta Torgrimson-Ojerio [a], Rebecca L. Ross [a,b], Nathan F. Dieckmann [a], Stephanie Avery [a,c], Robert M. Bennett [a], Kim D. Jones [a], Anthony J. Guarino [d], Lisa J. Wood [a,e,*]

[a] School of Nursing, Oregon Health Science University, Portland, OR 97239, United States
[b] Hope Tucson, Nueva Luz Center, Tucson, AZ 85716, United States
[c] Adventist Medical Center, Portland, OR 97216, United States
[d] MGH Institute of Health Professions, Boston MA 02129, United States
[e] School of Nursing, MGH Institute of Health Professions, Boston, MA 02129, United States

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ABSTRACT

Exercise intolerance, as evidenced by a worsening of pain, fatigue, and stiffness after novel exertion, is a key feature of fibromyalgia (FM). In this pilot study, we investigate whether; insufficient muscle repair processes and impaired anti-inflammatory mechanisms result in an exaggerated pro-inflammatory cytokine response to exhaustive exercise, and consequently a worsening of muscle pain, stiffness and fatigue in the days post-exercise. We measured changes in muscle pain and tenderness, fatigue, stiffness, and serum levels of neuroendocrine and inflammatory cytokine markers in 20 women with FM and 16 healthy controls (HCs) before and after exhaustive treadmill exercise. Compared to HCs, FM participants failed to mount the expected anti-inflammatory response to exercise and experienced a worsening of symptoms post-exercise. However, changes in post-exertional symptoms were not mediated by post-exertional changes in pro-inflammatory cytokine levels. Implications of these findings are discussed.

1. Introduction

Fibromyalgia (FM) is a chronic and often debilitating disorder characterized by widespread pain; other symptoms commonly include tenderness, stiffness, fatigue, sleep, mood disturbances and reports of worsening symptoms following novel exertion. FM affects an estimated 11 million persons in the United States, 80–90% of whom are women (Queiroz, 2013). FM patients are typically sedentary and overweight or obese (Yunus et al., 2002) with physical inactivity contributing to an increased risk for metabolic related co-morbidities in this population (Loevinger et al., 2007). Regular exercise is a key component of most comprehensive FM-management programs (Busch et al., 2013). Of the >120 exercise interventions in FM, most have failed to meet the current exercise recommendation for health by The American College of Sports Medicine (ACSM) and the American Heart Association (AHA) guidelines. These organizations recommend moderate to vigorous intensity exercise to prevent adverse health outcomes related to sedentary lifestyles (Nelson et al., 2007; Garber et al., 2011; Busch et al., 2013). Prior exercise studies modified for FM suggest that individuals who can tolerate the intervention can improve aerobic capacity, muscle strength, balance and flexibility and attain some symptom relief, particularly decreased pain, tenderness, fatigue, and stiffness (Busch et al., 2013). Yet FM patients often reported several days of increased pain and tenderness following moderate to high-intensity exercise, which may explain why many of these prior exercise interventions suffered from high attrition rates and inconsistent effect sizes (Jones et al., 2006). FM represents an important clinical population that would benefit from establishing specific exercise guidelines that would maximize benefits while minimizing post-exertional symptom exacerbation. Understanding the molecular mechanisms underlying FM symptom exacerbation following moderate to high-intensity exercise may help to guide the development of exercise guidelines in FM. The overall hypothesis guiding the present study is that increased post-exertional symptom exacerbation in FM is related to an abnormal neuroendocrine and immune system response to moderate to high-intensity exercise. Consistent with this hypothesis are reports of a blunted GH response to high-intensity exercise and lower resting levels of its primary downstream effecter, insulin-like growth factor 1 (IGF-1), in people with FM (Paiva et al., 2002; Ross et al., 2010; Bote et al., 2012). GH is just

* Corresponding author at: School of Nursing MGH Institute of Health Professions, 36 1st Avenue, Charlestown Navy Yard, MA 02129, United States. Tel.: +1 617 724 3454.
E-mail addresses: torgrims@ohsu.edu (B. Torgrimson-Ojerio), RebeccaRoss@hopetucson.org (R.L. Ross), dieckman@ohsu.edu (N.F. Dieckmann), stephanieavery@gmail.com (S. Avery), bennetro@ohsu.edu (R.M. Bennett), joneskim@ohsu.edu (K.D. Jones), ajguarino@mgh.harvard.edu (A.J. Guarino), ljwood@mghihp.edu (L.J. Wood).

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one of several neuroendocrine and inflammatory factors including ACTH, cortisol, IL-6, IL-10, and IL-1RA that are up-regulated during exercise (Walsh et al., 2011). The exercise-induced inflammatory cytokine response was originally attributed to muscle microtrauma (Bruunsgaard et al., 1997), which can occur during high-intensity exercise or unnacustomed exercise in a deconditioned individual. Muscle microtrauma triggers the localized production of the pro-inflammatory cytokines IL-1β and TNF-α which promote the infiltration of immune cells into the damaged area. These infiltrating immune cells secrete IL-1β, TNF-α and other inflammatory molecules including IL-6, IL-8, IL-1RA and IL-10 (Nieman et al., 2006a, 2006b). The ability of IL-1β and TNF-α to stimulate muscle nociceptors likely explains the characteristic pain and tenderness following muscle damaging exercise (Borghi et al., 2014a, 2014b). In addition IL-1β and TNF-α play a central role in the development of sickness behavior, the predominant symptom of which is fatigue (Dantzer, 2009). However, it has since been shown that exercise-induced increases in circulating IL-6, IL-10, and IL-1RA can occur in the absence of muscle microtrauma, and in this context their production is not preceded by IL-1β or TNF-α (Welc and Clanton, 2013). Further studies revealed that the predominant source of IL-6 released during non-muscle damaging exercise is exercising muscle cells which led to the classification of IL-6 as a "myokine" (Pedersen and Febbraio, 2012). Exercise-induced increases in circulating ACTH, GH, cortisol, IL-10, and IL-1RA can be attributed to muscle-derived IL-6 (Traustadottir et al., 2004; Walsh et al., 2011; Bote et al., 2012). By stimulating the production of anti-inflammatory molecules such as cortisol, IL-1RA, and IL-10, muscle-derived IL-6 has a net anti-inflammatory effect and elevated IL-6 either from infusion or exercise can decrease TNF-α levels in both rodents and humans (Starkie et al., 2003; Petersen and Pedersen, 2005; Ploeger et al., 2009). GH regulates the synthesis of IGF-1 which plays an important role in controlling the pro-inflammatory cytokine response to muscle microtrauma and coordinating the repair processes thereafter (Matheny et al., 2010). Taken together, we concluded that insufficient muscle repair processes (GH/IGF-1 axis defect) and impaired anti-inflammatory mechanisms (blunted cortisol, IL-10 and IL-1RA) in FM would result in an exaggerated pro-inflammatory cytokine response (elevated IL-1β, TNF-α, IL-6, and IL-8) to unaccustomed exercise and consequently a worsening of muscle pain, stiffness and fatigue in the days post-exercise. The purpose of the present study was to generate preliminary evidence to support this hypothesis.

2. Methods and procedures

2.1. Inclusion and exclusion criteria

The target FM population was women less than 60 years of age, diagnosed with FM by 1990 ACR criteria for at least two years, who had experienced FM symptoms ≥6 years, and were willing to undergo the testing protocol. The upper age cut-off was chosen to reduce the risk of adverse cardiac event during treadmill stress testing. Healthy controls (HCs) were women pair matched to FM patients (see below). Exclusion criteria for both groups were; 1) regular participation in aerobic or strength programs for more than 30 min three times a week, 2) pregnant or nursing, 3) major depressive disorder, 4) daily use of opioids, 5) current or past malignancy, 6) major organ disease or autoimmune/inflammatory disease, 7) elective surgery 30 days prior or during the 12 day study, and 8) involvement in disability litigation hearings. Participants were requested not to change medications or non-pharmacologics (e.g., exercise, physical therapy) during the course of the 12-day study.

2.2. Procedure for participant recruitment

A database of confirmed FM patients managed by the Fibromyalgia Information Foundation was used for subject recruitment. Field codes identified zip code, age and sex for inclusion/exclusion criteria and demographics. E-Blasts were sent to 344 potential subjects. Of those, 86 candidates completed an online interest form and were called for a telephone screening by research staff. At that point, the potential subjects were asked to confirm further inclusion/exclusion criteria and then scheduled for a study appointment. The HC participants were recruited using an interested person database repository of previous research participants who gave consent to be re-contacted for other research opportunities, and in addition, participants were recruited by posting a local craigslist ad in the Portland Metro area. Eligibility of interested persons was assessed by phone. Interested and eligible HC participants were then evaluated based on age, estimated BMI to determine whether they may be a potential 'match' for an FM patient enrolled in the study. In total, 87 interested women responded to recruitment material as HCs and of those, 17 were eligible and confirmed matches. Once a match was confirmed, the HC participant was scheduled for the study testing procedures. One HC participant was unable to complete the treadmill testing due to an acute illness during the 12-day protocol, so 16 women completed the entire protocol as HC matches. FM and HCs were females matched ton age (±5 years), percentage of body fat (±15%), and menopausal status. There were 4 FM patients that were included in the present analysis for which no matched control could be identified.

2.3. Procedure overview

Eligible participants underwent four study visits during 12-days of data collection. At Visit 1 (Day 1), written informed consent was obtained and participants underwent a manual tender-point assessment and completed the Revised Beck Depression Inventory (BDI-R) questionnaire to confirm eligibility. Each participant then underwent pressure pain threshold (PPT) testing and body composition testing by DEXA to measure the percentage of body fat. Visit 2 occurred between 8 and 11:00 am 7-days after Visit 1 with fasting treadmill exercise to VO_2 peak using the modified Balke protocol (ACSM Guidelines). The modified Balke protocol was chosen for this study because the incremental increase in exercise intensity is gradual but still allows for the accurate assessment of $V0_2$ peak in FM patients. In addition, this protocol has been used previously to examine the GH response to exhaustive exercise (Paiva et al., 2002; Jones et al., 2007). Upon arrival at the CTU participants had an indwelling intravenous catheter placed in their forearms by a study nurse 1 h prior to the treadmill test. During this hour, participants completed study surveys. Blood was collected through the catheter three times during the treadmill test; immediately before exercise, at peak exercise (VO_2 peak), and then 60-minutes after peak exercise. All participants returned 2- and 4-days after the treadmill test for repeat PPT assessments and peripheral blood draws, and completion of the FIQR/SIQR (Day 4 post-exercise only). The study protocol was approved by the University's Institutional Review Board.

2.3.1. Demographic data

Demographic data was obtained using an investigator-designed questionnaire (disability, menopausal status and hormone replacement therapy in women, medications, and duration of FM).

2.3.2. Revised Fibromyalgia Impact Questionnaire (FIQR) and the Revised Symptom Impact Questionnaire (SIQR)

Participants completed the FIQR or SIQR at the beginning and end of the study period. The FIQR is a self-report 21-item instrument that assesses symptoms during the past week using a 0 to 10 scale (Bennett et al., 2009). The FIQR has three domains: physical function, overall effect of FM, and FM symptoms (pain, fatigue, un-refreshing sleep, stiffness, anxiety, depression, tenderness to touch, memory, balance and environmental sensitivity). The SIQR is the same as the FIQR except the word fibromyalgia is replaced with "symptom." The SIQR is used to assess symptomatology in non-fibromyalgia patients (Friend and