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Review Article

Deviant Cellular and Physiological Responses to Exercise in Myalgic Encephalomyelitis and Chronic Fatigue Syndrome

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Abstract

Post-exertional "malaise" is a hallmark symptom of Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS). Various abnormalities, including abnormal physiological responses to exertion, can account for post-exertional "malaise" and "exercise avoidance". Since these abnormalities are not observed in sedentary healthy controls, the abnormalities and deviant responses cannot be explained by "exercise avoidance" and subsequent deconditioning, nor by psychogenic factors.

Keywords: Myalgic Encephalomyelitis; Chronic Fatigue Syndrome; Exercise Physiology; Energetics; Immune System; Oxidative And Nitrosative Stress

Introduction

Post-exertional "malaise", a (prolonged) aggravation of symptoms after a minor exertion, is a discriminative symptom of Myalgic Encephalomyelitis (ME) [1-3] / Chronic Fatigue Syndrome (CFS) [4]. Several abnormalities observed in ME/CFS, such as a prolonged fall in oxygen uptake after exercise, and a post-exertional increase in metabolite-detecting (pain) receptors [5], can plausibly account for "exercise intolerance" reported by ME/CFS patients and the lack of the success of rehabilitation protocols. Since these abnormalities are not observed in sedentary controls, deconditioning (alone) cannot account for the physiological aberrations in ME/CFS after exertion. The exercise-induced abnormalities, which cannot be explained by psychogenic factors, appear strong correlates of ME/CFS.

Abnormalities relating to exercise and its effect

Energetic abnormalities and reduced oxygen uptake amplified by exertion

Various findings implicate impaired mitochondrial function [6-9], and gene expression studies also indicate mitochondrial dysfunction in ME/CFS [10-12]. Perturbation of mitochondrial function could, at least partially, account for the (profoundly) low exercise capacity observed in ME/CFS, indicated by a low maximal oxygen uptake ($VO2_{max)}$, workload ($WL_{max)}$ and heart rate (HR_{max}), and oxygen uptake at the ventilatory threshold compared to sedentary controls [13-15]. ME/CFS is associated with early intracellular acidosis in muscles [16] and impaired and delayed capacity to recover from intramuscular pH in response to exercise [14,17]. One study [14] revealed two CFS [4] subgroups: patients with normal PCr depletion in response to exercise (45%) and patients with low PCr depletion (55%). However, one of the most characteristic abnormalities in ME/CFS seems to be a decline of the exercise performance levels at a second cardiopulmonary exercise test (CPET) when compared to the exercise performance levels 24 hours earlier at a first CPET [18,19]. Energetic abnormalities, amplified by exercise, point to deviant physiological pathways that could

account for post-exertional "malaise" and slowed "recovery" in ME/CFS.

Muscular abnormalities related to exercise

Several observations implicate muscle membrane dysfunction in ME/CFS at rest [20,21] and during exercise and recovery [22,23]. Research suggests muscle power, endurance and recovery to be profoundly reduced [24,25]. Findings indicate a shift from type I "slow-twitch" oxidative to type II "fast-twitch" muscle fibers [12], which may explain the early onset of "muscle fatigue" during exercise. Recent observations [26] suggest 'an exercise-related defect' of muscle cells in ME/CFS. Muscle cell cultures of ME/CFS patients show no increase in AMPK phosphorylation and glucose uptake in response to electrical pulse-stimulation (EPS) ("exercise"), while glucose uptake showed to be responsive to insulin in patient cultures in rest and during EPS [26].

Long-lasting oxidative stress in response to exercise

ME/CFS has been associated with oxidative (and nitrosative) stress repeatedly, indicated by oxidative damage to DNA, lipid peroxidation, and increased activity / depletion of antioxidants [27-30]. Musculoskeletal symptoms/post-exertional '"malaise" and oxidative stress seem to be interrelated [31,32]. Several observations implicate that exercise amplifies long-lasting oxidative stress [15,23,33]. A prolonged 'abnormal or defective adaptive response to oxidative stress' is also associated with alter heat shock protein (HSP) expression responses, falling below normal levels up to seven days post-exercise [22,34,35]. HSPs could be useful biomarkers of exercise-induced cellular stress in ME/CFS.

Increased pain sensitivity and lower pain thresholds during and after exercise

Basal pain thresholds appear to be decreased in ME/CFS [36] and, in contrast to a positive effect in healthy (sedentary) controls, exercise seems to have a negative effect on pain thresholds in ME/CFS [37,38]. A decrease of pain thresholds after exercise has been associated with postexertional "malaise" [39] and observations suggest that a prolonged increase of pain after exercise is associated with an exercise-induced increase of the metabolite sensing molecular receptors [40,41]. One study found [42] uncovered two CFS [4] patients subgroups, the largest (71%) showing a long-lasting rise of the gene expression for these "pain-and-fatigue"-receptors, the smaller patient group (21%) exhibited no increase in gene expression for these receptors. Considering the observations that pain thresholds are normal in skin and subcutis, but significantly lower than normal in the deltoid, trapezius and quadriceps [43], muscle pain in ME/CFS can not solely be attributed to "central sensitisation" but also involves muscular abnormalities.

Immunologic abnormalities in response to exertion

Observations [44] suggest that mild walking exercise accentuates substantially elevated resting serum transforming growth factor beta (TGF-β) levels. Travelling to the hospital is sufficient to induce a profound rise of TGF-β, while exercise induces a prolonged increase in plasma tumor necrosis factor-alpha levels in ME/CFS patients, not in sedentary controls [45]. Findings also implicate a deviant response of the complement system to exercise in CFS [46,47], a prolonged increase in gene expression for interleukin (IL)-10 in CFS after moderate exercise [40] and a link between "symptom flare" and serum IL-10 [48]. A follow-up study [42] showed a long-lasting rise of IL-10 gene expression after exercise in a large subgroup of CFS [4] patients (71%), but not in the smaller subgroup of CFS [4] patients (29%). Although increased serum IL-6 levels are associated with high "symptom flare" after exercise [48], muscle cell cultures of ME/CFS patients exhibit decreased IL-6 levels both during differentiation and in response to EPS [26]. While IL-6 is a mediator of the acute phase response of inflammation in serum [49], IL-6 is also a myokine, playing an important role in muscle cell proliferation and differentiation [50]. So, findings suggest that exercise amplifies inflammatory and anti-inflammatory pathways in ME/CFS, while a rise of muscular IL-6 in response to exercise seems to be absent.

Cardiovascular dysfunction related to exertion and orthostasis

Reaching the age-predicted maximal heart rate seems to be an important constraint for ME/CFS patients to achieve maximal effort during exercise [13,51] and exercise appears to have a negative effect on the HRmax at a second exercise test 24 h later [52]. A cardiac energetic deficit [53] could account for a low HRmax seen in ME/CFS. Several studies indicate reduced cardiac volume in ME/CFS [54-56), associated with a low cardiac output/index [57] and reduced myocardial contractility [58], while other studies observed various (exercise-induced) cardiac abnormalities [54,59,60]. Low cerebral blood flow has been found in ME/CFS repetitively [61-63], indicating circulatory control dysfunction. Low level exercise seems to have a negative effect on the cerebral blood flow in [44]. Aside from the effects of orthostasis on cerebral blood flow, this could account for prolonged "brain fog" after physical exercise [64].

Autonomic abnormalities associated with exercise and orthostatic stress

Several studies indicate autonomic dysfunction and postural orthostatic tachycardia syndrome (POTS), at least in a (minor) subgroup of ME/CFS patients [65,66]. Aside from the effects of orthostatic stress [67-69], physical and mental exertion seems to associated with abnormal cardiovascular responses in ME/CFS [70,71].

Neurologic abnormalities in relation to physical and mental exertion

Several studies [72-74], observed reduced motor cortical excitability during and after (low-level) muscle exercise, potentially related to impaired motor performance in ME/CFS [75]. Patients present with abnormal central nervous system signals controlling voluntary muscle exercise, especially when the exercise induces muscle fatigue [25], while mental exertion also seems to be involve deviant neurological responses, suggesting 'dysfunctional motor planning' in ME/CFS [76], and significantly more brain activity during more complex cognitive tasks [77-79].

Conclusion

Post-exertional "malaise" and "exercise intolerance" are hallmark symptoms [80] of Myalgic Encephalomyelitis (ME) [1-3] and Chronic Fatigue Syndrome (CFS) [4]. This article reviews observations which support the position that post-exertional "malaise" in ME/CFS may be linked to a number of observable deviant physiological responses to exercise, including muscle weakness and myalgia, a substantial fall of oxygen uptake after exercise, an increase in metabolite-detecting (pain) receptors, increased acidosis, abnormal immune responses, and orthostatic intolerance. Such findings go some way to explain why many ME/CFS sufferers either avoid exercise or report negative effects of exercised-based rehabilitation protocols, such as graded exercise therapy (GET). The physiological abnormalities induced by ME/CFS cannot be simply explained by a sedentary life style and deconditioning [81], or psychogenic factors [82]. While we acknowledge the importance of physical activity in illness rehabilitation, our findings cast doubt on the efficacy of exercise protocols as a therapeutic approach. More research into exercise-induced cellular and physiological abnormalities in ME/CFS is needed to better understanding the illness and its impact on patients, and to develop appropriate treatments.

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