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Review Article

Effects of resistance exercise on fibromyalgia: a signaling pathway on mitochondrial functions.

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Abstract

Fibromyalgia (FM) is one of the most prevalent disorders that affects the muscular tissue and is characterized by pain, stiffness, and soreness in the muscles, tendons, and joints. FM affects about 5% of the world population. The incidence is higher in women than in men. However, the pathophysiological factors of FM are not yet well known. Mitochondrial dysfunction may have a role in the pathogenesis of FM but the exact mechanism is unclear. Mitochondrial dysfunction was associated with increased expression of autophagic genes and the elimination of dysfunctional mitochondria by mitophagy . Exercise increases mitochondrial capacity, oxidative phosphorylation, and mitochondrial respiratory capacity. Resistance exercise may improve the mitochondrial quality probably through increasing mitophagy through PINK1/PARKIN pathway. Therefore, resistant exercise could be an important part of managing FM. The purpose of this review is to update information on the effects of resistance exercise on FM, specifically in relation to signaling pathways and biological processes

Keywords: Mitochondrion, Mitophagy, PINK, PARKIN.

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Introduction

Fibromyalgia (FM) is a disorder marked by persistent musculoskeletal pain. Its core symptoms include sleep disturbances, fatigue, mood swings, cognitive issues, anxiety, depression, general hypersensitivity, and a reduced capacity to perform routine activities .[1]

FM affects between 2% and 5% of the adult population and ranks as the second most common condition seen by rheumatologists, following osteoarthritis.[2]

The condition generally manifests between the ages of 30 and 35, but despite its prevalence, FM is still poorly understood and challenging to diagnose due to its unclear pathophysiology. [3]

FM primarily impacts the muscles, tendons, and joints, often presenting as pain, stiffness, and tenderness. The severity of its symptoms tends to vary over time and is frequently linked to stress. [4]

Initially described in the 19th century, FM was later categorized as a "pain syndrome" without a specific organic cause in 1950. Subsequently, "pain points" were identified, referring to areas of extreme tenderness where a pressure of approximately 4 kg triggers pain. [5]

In 1990, the American College of Rheumatology (ACR) established diagnostic criteria for FM, which have since been updated. These criteria include two key components: (i) widespread pain above and below the waist lasting at least three months and (ii) tenderness at 11 of 18 specific body sites. [6]

FM is thought to result from abnormal pain processing in the brain, leading to heightened pain sensitivity, which can also contribute to psychological symptoms. [7]

Mitochondria are cellular organelles originating from ancient prokaryotic cells that merged with host cells. These organelles are crucial for ATP production and cellular longevity across various biological systems. [5]

Often referred to as the "powerhouses of the cell," mitochondria are central to numerous cellular processes, including energy metabolism and signaling. Their importance is underscored by a growing volume of research, which has significantly expanded over the last two decades .[9] Mitochondrial dysfunction, characterized by increased expression of autophagy-related genes and the removal of damaged mitochondria via mitophagy, has been implicated in FM, though the precise mechanisms remain unclear. [10]

Exercise has been widely studied for its potential to alleviate FM symptoms, yet the exact biological mechanisms behind these benefits remain uncertain. [11]

This study aims to provide updated insights into how resistance exercise influences FM, with a particular focus on its effects on signaling pathways and biological processes.

Methodology

Systematic literature search was performed in PubMed, Egyptian Knowledge Bank and Web of Science. Information was extracted from the included studies for review. This review updated the last two decades available information on the effect of resistance exercise on FM in terms of mitochondrial functions.

Animal models of FM

Animal models of disease are essential for understanding pathogenesis and developing new treatments. These models should replicate the symptoms and pathology of the disease while also being predictive of effective therapies. This review highlights animal models that simulate the signs and symptoms of FM. All the proposed models exhibit widespread, long-lasting hyperalgesia without significant peripheral tissue damage, thereby closely resembling the clinical features of FM .[12]

These animal models have provided valuable opportunities to extensively study FM symptoms, underlying mechanisms, and potential therapeutic approaches. Current experimental FM models include reserpine-induced systemic depletion of biogenic amines, acid saline injections into muscles, and stress-based methods such as exposure to cold, sound, or swim stress, along with other emerging techniques. Effective FM models should fulfill the following criteria: (i) replicate the core symptoms and complaints experienced by FM patients, including spontaneous pain, muscle pain, and

hypersensitivity; (ii) reflect major comorbidities that negatively impact quality of life, such as fatigue, sleep disturbances, depression, and anxiety; (iii) emulate key pathological mechanisms, including peripheral and central sensitization, inflammation or neuroinflammation, and imbalances in excitatory and inhibitory neurotransmitter levels; and (iv) exhibit a pharmacological response that aligns with clinical FM treatments.[13]

Reserpine-induced FM model

Reserpine is an indole alkaloid derived from the Indian snakeroot plant Rauwolfia serpentina. It functions by inhibiting vesicular monoamine transporter 1 in peripheral tissues and vesicular monoamine transporter 2 in both the periphery and the brain, leading to a reduction in biogenic amine levels. Initially, reserpine was clinically used to treat hypertension due to its sympatholytic and sedative effects, which lower heart rate and promote vasodilation. When administered subcutaneously once daily for three consecutive days, reserpine induces FM-like symptoms in rats. Commonly used doses are 1 mg/kg for rats and 0.25–1 mg/kg for mice. The reserpine solution is typically prepared using distilled water or 0.9% saline, with acetic acid (final concentration of 0.1–0.5%) added to enhance its solubility. [13]

Acid saline-induced FM model

This model is classified as a non-inflammatory pain model targeting the musculoskeletal system and was initially developed to study nociception mechanisms. The protocol involves two unilateral injections of acid saline (pH 4.0) into the gastrocnemius muscle, typically spaced two or five days apart, with five days being more common. The first injection causes rapid but short-lived hyperalgesia in both hind paws, which subsides within 24 hours. This initial injection sensitizes muscle nociceptors, priming them for the second injection of the same acid solution. The second injection induces long-lasting, widespread mechanical hyperalgesia that can persist for up to four weeks. This model is applied to both rats and mice, with rats receiving 100 μL of acid saline and mice receiving 20 μL. Control animals are given two intramuscular injections of a standard saline solution (pH 7.0–7.4), which does not produce hypersensitivity in rodents. [13]

Stress-based FM models

Stressful situations can initiate or exacerbate FM symptoms and underlying pathophysiology. In this context, experimental FM models have been developed using rodents exposed to physical or psychological stress. Non-noxious stressors such as cold, sound, forced swimming, and restraint are commonly employed. Research indicates that brief exposure to acute or chronic non-noxious stress can influence nociceptive pathways, leading to pain-related behaviors in animals. Recent studies have shown that psychological stress, such as empathy, can induce generalized pain in mice, exhibiting pathophysiological and pharmacological characteristics similar to clinical FM. Additionally, numerous studies highlight the connection between stress and pain in both humans and animals. Among the most widely used stress-based FM models are intermittent cold exposure, sound stress, and repeated swim stress, while newer models include chronic restraint, ultrasonic vocalization, and intermittent psychological stress. [15]

Intermittent cold stress-induced FM model

Intermittent Cold Stress (ICS)-Induced Generalized Pain (ICGP) Model. In this protocol, male and female C57BL/6J mice weighing 18–22 g were used. The mice were housed in a room maintained at 22 ± 2 °C with 60 ± 5% humidity and had ad libitum access to a standard laboratory diet and tap water.

The intermittent cold stress (ICS) procedure began with two mice per group placed in a cold room at 4 ± 2 °C at 16:30 on day 0. Trials with varying numbers of mice per cage (ranging from one to eight) determined that two mice per cage were optimal. Food pellets and gelatin were provided on the cage floor ad labium medical refrigerator with a transparent sliding door was preferred for maintaining a similar light/dark cycle even in the cold room. To ensure stable hyperalgesia and allodynia, the refrigerator temperature was kept below 6 °C. Mice were placed on a stainless-steel floor for rapid

temperature changes and housed in plexiglass cages. On the next morning (day 1) at 10:00, the mice were removed from the cold room and placed at room temperature (24 ± 2 °C) for 30 minutes. They were then returned to the cold room for another 30 minutes.

This alternating temperature process was repeated until 16:30, after which the mice remained in the cold room overnight. The same procedure was repeated on day 2. On day 3 (post-stress day 1/P1), the mice were removed from the cold room at 10:00 and allowed to adapt at room temperature for at least 1 hour before undergoing nociception tests. To ensure the mice remained healthy during the cold stress, food pellets and gelatin were placed on the cage floor to maintain their spontaneous activity. Nociception tests were conducted after an adaptation period of at least 1 hour to achieve stable noci-ception scores. For reference, a constant cold stress (CCS) model was also used, where mice were kept in the cold room continuously without alternating temperature changes for three consecutive nights. Both ICS and CCS caused a body weight reduction of approximately 10% by post-stress days 2 and 3 (P2–P3), with body weight returning to normal levels by day 5 (P5). However, approximately 2% of mice in the ICS or CCS groups experienced a body weight reduction of up to 20%. [16]

Sound stress-induced FM model

Sound stress exposure is carried out over four days, specifically on days one, three, and four. During this process, animals are placed in a cage positioned 25 cm away from a speaker emitting pure tones at frequencies of 5, 11, 15, and 19 kHz. The sound amplitudes range randomly between 20 and 110 dB, lasting for five or ten seconds at random intervals each minute. Each daily exposure typically lasts 30 minutes. To refine this FM model, a modified protocol known as repeated and intermittent sound stress (RISS) was introduced. This involves sound exposure every three hours, repeated six times per day, on the same experimental days (one, three, and four). Control animals are placed in the sound chamber for the same duration but are not exposed to the sound stimuli. The applicability of the sound stress model is somewhat limited, as it has primarily been tested in male rats. Further research is needed to evaluate its effects on both male and female rodents across different strains .[18]

Intermittent Psychological Stress (IPS)-Induced Generalized Pain (IPGP) Model

This pain model involves exposing mice to intermittent psychological stress, also referred to as empathic stress. Mice weighing 20–25 g were placed in a communication box containing nine compartments (10 cm × 10 cm), separated by transparent plexiglass walls. Five of the compartments had grid floors designed to deliver electrical shocks, while the remaining four compartments had grid floors covered with insulating plastic plates. Five mice in the shock compartments received foot shocks generated by a shock device, while the other four mice in the insulated compartments were exposed to psychological stress caused by the visual, auditory, and olfactory cues from the shocked mice. For the repeated foot shock stress (RFS) paradigm, short electrical shocks (0.6 mA, 1 second) were delivered every 47 seconds for a total of 120 shocks. In the randomly programmed intermittent foot shock stress (IFS) paradigm, the same number of shocks was delivered over a period of 24–96 minutes. In contrast, groups without direct foot shocks experienced repeated psychological stress (RPS) or intermittent psychological stress (IPS). Across all experimental paradigms, stress exposure occurred once daily for five consecutive days. [16]

Although there has been a notable increase in studies utilizing preclinical FM models in recent years, these models still present significant challenges. It remains difficult to replicate the full range of symptoms and characteristics observed in FM patients using experimental animal models.

Effect of FM on mitochondrial function and mitophagy

Although the exact mechanisms underlying FM remain uncertain, several theories have been proposed to explain its pathogenesis.

Central Augmentation of Sensory Input

Research indicates that FM patients require approximately 50% less stimulus intensity to trigger

a pain response compared to healthy individuals. This heightened pain sensitivity, known as hyperalgesia and allodynia, appears to stem from abnormalities in both central cortical processing and spinal cord-level regulation of the central nervous system. Chronic stimulation of C-fibers, common in prolonged pain conditions like FM, may lead to the apoptosis of inhibitory interneurons associated with opioid and GABA signaling. This reduction in inhibitory neurons results in the excessive release of excitatory substances such as glutamate, substance P, and nerve growth factors. These changes, coupled with central reductions in opioid and serotonin levels, contribute to a phenomenon known as "wind-up," characterized by an escalation in ascending pain signals and diminished descending pain inhibition. [12,13]

Autonomic Nervous Dysfunction

FM patients frequently exhibit dysregulation in the autonomic nervous system (ANS). These abnormalities include reduced microcirculatory responses to aural stimulation and attenuated vasoconstriction during cold pressor tests. Such ANS dysfunctions can impair stress-related physiological reactions, contributing to increased pain perception, elevated blood pressure, and inhibited pain management through reduced production of growth hormone (GH) and insulin-like growth factor (IGF-1) .[14,15]

Immune Responses and Inflammation

Abnormal immune responses, particularly involving immunoglobulin G (IgG), have been linked to FM. In animal studies, transferring IgG from FM patients to mice resulted in symptoms such as decreased locomotor activity, reduced strength, and nerve damage. Additionally, (IgG) binding to satellite glia cells (SGCs) in FM patients correlated with symptom severity. These findings suggest the potential for developing diagnostic tests targeting autoantibodies like anti-SGC antibodies to support personalized treatment strategies. [7,16]

Endocrine Dysfunctions

FM is also associated with disruptions in endocrine function, particularly in the hypothalamic-pituitary-adrenal (HPA) axis. This axis, responsible for producing hormones like ACTH, cortisol, and endorphin-releasing hormones, is observed to be hypoactive in FM patients. Adrenal insufficiency resulting from HPA axis dysfunction may help explain common FM symptoms such as chronic fatigue, poor exercise tolerance, and decreased muscle performance. [10,13]

4.5 Mitochondrial Dysfunction, Mitophagy, and Oxidative Stress

Mitochondrial dysfunction is thought to play a significant role in FM pathogenesis. Reduced levels of coenzyme Q10 (CoQ10) and increased production of reactive oxygen species (ROS) in FM patients provide direct evidence of cellular oxidative stress. CoQ10, essential for mitochondrial energy metabolism, acts as an electron carrier in the respiratory chain and regulates mitochondrial functions like permeability, fatty acid oxidation, and nucleotide biosynthesis. Deficiency in CoQ10 leads to impaired mitochondrial activities, reduced membrane potential, increased ROS production, and activation of mitophagy to eliminate damaged mitochondria. [17,18]

Furthermore, oxidative stress in FM has been demonstrated through elevated lipid peroxidation, increased malondialdehyde levels in blood cells, and reduced antioxidant enzyme activity such as catalase. Dysregulation of inflammation is evident through elevated levels of pro-inflammatory cytokines like TNF-α, IL-8, IL-1Ra, IL-1B, and IL-18. These factors, combined with decreased mitochondrial DNA content, ATP levels, and respiratory chain activity, strongly support the hypothesis of mitochondrial dysfunction as a contributing factor to FM. [13,19]

Diagnostic Biomarkers

The diagnosis of FM currently relies solely on a thorough clinical evaluation. Until 2010, it was based on the 1990 ACR criteria, which required widespread pain for at least three consecutive months and the identification of "pain points" through digital palpation. Since 2010, new ACR criteria have been used, incorporating two key factors: the diffuse pain index and the symptom severity scale score, which accounts for both

somatic and cognitive aspects. Tender points and pressure pain threshold measurements remain important for a comprehensive musculoskeletal clinical examination and for ruling out other conditions. In 2016, the previous criteria were revised to reduce the likelihood of incorrect FM diagnoses. However, due to individual variability and the presence of other coexisting conditions, clinical evaluations may not always be sufficient for a precise diagnosis, preventing the establishment of universal diagnostic criteria for FM. Additionally, specific biomarkers for FM are not yet available, and research is focused on identifying new indicators for objective diagnosis by exploring the genetic, environmental, and epigenetic factors that contribute to FM's physiopathology. [19]

Resistance Exercise and Mitochondrial Functions: Signaling Pathways:

Effect of Resistance Exercise on Mitochondrial Quality

Resistance exercise is traditionally known for promoting muscle hypertrophy and improving strength, rather than enhancing fatigue resistance or aerobic energy metabolism. Hypertrophy, which increases muscle cell size, has been historically associated with a dilution of mitochondrial content. This effect is particularly notable in older individuals or those with muscle-related diseases like sporadic inclusion body myositis, where basal mitochondrial gene expression and content are already reduced. [20]

However, exercise is recognized as a potent stimulus for activating signaling pathways that improve mitochondrial quantity and quality. These adaptations enhance muscle health by increasing mitochondrial content, oxidative phosphorylation, and respiratory capacity per mitochondrion. Researchers have focused on identifying the specific signaling mechanisms that regulate mitochondrial quality control, including processes like biogenesis, fusion, fission, and mitophagy .[21]

Effect of Resistance Exercise on Mitophagy via PINK1/PARKIN Pathway

Under normal physiological conditions, autophagy eliminates dysfunctional cellular components. However, excessive autophagy in FM may exacerbate oxidative stress and cellular damage .[13]Mitophagy, a specialized form of autophagy, involves the encapsulation of damaged mitochondria in autophagosomes, marking them for degradation. This process is regulated by proteins such as PINK1 and PARKIN. [22]

Under normal conditions, PINK1 is imported into mitochondria and degraded by proteases. However, when mitochondrial membrane potential decreases, PINK1 accumulates on the outer mitochondrial membrane, where it recruits PARKIN, an E3-ubiquitin ligase. PARKIN mediates the ubiquitination of proteins like Mfn2 and the voltage-dependent anion channel (VDAC), signaling the mitochondria for degradation. [22,23]

The process of mitophagy begins with the lipidation of LC3-I to LC3-II, facilitated by autophagy-related genes such as ATG7. The adapter protein p62 binds both LC3-II and ubiquitinated mitochondria, enabling the formation of autophagosomes. These structures later fuse with lysosomes to degrade the encapsulated mitochondria. Maintaining lysosomal health is therefore critical for mitochondrial quality in skeletal muscle. Studies show that acute exercise rapidly promotes PARKIN localization to mitochondria and increases mitophagy markers, such as LC3-II, p62, and ubiquitin, immediately post-exercise. This response is essential for preserving mitochondrial health .[24,25]

Mitophagy is also regulated by energy stress during exercise. An increased AMP/ATP ratio activates AMPK and its downstream target ULK1, while inhibiting mTORC1, which typically suppresses autophagy. The exercise-induced increase in mitophagy signaling also appears to depend on PGC-1α, as studies with PGC-1α knockout animals did not show this response. [25,26]

Effect of Resistance Exercise on Lysosomal Biogenesis

TFEB is a transcription factor that regulates lysosomal biogenesis. Overexpression of TFEB and TFE3 leads to an increase in lysosomal numbers and enzymes, enhancing cellular catabolic activity. Conversely, TFEB depletion reduces lysosomal gene expression.

TFEB also coordinates the expression of genes involved in autophagosome biogenesis and lysosome fusion. Exercise stimulates TFEB activation, likely through transient calcium fluxes and calcineurin-mediated dephosphorylation, facilitating its translocation to the nucleus. Exercise acts as a stimulus for both PGC-1α and TFEB, which work together to promote mitochondrial biogenesis and mitophagy. These processes ensure the maintenance of mitochondrial health and functionality within skeletal muscle [27,28]

Implications of the study

The role of resistant exercise in the management of FM syndrome must be evaluated. Also, the effect of enhancement of mitochondrial function on FM symptoms should be detected. A brief overview of the pathogenesis of FM was provided in this study.

Conclusion

As the mechanism of FM is unclear, mitochondrial dysfunction may have role in the pathogenesis of FM due to associated defect in mitophagy. Resistant exercise has an important role in improving mitochondrial function through improving the mitophagy of skeletal muscle.

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