Magnetic mitohormesis: A non-invasive therapy for inflammatory disorders?

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Abstract: An organism’s survival depends on its ability to adapt to stress. Mitochondria are the cellular integrators of environmental stressors that ultimately translate their responses at the organismal level, and are thus central to the process whereby organisms adapt to their respective environments. Mitochondria produce molecular energy via oxidative phosphorylation that then allows cells to biosynthetically respond and adapt to changes in their environment. Reactive oxygen species (ROS) are by-products of oxidative phosphorylation that can be either beneficial or damaging, depending on the context; ROS are hence both the conveyors of environmental stress as well as cellular “adaptogens”. Mitohormesis refers to the process whereby low levels of oxidative stress spur survival adaptations, whereas excessive levels stymie survival. Low energy and frequency pulsing electromagnetic fields have been recently shown capable of stimulating mitochondrial respiration and ROS production and instilling mitohormetic survival adaptations, similarly to, yet independently of, exercise, opening avenues for the future development of Magnetic Mitohormetic interventions for the improvement of human health. This viewpoint explores the possibilities and nuances of magnetic-based therapies as a form of clinical intervention to non-invasively activate magnetic mitohormesis for the management of chronic diseases.

Introduction

Human health and mitochondrial function are inextricably coupled statuses (Nunnari and Suomalainen, 2012; Louzada et al., 2020). Nearly all of life’s processes require cellular-based energy production to be executed. These include growth, repair, and immunological defense. The requisite energy for biosynthesis is predominantly supplied by the mitochondria with the participation of molecular oxygen to serve as the final electron acceptor during cellular respiration. The capacity of molecular oxygen to successfully accept respiratory electrons (to form water) places an upper limit on the respiratory capacity that, when exceeded, results in the production of potentially deleterious respiratory by-products. In this respect, mitochondria are the greatest producers of reactive oxygen species (ROS) (Oyewole and Birch-Machin, 2015). Approximately 0.2–2% of the electrons processed via the mitochondrial electron transport chain are unable to fully reduce molecular oxygen and ultimately produce superoxide or hydrogen peroxide, the two most predominant ROS species (Geto et al., 2020). In cases where the existing antioxidant defenses of the mitochondria are inadequate to neutralize constitutive ROS production, or under circumstances where energy requirement exceeds the antioxidant capacity of the mitochondria, ROS levels can rise sufficiently to oxidatively damage proteins and nucleic acids or cause lipid peroxidation within cellular membrane-delimited domains that, on one level, compromise the functioning and viability of the directly implicated cell, while on another level result in the release of mitochondrial DNA and mitochondrial breakdown products into the extracellular environment. Due to its close proximity to the source of ROS production and the absence of nuclear-like DNA repair mechanisms, the mitochondrial genome is particularly susceptible to oxidative damage wherein mutations are not corrected and perpetuated, ultimately compromising energy production, cellular repair, and membrane integrity and result in the escape of mitochondrial components into the general circulation where they induce systemic inflammation. Systemic inflammation, in turn, undermines tissue regeneration and maintenance as well as disrupts systemic metabolism and immunity. Accordingly, a deterioration in

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mitochondrial respiratory and antioxidant efficiency is associated with accelerated aging (Wang and Hekimi, 2015; Gallage and Gil, 2016; Ferri et al., 2020; Lima et al., 2022).

The muscular mitochondrial pool is critically important for organismal health and longevity (Russell et al., 2014; Hood et al., 2019; De Mario et al., 2021; Fealy et al., 2021). Indeed, metabolism, systemic inflammatory status and resilience to disease all have mitochondrial origins that can be linked back to mitochondrial ROS (Ristow and Schmeisser, 2014). Mitochondrial fusion facilitates the sharing of mitochondrial metabolites, energy substrates, and mitochondrial DNA, enhancing mitochondrial resistance to oxidative stress as well as forestalling mitochondrial fragmentation in preparation for clearance via mitophagy. Routine aerobic exercise also enhances the mitochondrial antioxidant defenses and efficiency of oxidation phosphorylation (ATP production) and results in a shift in substrate utilization towards lipids, all of which are metabolically beneficial conditions. By contrast, low levels of physical activity are associated with the reduced mitochondrial number, attenuated respiratory efficiency, mitochondrial fragmentation, mitophagy, and extracellular expulsion. A sedentary lifestyle is hence characterized by mitochondrial mitochondrial respiratory and antioxidant efficiency is associated with accelerated aging (Wang and Hekimi, 2015; Gallage and Gil, 2016; Ferri et al., 2020; Lima et al., 2022).

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Mitohormesis

Counter to conventional wisdom, ROS are not exclusively evil. In a microcosmic parallel to physical exercise, whereby muscular activity improves physical performance, mitochondria adapt to their own usage. In essence, mitochondria respond to the same ROS they produce during oxidative energy production by enhancing mitochondrial function, and moreover, they underlie exercise adaptations on the organismal level. Key to this adaptive process is Pparg coactivator-1a (PGC-1a), the ROS/Redox-responsive master gene involved in mitochondriogenesis and exercise-based physical adaptations (Thirupathi and de Souza, 2017; Louzada et al., 2020). Stimulated mitochondrial energy production during physical activity hence, reinforces mitochondrial respiratory fitness by increasing mitochondrial number and expanding the interconnected mitochondrial network (Hood et al., 2019; Geto et al., 2020; Philip et al., 2021). Mitochondrial fusion facilitates the sharing of mitochondrial metabolites, energy substrates, and mitochondrial DNA, enhancing mitochondrial resistance to oxidative stress as well as forestalling mitochondrial fragmentation in preparation for clearance via mitophagy. Routine aerobic exercise also enhances the mitochondrial mitochondrial respiratory and antioxidant efficiency is associated with accelerated aging (Wang and Hekimi, 2015; Gallage and Gil, 2016; Ferri et al., 2020; Lima et al., 2022).

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Mitohormesis refers to the process whereby an organism adapts to mitochondrial ROS (Ristow and Schmeisser, 2014). Energy-consuming processes that are not pathologically inflammatory in nature, generally promote organ health and maintenance with functional consequences. In this manner, normal exercise benefits muscle energetics and systemic health. This adaptive process is short-circuited in persons that are physically incapacitated due to frailty, age, disease, or trauma. Developing methods to re-engage muscular mitochondrial-based adaptations in the clinically immobilized has thus been a major focus of the physical rehabilitation sciences. A noted caveat to these efforts is the fact that mitochondrial energy expenditure is more metabolically relevant than mere movement per se, and therefore, assisted movement of the body by a physical therapist would not be sufficient to fully re-engage the response. A manner to non-invasively activate mitochondrial respiration would be beneficial.

Muscular Mitohormesis: Harnessing the Innate Endocrine Function of Skeletal Muscle

Muscle, as our largest unified tissue mass, is also our greatest unified source of mitochondria. Exercise or physical movement, by virtue of their requirement for mitochondrial energy production, is thus the most natural manner to induce systemic mitohormesis with a positive consequence over systemic inflammation. This role of muscles is largely mediated via the actions of its secretome (Louzada et al., 2020). The production of mitochondrial ROS has been shown to be a key stimulus in activating growth factor pathways within muscles (Auten and Davis, 2009; Scheele et al., 2009). Energy-dependent muscle secretome release and distribution to peripheral tissues (and muscle) is a key reason behind the described healthful benefits of exercise. In these collateral tissues, the muscle secretome influences tissue as well as mitochondrial homeostasis (Romanello, 2020), particularly in adipose and bone tissues (Kirk et al., 2020; Gomarasca et al., 2020). Adipose tissue in sedentary individuals releases proinflammatory cytokines (adipokines) into the systemic circulation, and via this pathway, adipose tissue inflammation gives rise to system-wide metabolic disorders. On the other hand, myokines released from the muscle in response to exercise promote adipose browning characterized by enhanced mitochondriogenesis, thermogenesis, lipolysis, and a shift in adipokine secretory profile. Adipose tissue responds to myokine conditioning by attenuating inflammatory adipokine secretion, thereby reinforcing muscle and systemic metabolism. In this manner, cytokine-mediated muscle-adipose crosstalk is a major regulator of systemic inflammatory status, metabolic balance, and microbiome diversity (Li et al., 2017; Leal et al., 2018, 2021; Gomarasca et al., 2020; Suriano et al., 2020; Zhang and Sun, 2021). Accordingly, evidence supports the role of the muscle secretome in immunometabolism and its importance for the control of tumor growth and chronic inflammation (Bay and Pedersen, 2020). A detailed discussion of the muscle secretome components mediating systemic immunomodulation and anti-inflammatory roles is beyond the scope of this viewpoint and has been comprehensively discussed elsewhere (Bay and Pedersen, 2020; Louzada et al., 2020).

Muscular Magnetic Mitohormesis & Muscle Secretome Activation

Low amplitude and extremely low-frequency pulsed electromagnetic fields (PEMFs) were shown capable of inducing mitochondrial respiration and mitohormetic
responses in muscle, both in vitro (Yap et al., 2019) and in vivo (Tai et al., 2020), downstream of PGC-1α activation. The employed Helmholtz coil systems create a three-dimensional volume of field uniformity (Crocetti et al., 2013; Wong et al., 2022) that is essential for achieving optimal biological efficacy (Parate et al., 2017; Yap et al., 2019; Madanagopal et al., 2021). Muscle was found to be most responsive to PEMFs at an amplitude of 1.5 milliTesla (mT) delivered once a week for 10 min (Yap et al., 2019), whereas smaller or greater amplitude PEMFs, shorter or longer duration, or more frequent exposures, did not render additional benefits or were even less effective. These weak magnetic fields are only ~20–30 times greater in amplitude than the standing geomagnetic field of the Earth and are in the extremely low-frequency range (Hz–kHz) and hence, are non-ionizing. Analogous PEMFs were shown to protect against inflammatory stress (Parate et al., 2020). Moreover, as the fields work on the quantum physical level to stimulate mitochondrial electron transport (Usselman et al., 2016), they are too weak to act as a vicarious form of mechanical stimulation. That is, by inadvertently causing muscle fiber or cell contraction, they exert no mechanical stress. Nonetheless, as they do activate mitochondrial respiration and downstream ROS production, generating mitohormetic levels of oxidative stress, prudence is advised, and overexposure should be avoided.

In isolated muscle cells, Magnetic Mitohormesis was associated with increased mitochondriogenesis, mitochondrial respiration, and reduced apoptosis (Yap et al., 2019). In mice, muscular Magnetic Mitohormesis was shown to improve running performance after as little as five weeks of weekly exposure (10 min/wk for a total of 50 min of exposure), enhance muscle oxidative capacity (increase type muscle fiber expression governing aerobic/endurance activities), increase muscle and adipose mitochondriogenesis, induce adipose browning, improve insulin sensitivity, augment fatty acid oxidation, and induce shifts in the microbiome indicative of leaner phenotype as previously described with exercise training (Tai et al., 2020). The observed effects are correlated with the magnetically-induced activation of the muscle secretome (Wong et al., 2022), as previously demonstrated in the stem cell niche with anti-inflammatory attributes (Parate et al., 2020). Indeed, Magnetic Mitohormesis recapitulates many of the hallmark metabolic indices typically associated with habitual exercise (Fig. 1).

### Mitochondrial Fitness and COVID-19 Vulnerability

Measures are currently being urgently sought to curtail the damaging consequences of the global COVID-19 pandemic. COVID-19 is commonly associated with damage to the respiratory system, endothelial inflammation, and multiple organ failure that are triggered by excessive production of proinflammatory cytokines (Filgueira et al., 2021). On the other hand, physical activity induces the production of myokines that mitigate low-grade systemic inflammation. Moreover, long COVID is similarly linked to systemic inflammatory status and is likewise ameliorated by muscular

![Magnetic Mitohormesis Therapy for Human Disease Management](infographic.png)

**FIGURE 1.** Magnetic mitohormesis, mechanisms, and responses. Adapted from NUH Médico (MCI (P) 121/03/2020).
respiratory fitness (Burscher et al., 2020; Ranasinghe et al., 2020; Sies and Ursini, 2021). Available evidence thus supports that vulnerability to COVID-19 is improved by physical and mitochondrial fitness.

Therefore, the development of safe and non-exertional methods to improve mitochondrial fitness may serve to manage persistent COVID-19 symptoms. Although this notion is provocative to contemplate, it remains to be shown in large-scale randomized clinical trials whether analogous magnetic therapies will one day prove a viable COVID-19 intervention.

Conclusions

The magnetic paradigm discussed here has been shown to invoke mitohormetic responses in muscle cells and stem cell classes associated with the production of ROS and the correspondent cellular responses, including enhanced mitochondriogenesis, improved survival, and enhanced tissue differentiation (Yap et al., 2019; Parate et al., 2020; Tai et al., 2020; Celik et al., 2021; Madanagopal et al., 2021; Wong et al., 2022). It is widely agreed that actively stimulating muscular mitochondrial energy production has clear health benefits. Physical exercise is the best method to achieve this objective as it also gives rise to a fuller breadth of collateral responses, contributed by the mechanobiological stimulation of muscle and bone, as well as the direct neurological and endocrine engagement during the execution of the exercise. However, if one is limited in physical capacity due to age, disease, or general frailty, then magnetic mitohormesis may serve as a valid and safe alternative to help sustain metabolic balance; treatment in animals and humans requires only 10 min per week. Moreover, the absence of mechanical stress afforded by Magnetic Mitohormesis may be a valuable asset in some clinical scenarios where muscle loading is ill-advised or unfeasible. The provocative implications are that analogous magnetic field therapies may one day be exploitable as a manner to forestall the onset, or in the management, of chronic diseases and await clinical validation.

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Conflicts of Interest: AFO is an inventor on patent WO 2019/17863 A1, System, and Method for Applying Pulsed Electromagnetic Fields, as well as a contributor to QuantumTx Pte, Ltd., which elaborates electromagnetic field devices for human use.


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