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A new perspective on the possibility of chronic pain therapy through physical exercise

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Abstract

The paper reviews the literature on pathophysiology of mitochondria and the involvement of these cellular organisms in pain therapy through physical activity. The main algogenic mechanism of mitochondrial dysfunctions - cellular respiration disorders, can be countered by endurance effort. Endurance exercises can also improve the morpho-functionality of neuronal mitochondria, thus being effective in treating pain associated with Alzheimer's disease. During recovery after endurance training, exacerbation of incisional pain may occur, which can be alleviated by the administration of resveratrol. Coenzyme Q10 may be used as an adjuvant to exercise pain therapy. Exercise can also treat inflammatory pain by promoting the anti-inflammatory phenotype of macrophages.

Key words: neuropathic pain, endurance exercises

Introduction

The present study on domain literature attempts to clarify how some mitochondrial processes are involved in the algic phenomenon, and how exercise can influence these processes. Exercise is recommended for pain management, especially in elderly patients (Gloth and Matesi, 2001). Chronic pains benefit from physiotherapy, but the impact of exercise on the underlying condition is generally unknown (Ambrose and Golightly, 2015). In the literature, the possibilities of pharmacological and non-pharmacological treatment of musculoskeletal pain (Hagiu, 2013) are presented without attempting to corroborate common mechanisms of action, so as to establish the interactions and possibilities of potentiation. In order to elucidate these aspects, this paper proposes the revision of elements of physiopharmacology of mitochondria, since the lesions of these organisms play an important role in the pathogenesis of various diseases, which do not seem to have any connection between them, among which are some having pain included in symptoms: migraines, neuropathic pain, fibromyalgia (Neustadt and Pieczenik, 2008). So, the purpose for which we wrote the article is to determine what type of effort is indicated or contra-indicated for various kinds of pain. We also want to elucidate drug interactions. As will be seen, it is physical and mental pain, in individuals with various pathologies or injured athletes.

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Algogenic effects of mitochondrial dysfunctions

The role of mitochondria in the pathogenesis of chronic pain is relatively well known: the mitochondrial energy generating system, the generation of reactive oxygen species, the permeability pores, apoptotic pathways, and intracellular calcium mobilization represent five major mitochondrial functions that can play critical roles in the pathogenesis of neuropathic and inflammatory pain (Sui et al., 2013). In experimental models (mice) that induce acute inflammatory pain, persistent pain and neuropathic pain, there was an increase in cluster type mitochondria in sensory neurons in the dorsal spinal cord, the authors of the study concluding that this abnormal distribution would contribute to the genesis of neuropathic pain and some forms of inflammatory pain (Guo et al., 2013). Cluster type mitochondria are characterized by the presence of [4Fe-4S] (Brancaccio et al., 2014) aggregates in these cellular organisms, Fe-S proteins being involved in the functioning of respiratory chains I-III (Stehling and Lill, 2013). It is also known that mitochondrial dysfunctions, which result in increased free radical generation, participate in the pathophysiology of fibromyalgia, being possible that to the increase in oxidative stress also contributes deficiency of coenzyme Q10 (CoQ10), which plays a role in the mitochondrial respiratory chain (Cordero et al., 2010).

It is possible that the destruction of the myelin sheath by the free radicals generated by the mitochondrial dysfunction is a mechanism of neuropathic pain production. Also, mitochondria play a key role in the plasticity of the spinal neurons (synaptic plasticity), as a cause of persistent pain (for this being incriminated a change in the mitochondrial uptake of calcium ions (Kim et al., 2011), and mitochondrial dysfunctions are present in pain-induced traumatic neuropathies (Lim et al., 2015). The involvement of mitochondria in the genesis of painful sensations is also suggested by the adverse reactions of some mitochondrial drugs and toxins (Xiao and Bennett, 2012):

- the dose-dependent adverse effects of taxane therapies, platinum complexes and other types of anticancer drugs are chronic, distal, bilateral and symmetrical peripheral sensory neuropathy, which is often accompanied by neuropathic pain
- animal experimentations have shown that neuropathy is the consequence of mitochondrial toxic effects in sensory afferent primary neurons and the administration in rat with painful peripheral neuropathy induced by paclitaxel and oxaliplatin of mitochondrial toxics (rotenone - inhibitor of respiratory complexI, oligomicin - an adenosine triphosphate synthase inhibitor and auranofin - an inhibitor of one of the mitochondrial antioxidant systems)

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resulted in an increase in the severity of mecano-allodynia and mecano-hyperalgesia (caused by paclitaxel and oxaliplatin).

Thus, two major mechanisms of the genesis of painful sensations seems to be produced by mitochondrial dysfunctions, the first by increasing oxidative stress with pro-inflammatory effect, and the second by modifying the respiratory chains in the spinal sensory neurons. As is appreciated in the literature, protecting mitochondrial function can be a promising strategy for ameliorating or preventing chronic pain (Sui et al., 2013). Pain produced by mitochondrial dysfunction generated by repetitive efforts that lead to muscle fatigue can be "masked" by using kinesio taping. Thus, at tennis players, application of kinesio taping on the wrist extensors, extensor carpi radialis brevis and longus muscles have an effect on pain prevention (Kafkas et al., 2018).

Improving functionality and increasing the number of mitochondria through exercises

The biogenesis of mitochondria is stimulated by physical exercises by releasing the nuclear respiratory factor-1/2 (NRF-1/2) from the mionuclei (Bouchard, 2015). Skeletal mitochondria are involved in the development of age-related diseases and increased insulin resistance, physical exercises increasing the activity of the electron transport mitochondrial chain in the elderly striatal muscle, particularly in sub-sarcoplasmic mitochondria, related to the increase in mitochondrial biogenesis (Menshikova et al., 2006). Regarding the regulation of the biogenesis of muscle mitochondria through exercise, the following are known (Irrcher et al., 2003):

- environmental or hereditary pathological factors can reduce the mitochondrial volume and specific functions of these cellular organisms, which reduces sports performance, phenomenon manifesting both at reduced and increased effort
- a program that uses constant endurance exercises,performed for periods of weeks, results in significant adaptive changes in skeletal muscles, including a notable improvement in oxidative capacity
- in this way, the decline in performance on effort can be attenuate
- this fact is important not only for athletes, but also for sedentary individuals, for whom the quality of life can be improved

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- endurance training programs can positively influence the decline caused by the aging of muscular mitochondrial content, as well as the evolution of pathogenic diseases related to physical inactivity

Recent research states that physical exercise modulates differentially mitochondrial respiratory complexes, the most potent stimulation taking place at complex I level (Greggio et al., 2017) mentioned above, that it is involved in the transmission of pain and is affected by mitochondrial toxics wich exacerbates pain in drug induced neuropathies. Due to the fact that strenght exercises and endurance exercises have different effects on improving mitochondrial content, respectively biogenesis, dynamics, turnover and genotype, combined physical activity programs should be individually prescribed to potentiate anti-aging effects (Barbieri et al., 2015). In the elderly, not only the prevention and combat of sarcopenia are the benefits of exercise programs, but also pain therapy, as chronic pain is known to be more common in elderly patients (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education (Editors), 2011). It follows from the above that one of the causes of the increased incidence of chronic pain in the elderly is the reduction in the number and decrease in mitochondrial function; a lifestyle based on practicing physical exercise can prevent the chronic pain of the elderly. The association of Alzheimer's disease with chronic pain and mitochondrial dysfunctions - possibilities of treatment through exercise

A relatively recent study showed that, in contrast to older results showing that patients with Alzheimer's have a reduced sensitivity to pain, they actually feel more pain compared to healthy people (Jensen-Dahm et al., 2012). Neuronal mitochondrial dysfunction contributes to the pathogenesis of neurodegenerative diseases (Hasegawa et al., 2016), and mitochondria seems to regulate the main aspects of brain function (Picard and McEwen, 2014). For the hypothesis that physical exercise promotes the biogenesis of neuronal mitochondria and improves their functionality, thus preventing (or at least delaying) the installation of dementia and increased sensitivity to pain, the literature suggests some arguments.

Thus, the use of lactate by the adult brain increases during intense physical exercise resulting in increased plasma levels of the metabolite (Dienel,2012). The accumulation of lactate, associated with a decrease in sports performance, also has beneficial effects, among which the use as an energy substrate in both type I and type II striated muscle fibers, the increase in oxidative capacity through mitochondria biogenesis, the use by lactate-neuronand lactate-astrocyte circuitsto support cognitive functions during periods of hypoglycaemia that occur, for example, during prolonged aerobic exercise (Todd, 2014). It results that endurance exercise supports cerebral plasticity and even neurogenesis, along with the prophylaxis or

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even treatment of chronic pain and Alzheimer's disease. From the data presented, it also results that increased blood lactate acid results in the biogenesis and functional improvement of muscle and neuronal mitochondria, which can be useful for pain therapy by physical exercise.

Resistance training and incisional pain

In the context of the above, it should also be mentioned that the J147 experimental drug modulates mitochondrial activity with therapeutic effects for Alzheimer's disease (and anti-aging action) by activating the AMPK/mTOR pathway (Goldberg, 2018). Although mTOR co-ordinates mitochondrial functions and proliferation of these organelles (Morita et al., 2015), and data from this paper suggest that the therapeutic effects of J147 would also be exerted by improving mitochondrial metabolism, consideration should be given to the fact that there are substances such as resveratrol that activates AMPK in the sense of attenuating the ERK and mTOR signals in sensory neurons, thereby inhibiting both acute and chronic incisional pain (Tillu et al., 2012). During resistance exercises, occurs an acute suppression of mTOR activity by AMPK (for inhibition of protein synthesis and amino acid addition to energy metabolism), but during recovery, mTOR activity is maximized in the presence of amino acids (Deldicque et al., 2005). In the light of the data presented, it results that resistance exercises can improve neuropathic pain, but incisional pain can be exacerbated during recovery. The effect may possibly be attenuated by the administration of resveratrol or other ERK and mTOR signal inhibitors in sensory neurons.

Physical exercises and inflammatory pain

The therapeutic restoration of mitochondrial functions (especially oxidative metabolism) can improve the reprogramming of inflammatory macrophages (M1) in the anti-inflammatory form of these cells (M2) (Van den Bossche et al., 2016). Given that exercise improves mitochondrial respiration (Greggio et al., 2017), it can be assumed that it also favors the appearance of the anti-inflammatory form of macrophages. Knowing that macrophages mediate inflammatory pain through ATP signals (Jakobsson,2010), it is obvious that exercise can combat this type of pain, the mechanism being the improvement of the oxidative metabolism of mitochondria.

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Targeting antioxidants for mitochondria

The mitochondrial respiratory chains, especially type I, appear to be involved in the transmission of pain through spinal sensory neurons. Moreover, mitochondrial dysfunctions seem to be involved in increased susceptibility to pain from Alzheimer's disease. Based on the above, it is tempting to use targeting antioxidants to mitochondria as new analgesic agents, possibly in combination with physical therapy, which has beneficial effects on cellular respiration. Coenzyme Q10 and tiron (chemical compound that forms stable complexes with iron and titanium) are targeting antioxidants for mitochondria, crossing the phospho-lipidic barrier of the cellular organelles and neutralizing free radicals (Oyewole and Birch-Machin, 2015). The importance of targeting antioxidants for mitochondria in the control of oxidative stress exerted on the electron transport (respiratory) chain is known (Cortés-Rojo and Rodríguez-Orozco, 2011). In consensus, coenzyme Q10 alleviates pain and cartilage degradation in an experimental (rat) model for osteoarthritis by regulating nitric oxide and inflammatory cytokines (Lee et al., 2013). It is very likely that analgesic action is also due to the effect on mitochondria in spinal or even cerebral sensory neurons. Since supplementation with Q10 has long been used to increase performance by delaying fatigue (Cooke et al.,2008), but also reducing the level of inflammation indicators raised by exercise (Armanfar et al., 2015), we propose this coenzyme as an adjuvant analgesic for physical therapy.

Discussions

Here is why the correlations medication-exercises-pain involve more pathophysiological links (Systematization is done in Table 1).

The considerations in this paper are useful to physicians, who can appropriately associate drug therapy with exercise prescriptions, physiotherapists, who were able to make appropriate kinetotherapy programs, and and coaches, who can interfere properly or prevent injuries. To avoid exacerbation of pain, attention should be paid to drugs with toxic effects on mitochondria. It is known that not only physicians and pharmacists, but also coaches and athletes need to be educated about the impact of various drugs on performance, benefits and risks (Álaranta et al., 2008). Considering the possibility of developing muscle strength through resistance, cardio and Pilates exercises in sedentary individuals (Kafkas et al., 2014), and also of mitochondrial density, one can discuss a prophylaxis of exaggerated sensitivity to pain.

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Table 1. Systematization

Drug/type of effort	Targeting antioxidants for mitochondria (coenzyme Q10)	Physical exercises (generally)	Endurance	Resveratrol or other ERK and mTOR signal inhibitors in sensory neurons	Combined physical activity programs
Pain/type of effort	Osteoarthriti, Muscle soreness	İnflammatory pain	neuropathic pain, Alzheimer's disease (accompanied by pain)	Exacerbation of incisional pain, *that can occur after resistance exercises*	Preventing pain associated with advanced age

Conclusion

One of the algogenic mechanisms of mitochondrial dysfunctions, the alteration of cellular respiration, possibly occurring as an unwanted effect of medication, can be counteracted by practicing exercise, especially of endurance. Effects may be particularly beneficial for neuropathic pain. In the elderly, endurance exercise may even have the effect of prophylaxis of Alzheimer's disease, a condition accompanied by increased pain sensitivity, obtained by improving the functionality of neuronal mitochondria. During recovery after resistance exercises, possibly related to mitochondrial metabolism, exacerbation of incisional pain may occur, which can be alleviated by the administration of resveratrol or other ERK and mTOR signal inhibitors in sensory neurons. By restoring mitochondrial oxidative processes, exercise can treat inflammatory pain, one of the mechanisms being the promotion of the macrophage anti-inflammatory phenotype. Coenzyme Q10, the mitochondrial targeting antioxidant, which also has an effect on improving performance by delaying fatigue, can be used as a pharmacological adjunct to physical exercises for pain therapy.

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