Commentary

What do over-trained athletes and patients with neurodegenerative diseases have in common? Mitochondrial dysfunction

Sergej M Ostojic[1,2], Laszlo Ratgeber[2], Andras Olah[2], Jozsef Betlehem[2] and Acs Pongras[2]

[1]Faculty of Sport and Physical Education, University of Novi Sad, 21000 Novi Sad, Serbia; [2]Faculty of Health Sciences, University of Pécs, 7622 Pécs, Hungary

Corresponding author: Sergej M Ostojic. Email: sergej.ostojic@chess.edu.rs

Impact statement

Strenuous exhaustive exercise and neurodegenerative disorders share defects in mitochondrial function that may fiercely disrupt the integrity and homeostasis of the organelle, leading to perennial pathological substrates. Possible similarities between the two conditions could contribute to developing tissue-specific biomarkers of mitochondrial dysfunction and setting up new potential drug targets and mitochondria-specific therapeutics.

Abstract

Under pathological conditions and excessive stress, mitochondria may experience a severe and irreversible loss of function. Both strenuous exhaustive exercise and neurodegenerative disorders appear to share defects in mitochondrial function that may fiercely disrupt the integrity and homeostasis of the organelle, leading to perennial pathological substrates. Here, we overview similarities of mitochondrial dysfunction in two conditions and discuss possible areas of interdisciplinary collaboration and research translation between sports medicine and neurology.

Keywords: Mitochondria, exercise, neurodegeneration, reactive oxygen species, mitochondrial DNA

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Introduction

Mitochondria are high-octane organelles involved in many pivotal cellular functions. This includes energy production via oxidative phosphorylation, redox signaling, modulation of calcium fluxes, heme biosynthesis, and apoptosis, to mention but a few. These ever-changing double-membrane subcellular structures are abundantly present in many energy-demanding cells, including myocytes, neurons, and adipocytes. A highly sensitive to various stressors (e.g. physical exertion, food deprivation), a mitochondrial network usually responds well to stress by launching intensive adaptation programs to keep cell viability. However, under pathological conditions and excessive stress, the organelle may experience a severe (and often permanent) loss of function, known as mitochondrial dysfunction (mtD). mtD is characterized by a diminished capacity for energy output, inhibition of mitochondrial oxygen consumption, over-production of mitochondria-generated toxic reactive oxygen and nitrogen species (ROS/RNS), and delayed recovery from the stress. The central molecular event leading to mtD is not completely clear yet, however, it appears that both strenuous exhaustive exercise and neurodegenerative disorders share defects in mitochondrial function that may fiercely disrupt the integrity and homeostasis of the organelle, leading to perennial pathological substrates.

Mitochondrial dysfunction induced by exercise or neurodegeneration

St Clair Gibson et al.[1] were arguably the first who reported a heavy exercise-induced mtD in a professional cross-country runner. The authors described a puzzling case of an apparently healthy young athletic man in whom a long-term exhaustive exercise caused permanent damage in skeletal muscle mitochondria, accompanied by a progressive decline in running performance. Various structural and functional abnormalities of the organelle included large swollen mitochondria with dense matrices and coarse abnormal cristae, uneven mitochondrial distribution with lobular subsarcolemmal mitochondrial aggregation, and impaired activity of citrate synthase, a mitochondrial marker enzyme. A fact that the findings were localized only to lower limb muscles indicates that this was not a mitochondrial myopathy or drug-induced mitochondrial toxicity but rather a consequence of excessive exercise routine. A handful of succeeding studies described various markers of permanent

mitochondrial impairment induced by excessive exercise.[2] Those include deletions of mitochondrial DNA (mtDNA) that could diminish mitochondrial biogenesis and downregulate genes expression resulting in degeneration of the organelle, and the opening of mitochondrial permeability transition pore (mPTP) that alters calcium and protons flow leading to mitochondrial swelling and cell death.

Interestingly, quite similar abnormalities (e.g. mitochondrial swelling, deformed cristae, defects in respiratory chain activity, and a decrease in mtDNA copy number) are found in various neurodegenerative diseases. For example, neurons in multiple sclerosis are respiratory-deficient due to diffuse mtDNA deletions,[3] with the defects are likely to be irreversible and unresponsive to therapy. Alzheimer's disease and Parkinson's disease appear to augment membrane permeability and provoke mPTP opening that leads to mitochondrial distention and cell collapse.[4] Parallelism in mtD determined in neurodegenerative diseases and after heavy exercise perhaps implies a resemblance in pathogenesis for two clinical entities. What characterizes both conditions is a state of perpetuated and excessive oxidation, either due to increased oxygen flux during immoderate exercise or disrupted neuronal oxidative metabolism in neurodegeneration, leading to augmented production of mitochondrial ROS/RNS and concomitant oxidative stress. Oxidative stress can further prompt the wrecking of mtDNA,[5] with mtDNA deletions reported at diffuse locations (e.g. _mtDNA7052, _mtDNA699,[2] _mtDNA4977) after heavy exercise and neurodegeneration.[2,3] Moderate-to-large-scale mtDNA deletions that happen *ad nauseam* might be difficult or even impossible to recover,[6] which perhaps explains a rather immutable nature of both conditions. Although ROS/RNS-driven mtDNA damage could induce mtD, other mechanisms might be responsible as well. Case in point, a detrimental cascade of mtD may commence by repeated mechanical stress of the organelle enforced by exhaustive exercise,[7] or interaction of the amyloid beta-peptide with cyclophilin D in neurodegeneration,[8] with both pathways could induce a perpetual opening of mPTP resulting in biochemical malfunctions and mitochondrial enlargement. Another possible mechanism in both conditions might involve a disruption in mitohormesis, an adaptive mitochondrial response to low-concentration ROS/RNS produced by the organelle,[9] with possible disbalance caused by over-excessive ROS production. For instance, excessive ROS might modulate mitochondrial homeostasis by blunting the crosstalk between cyclic adenosine monophosphate and sirtuins, key regulatory and signaling molecules involved in mitochondrial proteins phosphorylation and deacetylation.[10] Superabundant ROS could also negatively affect nuclear DNA (nuDNA) and further mismatch mtDNA repair capacity by downregulating nuDNA-encoding genes needed for mtDNA maintenance and repair.[11]

It is also interesting to note that mtD could be caused by the lack of physical activity, and this is at the epicenter in the pathogenesis of Type 2 diabetes.[12] This perhaps suggests a parallelism between the two conditions in terms of mitochondrial damage for both insufficient and excessive physical activity. Since it seems that more sedentary people go from being sedentary (or even already active) to extreme and strenuous levels of physical activity,[13] individualized exercise prescription, as well as adequate monitoring of exercise programs, might be necessary in order to prevent strenuous exercise-induced mtD. This monitoring could also lead to the development of novel biomarkers to capture mitochondrial function changes with possible applications in neurology.

Neurology to sports medicine: Lost in translation?

Possible etiological similarities between two conditions could be put to good use in many instances; however, so far, this does not seem to be the case. From expanding a possible mechanistic tie-up for brain-muscle pathophysiology to mitochondria, to developing sensible tissue-specific biomarkers of mtD, to setting up new potential drug targets (e.g. mPTP, mtDNA), many areas of interdisciplinary collaboration and research translation are possible. Specifically, since neurodegeneration-triggered mtD is well described in terms of management, the use of innovative mitochondria-specific agents from neurology (such as cyclophilin D inhibitors)[8] could be applicable in sports medicine, having in mind that no treatment is currently available for exercise-driven mtD. Robust and well-designed human studies are thus warranted to corroborate a possible role of mtD in excessive prolonged exercise and related conditions (e.g. overtraining syndrome), and perhaps scrutinize novel therapeutics for these perplexing ailments in sports medicine.

Authors' contributions

Conceptualization, SMO and LR; validation, JB and PA; resources, SMO; writing—original draft preparation, SMO and LR; writing—review and editing, JB and PA; funding acquisition, SMO. All authors have read and agreed to the published version of the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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ORCID iD

Sergej M Ostojic https://orcid.org/0000-0002-7270-2541

REFERENCES

1. St Clair Gibson A, Lambert MI, Weston AR, Myburgh KH, Emms M, Kirby P, Marinaki AM, Owen PE, Derman W, Noakes TD. Exercise-

induced mitochondrial dysfunction in an elite athlete. *Clin J Sport Med* 1998;**8**:52–5
2. Ostojic SM. Exercise-induced mitochondrial dysfunction: a myth or reality? *Clin Sci (Lond)* 2016;**130**:1407–16
3. Campbell GR, Ziabreva I, Reeve AK, Krishnan KJ, Reynolds R, Howell O, Lassmann H, Turnbull DM, Mahad DJ. Mitochondrial DNA deletions and neurodegeneration in multiple sclerosis. *Ann Neurol* 2011;**69**:481–92
4. Hashimoto M, Rockenstein E, Crews L, Masliah E. Role of protein aggregation in mitochondrial dysfunction and neurodegeneration in Alzheimer's and Parkinson's diseases. *Neuromolecular Med* 2003;**4**:21–36
5. Shokolenko I, Venediktova N, Bochkareva A, Wilson GL, Alexeyev MF. Oxidative stress induces degradation of mitochondrial DNA. *Nucleic Acids Res* 2009;**37**:2539–48
6. Rocha MC, Rosa HS, Grady JP, Blakely EL, He L, Romain N, Haller RG, Newman J, McFarland R, Ng YS, Gorman GS, Schaefer AM, Tuppen HA, Taylor RW, Turnbull DM. Pathological mechanisms underlying single large-scale mitochondrial DNA deletions. *Ann Neurol* 2018;**83**:115–30
7. Tuan TC, Hsu TG, Fong MC, Hsu CF, Tsai KK, Lee CY, Kong CW. Deleterious effects of short-term, high-intensity exercise on immune function: evidence from leucocyte mitochondrial alterations and apoptosis. *Br J Sports Med* 2008;**42**:11–5
8. Rao VK, Carlson EA, Yan SS. Mitochondrial permeability transition pore is a potential drug target for neurodegeneration. *Biochim Biophys Acta* 2014;**1842**:1267–72
9. Gohel D, Singh R. Mitohormesis; potential implications in neurodegenerative diseases. *Mitochondrion* 2020;**56**:40–6
10. Palmeira CM, Teodoro JS, Amorim JA, Steegborn C, Sinclair DA, Rolo AP. Mitohormesis and metabolic health: the interplay between ROS, cAMP and sirtuins. *Free Radic Biol Med* 2019;**141**:483–91
11. Pichaud N, Bérubé R, Côté G, Belzile C, Dufresne F, Morrow G, Tanguay RM, Rand DM, Blier PU. Age dependent dysfunction of mitochondrial and ROS metabolism induced by mitonuclear mismatch. *Front Genet* 2019;**10:130**
12. Parish R, Petersen KF. Mitochondrial dysfunction and type 2 diabetes. *Curr Diab Rep* 2005;**5**:177–83
13. Scheer V. Participation trends of ultra endurance events. *Sports Med Arthrosc Rev* 2019;**27**:3–7

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