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Antiaging through Mitohormesis?

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LETTER TO THE EDITOR

We read with interest the article by Min, *et al*., about a review on mitohormesis as a treatment option for metabolic disorders and as an anti-ageing measure [Min, S. H. *et al*., 2024]. Cellular signalling pathways and communication mechanisms between organs through which mitochondrial stress leads to beneficial outcomes of diabetes, liver disease, ageing, and obesity have been reviewed and discussed [Min, S. H. *et al*., 2024]. It was concluded that the generation of mild mitochondrial stress has therapeutic potential in various human diseases associated with mitochondrial stress [Min, S. H. *et al*., 2024]. Adaptive responses to low-level or transient mitochondrial stress can promote health and resilience to impeding stress [Min, S. H. *et al*., 2024]. The review is attractive but raises concerns that should be discussed.

The first point is that the term mitochondrial stress has not been precisely defined. We should know whether the authors mean only physical activity or also mental activity. Do the authors mean shortened sleep duration, the use of mitochondrion-toxic drugs, or even a certain diet? Stress on mitochondria is very diverse and can be due to excessive exercise, sympathetic overactivity, psychiatric disease, exposure to toxins, radiation exposure, exposure to electromagnetic fields, mitochondrion-toxic drugs, exposure to pesticide-contaminated food, and hereditary mitochondrial dysfunction [Cheng, Y. W. *et al*., 2023].

The second point is that the term "low-grade" has not been precisely defined. Do the authors mean training below the anaerobic threshold or training at a certain percentage of maximum muscle strength? In order not to overtax the mitochondria, it is important to know the exact amount of stress exerted. To determine a dose-response relationship, it is also important to know the exact amount of stress exerted.

The third point relates to the term metabolic disorders. We should know whether the authors mean only diabetes, liver disease, and obesity, as discussed in the review [Min, S. H. *et al*., 2024], or also primary mitochondrial disorders, beta-oxidation defects, lysosomal disorders, hormonal dysfunction, hyperlipidemia, and electrolyte disorders.

A fourth point is that the effect of mitohormesis may be unpredictable until the nuclear and mitochondrial genomes are fully sequenced. Since mitochondrial fitness may not only depend on the number of mtDNA copies and the number of pathogenic mtDNA or nDNA variants; but also on haplotype, variants of unknown significance (VUS), and polymorphisms, it is imperative to genetically test every person who is to undergo mitohormesis before starting this type of "treatment".

The fifth point is that mitohormesis can lead to even greater stress on the mitochondria if their functional status is not determined before such a measure begins. In particular, in patients with a primary or secondary mitochondrial defect, who produce an increased amount of reactive oxidative species, and mtDNA mutations through their underlying defect, additional stress may further worsen the condition. Therefore, it is imperative to exclude these patients from any measures that will further damage their already damaged energy production system. There is currently no evidence that mitohormesis can be of benefit in patients with primary or secondary mitochondrial defects.

The sixth point is that comorbidities and comedications can also lead to mitochondrial stress. Therefore, it would have been imperative to consider these stresses on the energy system before recommending additional therapeutic mitochondrial stress with the intent of being beneficial rather than harmful.

In conclusion, this interesting study has limitations that put the results and their interpretation into

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perspective. Removing these limitations could strengthen the conclusions and reinforce the study's message. All unsolved questions must be clarified before readers can uncritically accept the study's message. Because oxidative stress comes from multiple sources and existing oxidative stress can potentially limit the effects of mitohormesis, it is important to know the level of mitochondrial oxidative stress before applying mitochondrial stress for therapeutic or anti-ageing reasons. As long as there are no translational studies confirming the positive effect of mitohormesis in healthy and diseased humans, its positive effect to humans remains unproven.

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