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Pioglitazone may exhibit beneficial and adverse effects on cybrid cells carrying the variant m.3243A>G

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1 LETTER TO THE EDITOR

With interest we read the article by Burgin et al. about a study on the effect of the peroxisome proliferator-activated receptor (PPAR) activator pioglitazone together with deoxyribonucleosides on ATP production in cybrid cells. containing >90% of the m.3243A>G mutation [1].The authors found that pioglitazone increased mtDNA copy number, oxygen Konsumption rate, and mitochondrial mass in cybrid cells and controls but did not affect cell proliferation [1]. Pioglitazone decreased the number of mtDNA encoded transcripts, further reducing the already reduced transcript levels [1]. Pioglitazone did not increase the steady state levels of mature respiratory chain complexes [1]. We have the following comments and concerns.

The authors concluded that pioglitazone increases respiratory functions of cybrid cells harboring the pathogenic mtDNA variant m.3243A>G [1]. We should know how to explain the increase of respiratory functions given the decrease of mtDNA-encoded transcripts and the unchanged steady state levels of respiratory chain complexes. We should know if ATP production was truly increased by pioglitazone.

Missing in this study is the investigation of the dose-effect relation. It should be investigated if the observed effects induced by pioglitazone were dose-dependent or not. Knowing this relation is crucial as high dosages may be associated with side effects in humans if this therapy ever reaches the translational stage.

Missing in this study is also the investigation of the effect of pioglitazone on the oxidative stress (i.e. the production of reactive oxygen species). We should know if pioglitazone had any effect on the anti-oxidative capacity of the mitochondria, particularly if the drug increased or deacresed the oxidative stress. In a previous study it has been shown that pioglitazone can decrease oxidative stress and endoplasmatic reticulum stress in renal tubular epithelial cells [2]. In another study, on the contrary, it has been shown that pioglitazone increased oxidative stress at concentrations of 12.5, 25 and 50 μg/ml [3]. In addition, pioglitazone reduced the mitochondrial membrane potential with consecutive swelling of the mitochondrion and release of cytochrome-c [3]. We should know if pioglitazoen in the present study increased or decreased apoptosis and if the agent was neuro- or cardio-toxic. In a study on nucleus pulposus mesenchymal stem cells it has been shown that pioglitoazine reduced the expression of apoptosis-associated proteins, such as cyto.cytochrome-c, Bax, cleaved caspase-9, and cleaved caspase-3 [4]. Additionaly, pioglitazone boostered the expression of Bcl-2 [4].

Further adverse effects of pioglitazone were reported from a study on renal epithelial LLC-PK1 cells, showing that pioglitazone can augment cadmium-induced oxidative injury and cell apoptosis [5].

Overall, the presetned study has a number of shortcomings and contradictions which need to be solved before final conclusion can be drawn. Whether pioglitazone truly exhibits a beneficial effect on mitochondria and on patients with MELAS requires more extensive studies, particularly in patients carrying the m.3243A>G variant.

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