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Commentary

A New Strategy to Treat Mitochondrial Disease Without Improvement of Mitochondrial Function?

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Pioglitazone is used to treat type 2 diabetes, along with a proper diet and exercise, to restore the sensitivity to insulin (Cippitelli et al., 2017). In addition to diabetes, pioglitazone also shows benefit to attenuate alcohol-induced neurodegeneration and cognitive damage in animals (Cippitelli et al. 2017). The work presented in this issue of *EBioMedicine* by Benit et al. (2017) provides a new aspect of pioglitazone treatment to potentially attenuate mitochondrial disease through inhibition of glycolysis. This is a new therapeutic target and initially appears to be a counterintuitive approach to treatment.

Mitochondrial diseases are a group of disorders caused by dysfunctional mitochondria, usually leading to decreased ATP production, imbalanced metabolism, and cell death. Approaches to their treatment are limited, though the traditional thought is to increase mitochondrial energy production through restoration of or bypass of the mitochondrial defect. Interestingly, the present work by Benit et al. shows that the mitochondrial defect-induced behavioral phenotype in harlequin (Hq) mice, which have a defect in electron transport chain complex I, can be attenuated by pioglitazone treatment (Benit et al. 2017). In contrast to traditional wisdom, pioglitazone improves behavioral ataxia in Hq mice through inhibition of glycolysis without restoration of the complex I defect and in the absence of an apparent increase in energy production.

The Hq mouse phenotype is attributed to genetic inactivation of apoptosis inducing factor (AIF), impairing mitochondrial respiration through destabilization of complex I (Vahsen et al., 2004). The deficiency of AIF leads to a behavioral problem in Hq mice starting from 5 months of age, thus serving as a model for human mitochondrial disease. Treatment of Hq mice using pioglitazone (a PPAR-γ agonist), but not bezafibrate (PPAR- α agonist), or melatonin (an antioxidant) improves the behavioral defect present in Hq mice (Benit et al. 2017). Whereas pioglitazone decreased blood glucose and weight in wild type mice, interestingly, pioglitazone did not decrease blood glucose in Hq mice. Rather, pioglitazone treatment restored the blood glucose level in Hq mice, which was lower than wild type mice at baseline, to near untreated control levels (Benit et al. 2017). Although chronic pioglitazone treatment improves behavior in Hq mice, it was not found to correct the AIF-dependent mitochondrial defect. As an adaptive response to decreased mitochondrial complex I activity in Hq mice, glycolysis is increased to compensate for decreased ATP production. Therefore, improved glycolysis is anticipated in pioglitazone-treated Hq mice. However, the opposite result is presented in the article by Benit et al. The authors show that pioglitazone decreases glycolysis in Hq mice through direct inhibition of GAPDH and attenuates apoptosis by decreasing translocation of GAPDH from cytosol to nucleus. These results indicate the complexity of the mitochondrial disease-mediated response. Although the complex I defect leads to decreased bioenergy production, the current study shows an improvement in a mitochondrial disease phenotype without improving energy production *per se*. Thus, the restoration of energy production may not be a priority to treat the mitochondrial disease phenotype, and further mechanistic studies may help identify targets beyond those traditionally thought of in mitochondrial diseases.

The impaired complex I function may lead to increased oxidative injury, calcium dysregulation and mitochondrial driven cell death (Karamanlidis et al., 2013). Thus, a further downregulation of electron transport flux through a damaged/diseased electron transport chain may reduce cell injury (Szczepanek et al., 2012). This concept had previously only been considered in the context of acute cellular injury, such as myocardial ischemia-reperfusion (Chen et al., 2007). The present study raises the intriguing possibility that downregulation of flux through the defective electron transport chain can be beneficial in chronic mitochondrial disease. Furthermore, downregulation of the flux by modulation of metabolism upstream of the electron transport chain in the present study (Benit et al. 2017) might be as effective as direct blockade of the electron transport chain itself (Chen et al., 2006). A partial decrease in electron transport that ideally does not impair mitochondrial membrane potential appears to be a reasonable criterion for protective modulation (Szczepanek et al. 2012) in contrast to greater inhibition that would essentially be an intensification of mitochondrial disease.

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It is intriguing to consider the present findings in other contexts. AIF deficiency affects not only the brain but also the heart. Cardiac injury is increased in Hq mice following *in vivo* ischemia-reperfusion (van Empel et al., 2005). Hq mice are also sensitive to heart failure development (van Empel et al. 2005). Thus, it will be interesting to observe if pioglitazone can decrease cardiac injury in Hq mice. A complex I defect contributes to Alzheimer's disease (Giachin et al., 2016). Given pioglitazone's effects on neurological symptoms in Hq mice, whether it is of benefit in dementia should be explored. Similar to pioglitazone, metformin is another antidiabetic drug that shows protection in multiple organs during stress conditions in part *via* downregulation of complex I (El-Mir et al., 2008). Whether metformin could correct deficits in Hq mice remains an interesting question. Of course, the potential clinical utility of pioglitazone in human patients with mitochondrial disorders is perhaps the most pertinent remaining question.

Taken together, the present pioneering study may show a complimentary approach to treating mitochondrial disease by focusing on reducing potential cell death rather than improving mitochondrial metabolic function.

Disclosure

The authors have no conflicts of interest to declare.

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References

Benit, P., Pelhaitre, A., Saunier, E., Bortoli, S., Coulibaly, A., Rak, M., Schiff, M., Kroemer, G., Zeviani, M., Rustin, P., 2017. Paradoxical inhibition of glycolysis by pioglitazone opposes the mitochondriopathy caused by AIF deficiency. EBioMedicine 17, 75–87.

Chen, Q., Moghaddas, S., Hoppel, C.L., Lesnefsky, E.J., 2006. Reversible blockade of electron transport during ischemia protects mitochondria and decreases myocardial injury following reperfusion. J. Pharmacol. Exp. Ther. 319, 1405–1412.

Chen, Q., Camara, A.K., Stowe, D.F., Hoppel, C.L., Lesnefsky, E.J., 2007. Modulation of electron transport protects cardiac mitochondria and decreases myocardial injury during ischemia and reperfusion. Am. J. Physiol. Cell Physiol. 292, C137–C147.

Cippitelli, A., Domi, E., Ubaldi, M., Douglas, J.C., Li, H.W., Demopulos, G., Gaitanaris, G., Roberto, M., Drew, P.D., Kane, C.J., Ciccocioppo, R., 2017. Protection against alcohol-induced neuronal and cognitive damage by the PPARgamma receptor agonist pioglitazone. Brain Behav. Immun.

El-Mir, M.Y., Detaille, D., R-Villanueva, G., Delgado-Esteban, M., Guigas, B., Attia, S., Fontaine, E., Almeida, A., Leverve, X., 2008. Neuroprotective role of antidiabetic drug metformin against apoptotic cell death in primary cortical neurons. J. Mol. Neurosci. 34, 77–87.

van Empel, V.P., Bertrand, A.T., van der Nagel, R., Kostin, S., Doevendans, P.A., Crijns, H.J., de Wit, E., Sluiter, W., Ackerman, S.L., De Windt, L.J., 2005. Downregulation of apoptosis-inducing factor in harlequin mutant mice sensitizes the myocardium to oxidative stress-related cell death and pressure overload-induced decompensation. Circ. Res. 96, e92–e101.

Giachin, G., Bouverot, R., Acajjaoui, S., Pantalone, S., Soler-Lopez, M., 2016. Dynamics of human mitochondrial complex I assembly: implications for neurodegenerative diseases. Front. Mol. Biosci. 3, 43.

Karamanlidis, G., Lee, C.F., Garcia-Menendez, L., Kolwicz Jr., S.C., Suthammarak, W., Gong, G., Sedensky, M.M., Morgan, P.G., Wang, W., Tian, R., 2013. Mitochondrial complex I deficiency increases protein acetylation and accelerates heart failure. Cell Metab. 18, 239–250.

Szczepanek, K., Chen, Q., Larner, A.C., Lesnefsky, E.J., 2012. Cytoprotection by the modulation of mitochondrial electron transport chain: the emerging role of mitochondrial STAT3. Mitochondrion 12, 180–189.

Vahsen, N., Cande, C., Briere, J.J., Benit, P., Joza, N., Larochette, N., Mastroberardino, P.G., Pequignot, M.O., Casares, N., Lazar, V., Feraud, O., Debili, N., Wissing, S., Engelhardt, S., Madeo, F., Piacentini, M., Penninger, J.M., Schagger, H., Rustin, P., Kroemer, G., 2004. AIF deficiency compromises oxidative phosphorylation. EMBO J. 23, 4679–4689.