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Abstract Title

n-3 PUFA downregulate electron transport chain complexes and reduce mitochondrial respiration in THP-1 monocytes

Authors

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Background

Obesity in children and adults is associated with low-grade chronic inflammation, contributing to the development of type 2 diabetes. Recent studies suggest a connection between sustained inflammation and heightened mitochondrial respiration in myeloid cells. Therefore, targeting cellular metabolism may represent a potential strategy to attenuate inflammation. Omega-3 polyunsaturated fatty acids (n-3 PUFA) such as docosahexaenoic acid (DHA) and α -linolenic acid (ALA) have demonstrated the potential to dampen mitochondrial respiration rates. However, the mechanism is not fully understood.

Objective

Our objective is to identify mechanistic candidates for further functional validation

Methods

THP-1 monocytes were treated with the Vehicle control, or 40 μ M of fatty acid (ALA, DHA, or oleic acid) every 24h for 48h total. We assessed mitochondrial respiration using a Seahorse XF Pro instrument, central carbon metabolites by targeted metabolomics, and electron transport chain (ETC) complexes by

western blotting.

Results

Results from 24-hour DHA treatment was comparable to control. However, 48-h DHA treatment reduced Basal mitochondrial and ATP-linked respiration rates by 33.2% ($p=0.0338$) and ~40% ($p=0.0271$) relative to control, respectively. Consistent with this, 48-h ALA and DHA treatment reduced the NAD⁺/NADH ratio by 24.8% ($p=0.0206$) and 31.4% ($p=0.0090$), respectively. Furthermore, DHA and ALA treatment reduced ETC complex I levels by 68.95% ($p=0.0087$) and 70.33% ($p=0.0075$), respectively. DHA also reduced complex IV by 60.82% ($p=0.0152$).

Conclusion

Our findings support that DHA and ALA effectively reduce mitochondrial respiration in THP-1 monocytes, likely through downregulation of ETC proteins. Functional validation in primary mouse monocytes is ongoing. Given the increasing prevalence of childhood obesity and its potential long-term consequences for metabolic health, investigating anti-inflammatory dietary agents such as n-3 PUFA may provide new avenues for prevention or therapy in children and adults.