Inhibition of PUFA mitochondrial metabolism: a novel approach to elevate PUFA levels

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Omega-3 polyunsaturated fatty acids (PUFAs) are renowned for their health benefits in managing cardiometabolic diseases. However, the findings from epidemiological studies present a paradox, with some large-scale investigations failing to confirm the advantageous effects of omega-3 PUFA supplementation. One potential explanation lies in the rapid mitochondrial oxidation of PUFAs compared to saturated fatty acids (FAs), which may hinder dietary supplementation efforts from raising PUFA levels.

Our study seeks to explore a novel strategy for enhancing PUFA levels by impeding PUFA breakdown in mitochondria. To investigate this hypothesis, we employed compounds such as methyl-GBB and meldonium, known to limit FA metabolism, alongside a knockout (KO) mouse model lacking the trimethyllysine hydroxylase epsilon (Tmlhe) gene, which results in lost activity of the first enzyme in the carnitine/acylcarnitine synthesis pathway.

In Tmlhe KO mice, we observed a 30% reduction in FA metabolism, resulting in a significant increase in PUFA levels and unsaturated lipids by up to twofold. Pharmacological inhibition of FA metabolism with methyl-GBB similarly elevated plasma PUFA levels in obese Zucker rats. Furthermore, in a cohort of 30 healthy volunteers, we evaluated whether supplementation combined with meldonium-mediated inhibition of carnitine and acylcarnitine biosynthesis could selectively augment PUFA levels. Meldonium treatment notably decreased short- and medium-chain acylcarnitine levels. Combining PUFA supplementation with meldonium treatment led to a 1.5-2-fold increase in serum EPA and DHA levels compared to meldonium or PUFA supplements alone.

In conclusion, inhibiting PUFA mitochondrial metabolism emerges as a promising approach for enhancing PUFA levels, offering potential therapeutic implications for cardiometabolic health.