Systemic metabolic effects of medium-chain fatty acids supplementation: Insights from murine models

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In the wake of surging interest and widespread acclaim for medium-chain triglyceride (MCT) supplementation for health optimization, scrutinizing the scientific foundation behind such functional food additives becomes imperative. MCT-derived medium-chain fatty acids (FAs) with chain lengths ≤ C10 are known for their ketogenic potential in humans, along with pronounced anti-inflammatory and metabolic effects in preclinical rodent models. Our prior investigations, revealing cellular cardiac adaptations when MCTs were incorporated into a long-chain triglyceride (LCT)-based ketogenic diet (KD), led us to hypothesize that an increase in C8 and C10 FA levels in tissues following MCT supplementation in mice would be accompanied by a corresponding transcriptional response in nutrient sensing and metabolism. Male C57BL/6NRJ mice were fed a standard diet (SD), LCT-KD, or a combination of LCTs and MCTs (LCT/MCT, 70/30) for eight weeks, with an interval fasting (IF) group (24h/24h, SD) serving as a fasting control. Tissue aliquots were analyzed using untargeted LC-MS-based metabolomics and lipidomics, as well as quantitative PCR. MCT addition showed no significant alteration in C8 FA levels in brown adipose tissue, heart, cortex, and striatum, but relative concentration levels were significantly elevated in the liver and skeletal muscle. C10 FA levels were significantly increased in LCT/MCT vs. SD in all tissues except the brain in line with absolute quantitation via targeted LC-MS/MS of free C10 FA in, e.g., heart: 0.112 ± 0.011 vs. 0.075 ± 0.022 µg/mg, cortex: 0.073 ± 0.021 vs. 0.092 ± 0.015 µg/mg. Interestingly, both LCT/MCT and IF feeding induced similar metabolism-specific gene expression. Given the overlap of IF and LCT/MCT gene expression, along with C8/C10 FA independent tissue responses, the current analysis aims to reveal the similarities in the tissue metabolome profiles, enabling us to discern the specific effects attributable to C8/C10 FAs from those that are not.