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Early-life dietary galactose decreases proximal small intestinal fatty acid oxidation while enhancing systemic fatty acid oxidation in fed post-weaning female mice

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Introduction: Replacing part of dietary glucose with galactose in the early-life post-weaning diet in mice, mimicking lactose and thus extended breastfeeding, has been shown to improve both short- and long-term physiological and metabolic health parameters including reduced obesity upon an obesogenic diet [1-3]. As the primary organ in nutrient absorption, we hypothesized the small intestines to be the main organ underlying the observed effects.

Methods: We investigated, therefore, the effects of a 3-weeks isocaloric galactose+glucose versus control glucose intervention (totalling 32energy% of total dietary energy on standard background [3]) in young, just weaned mice on metabolic and physiological parameters, with detailed analyses in females only, including proximal small intestine RNASeq transcriptomics and immunohistochemistry of fed mice.

Results: The inclusion of dietary galactose showed an increase in relative fatty acid oxidation (%FAO) versus carbohydrate oxidation based on lower whole-body 24-hour respiratory exchange ratio in females, without differences in body weight in both sexes, and energy expenditure in females. Also whole-body absolute FAO appeared to be increased. Contrasting, the proximal small intestine displayed a consistently lower expression of transcripts involved in FAO without effects on carbohydrate metabolism. Fewer enterocytic lipid droplets were seen, suggesting an increased involvement of proximal intestines in the lipid flux into circulation. In line with the decreased intestinal FAO, the expression levels of NADPH-independent and NADPH-dependent antioxidant enzymes were lower, including a decreased pentose phosphate pathway without alterations in lipid synthesis. The liver, the canonical organ involved in galactose metabolism, lacked galactose metabolic and lipid catabolic alterations, suggesting other organs are responsible for the increase in whole-body FAO.

Conclusion: Replacing half of post-weaning dietary glucose with galactose, mimicking continuing and prolonged lactose intake, has profound effects on substrate metabolism at both the systemic and small intestinal levels. We propose that galactose induced a lower local enteric FAO facilitating increased systemic, extra-hepatic FAO, which might underly the beneficial effects seen.

References

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