Proceedings of the Nutrition Society (2020), **79 (OCE2)**, E92 doi:10.1017/S0029665120000403

The 13th European Nutrition Conference, FENS 2019, was held at the Dublin Convention Centre, 15–18 October 2019

Microbiome transfer between IL-1RI-/- and wild-type mice during high or low-fat feeding alters metabolic tissue functionality but not glucose homeostasis.

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Abstract

Reduced inflammatory signaling (*IL-1RI*$^{-/-}$) alters metabolic responses to dietary challenges [(1)]. Inflammasome deficiency (e.g. *IL-18*$^{-/-}$, *Asc*$^{-/-}$) can modify gut microbiota concomitant with hepatosteatosis; an effect that was transferable to wild-type (WT) mice by co-housing [(2)]. Taken together, this evidence suggests that links between diet, microbiota and IL-1RI-signaling can influence metabolic health. Our aim was to determine whether IL-1RI-mediated signaling interacted with the gut microbiome to impact metabolic tissue functionality in a diet-specific fashion. Male WT (C57BL/J6) and *IL-1RI*$^{-/-}$ mice were fed either high-fat diet (HFD; 45% kcal) or low-fat diet (LFD; 10% kcal) for 24 weeks and were housed i) separately by genotype or ii) with genotypes co-housed together (i.e. isolated vs shared microbial environment; n = 8–10 mice per group). Glucose tolerance and insulin secretion response (1.5 g/kg i.p.), gut microbiota composition and caecal short-chain fatty acids (SCFA) were assessed. Liver and adipose tissue were harvested and examined for triacylglycerol (TAG) formation, cholesterol and metabolic markers (*Fasn*, *Cpt1α, Pparg, Scd1, Dgat1/2*), using histology, gas-chromatography and RT-PCR, respectively. Statistical analysis included 1-way or 2-way ANOVA, where appropriate, with Bonferroni post-hoc correction. Co-housing significantly affected gut microbiota composition, illustrated by clustering in PCoA (unweighted UniFrac distance) of co-housed mice but not their single-housed counterparts, on both HFD and LFD. The taxa driving these differences were primarily from *Lachnospiraceae* and *Ruminococcaceae* families. Single-housed WT had lower hepatic weight, TAG, cholesterol levels and *Fasn* despite HFD, an effect lost in their co-housed counterparts, who aligned more to *IL-1RI*$^{-/-}$ hepatic lipid status. Hepatic *Cpt1α* was lowest in co-housed WT. Adipose from *IL-1RI*$^{-/-}$ groups on HFD displayed increased adipocyte size and reduced adipocyte number compared to WT groups, but greater lipogenic potential (*Pparg, Scd1, Dgat2*) alongside a blunted IL-6 response to pro-inflammatory stimuli (~32%, $P = 0.025$). Whilst caecal SCFA concentrations were not different between groups, single-housed *IL-1RI*$^{-/-}$ adipocytes showed greatest sensitivity to SCFA-induced lipogenesis. Interestingly, differences in tissue functionality and gut microbiome occurred despite unaltered glucose tolerance; although there was a trend for phenotypic transfer of body weight via co-housing. For all endpoints examined, similar genotype/co-housing effects were observed for both HFD and LFD with the greatest impacts seen in HFD-fed mice. In conclusion, while the gut microbiome may be an important consideration in dietary interventions, these results question the magnitude of its impact in relation to the IL-1RI-dependent immunometabolism-glucose homeostasis axis.

Conflict of Interest

There is no confluict of interest.

References

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https://doi.org/10.1017/S0029665120000403 Published online by Cambridge University Press