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A gut-microbiome-peripheral nervous system signature in a mouse model of obesity and peripheral neuropathy

Aim: This study tested the correlations between dietary fat content, gut flora community structure, the plasma and sciatic nerve lipidome, the nerve transcriptome, and peripheral neuropathy (PN) phenotype in a murine diet-induced obesity model and dietary reversal to regular diet.
Methods: 4-week-old male C57BL/6 J mice were split into 3 groups (2 groups of *n*=16/group; 1 group of *n*=8/group) and fed standard diet (SD), deriving 10% kcal from fat. At 5 weeks of age, 1 group (*n*=16) was maintained on SD and 2 other groups were switched to high fat diet (HFD), deriving 60% kcal from fat. At 16 weeks of age, 1 HFD group (*n*=8) was subjected to dietary reversal (HFD-R) and switched back to SD until 24 weeks of age. Body weights, fasting blood glucose, glucose tolerance tests, oxidized low-density lipoprotein, insulin, cholesterol, and triglyceride lipoprotein profiles were evaluated in addition to neuropathy phenotyping using sciatic-tibial motor, sural sensory nerve conduction studies and intraepidermal nerve fiber density. Fecal pellets were collected directly from animals at 8, 10, 12, 16, 18, 20, 22, and 24 weeks of age, and data from the 8-, 16-, 18-, and 24-week time points and ileum, cecum, colon at end points. Fecal pellet amplification of the V4 region of the bacterial 16S rRNA was done and targeted lipidomics was conducted on plasma and sciatic nerve samples.
Results: A short duration of HFD altered microbiome structure in mice, which rapidly reversed when animals were placed back on SD. The HFD microbiota revealed increased abundance of bacteria belonging to Lachnospiraceae, Oscillospiraceae, and Clostridiaceae, families which contain pathogenic bacteria. Phyla abundance indicated that HFD promotes Firmicutes and reduces Bacteroidetes, i.e., high Firmicutes/Bacteroidetes ratio. Similarly, HFD enhances the proportion of butyrate-producing bacteria. The evaluation of functional implications of these differential amplicon sequence variant abundances showed that the gut niches were the pathways of tyrosine metabolism, arginine and proline metabolism, carbapenem biosynthesis, tropane, piperidine and pyridine alkaloid biosynthesis, and legionellosis. In the large intestine, insulin resistance was the most represented pathway, interestingly in fecal pellets, neurotransmitter pathways and serotonergic and dopaminergic synapse were highly present. Correlation analysis showed associations between elevated circulating sphingomyelins and lower triglycerides in HFD mice, which were negatively linked to *Bifidobacterium*, used in probiotics supplements. *Lactobacillus*, *Lachnoclostridium* and *Anaerotruncus* correlated negatively with LysoPC 16:1 in plasma and sciatic nerve. Moreover, *Lactobacillus*, *Lachnoclostridium*, and *Anaerotruncus* taxa variants correlated positively with plasma sphingomyelins and sciatic nerve triglycerides. Relationships were also present between specific PN-associated taxa variants and expression of genes of PN pathogenesis, as inflammation, lipid metabolism, or antioxidant pathways.
Conclusions: These findings link HFD-mediated PN to the gut microbiome and stress the importance of microbiota in PN pathogenesis. This paper offers more insight into innovative therapeutic strategies for PN including diet, probiotics or fecal microbial transplant.

Comments. This study highlights the importance of the gut microbiota and indicates that the gut microbes may affect nerve function and structure. However, as the authors mentioned, the study has limitation since it is a correlative study, not a causative one. More studies using mechanistic approaches in rodents and evaluating similar correlation in humans would be crucial in the future to understand how gut bacteria change peripheral neurons and cells. In addition, it would be interesting to evaluate sexual dimorphism. The authors evaluated the effect of a HFD which is important, however the westernized diet contains high sugar and ultra-processed food that has been shown to impact greatly human health and gut microbes. Such diet use in rodent research could be of importance to better understand the role of gut microbiota on PN.

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Reference. Guo K, Figueroa-Romero C, Noureldein M, Hinder LM, Sakowski SA, Rumora AE, Petit H, Savelieff MG, Hur J, Feldman EL. Gut microbiota in a mouse model of obesity and peripheral neuropathy associated with plasma and nerve lipidomics and nerve transcriptomics. Microbiome. 2023 Mar 15;11(1):52. doi: 10.1186/s40168-022-01436-3. PMID: 36922895; PMCID: PMC10015923.
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