Gut microbiota essential for PAHSAs' metabolic benefits in obese mice, study finds

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Illustration of bacteria in the human gut. Credit: Darryl Leja, National Human Genome Research Institute, National Institutes of Health

Dietary lipids play an essential role in regulating the function of the gut microbiota and gastrointestinal tract, and these luminal interactions
contribute to mediating host metabolism.

Palmitic acid hydroxy stearic acids (PAHSAs) are a family of lipids with antidiabetic and anti-inflammatory properties, but whether the gut microbiota contributes to their beneficial effects on host metabolism is unknown.

In *PNAS*, researchers report that treating chow-fed female and male germ-free (GF) mice with PAHSAs improves glucose tolerance, but these effects are lost upon high fat diet (HFD) feeding. However, transfer of feces from PAHSA-treated, but not vehicle-treated, chow-fed conventional mice increases insulin sensitivity in HFD-fed GF mice.

Thus, the gut microbiota is necessary for, and can transmit, the insulin-sensitizing effects of PAHSAs in HFD-fed GF male mice.

Analyses of the cecal metagenome and lipidome of PAHSA-treated mice identified multiple lipid species that associate with the gut commensal Bacteroides thetaiotaomicron (Bt) and with insulin sensitivity resulting from PAHSA treatment.

Supplementing live, and to some degree, heat-killed Bt to HFD-fed female mice prevented weight gain, reduced adiposity, improved glucose tolerance, fortified the colonic mucus barrier and reduced systemic inflammation compared to HFD-fed controls.

These effects were not observed in HFD-fed male mice. Furthermore, ovariectomy partially reversed the beneficial Bt effects on host metabolism, indicating a role for sex hormones in mediating the Bt probiotic effects. Altogether, these studies highlight the fact that PAHSAs can modulate the gut microbiota and that the microbiota is necessary for the beneficial metabolic effects of PAHSAs in HFD-fed mice.
Obesity in adults has nearly tripled worldwide in the last 50 y, and this is associated with comorbidities and complications that raise long-term health care costs and human disease burden. The gastrointestinal tract houses the gut microbiota, and its stratified organization of heterogeneous cell types provides both a physical barrier and immune protection to help regulate host metabolism.

Strong evidence supports an essential role for the gut microbiota in the development of obesity. Obesity caused by high fat diets (HFD) changes gut microbial composition and increases the production of gram-negative bacteria-derived lipopolysaccharide (LPS), which crosses the gut mucosal barrier that has been rendered leaky from the HFD.

This initiates the chronic low-grade inflammation observed in mice and in many humans with obesity. Thus, major efforts are focused on developing therapeutic gut-based strategies to restore gut microbiota composition and gut epithelial function to treat metabolic disease.

However, the gut microbiota is highly variable in taxonomy and function between individuals, and differences in experimental design further complicate findings and interpretation of results across studies.

Furthermore, few studies report sex-specific responses to gut microbial interventions, resulting in major knowledge gaps that limit the identification of optimal treatment strategies for women and men.

Palmitic acid hydroxy stearic acids (PAHSAs) are a family of lipids with antidiabetic and anti-inflammatory properties. PAHSAs were first identified from lipidomics analysis of white adipose tissue (WAT) from mice overexpressing the glucose transporter, Glut4 (AG4OX).

AG4OX mice despite having greater adiposity, have lower fasting glycemia, enhanced glucose tolerance, and markedly elevated PAHSA
levels in adipose tissue versus controls. Circulating and adipose PAHSA levels are low in insulin-resistant people and the levels correlate highly with insulin sensitivity in humans.

PAHSA treatment regulates multiple components of glucose homeostasis, including augmenting glucose-stimulated insulin secretion through the G-protein coupled receptor GPR40 in insulin-resistant aged chow-fed mice and in human islets, and enhancing insulin action on hepatic glucose production in diet-induced obese mice.

PAHSAs also have direct effects in the gastrointestinal tract. Daily PAHSA treatment delayed the onset and reduced the severity of dextran sodium sulfate-induced colitis in mice by modulating innate immune responses and attenuating inflammation.

Evidence that PAHSAs protect the gut from inflammatory injury along with their beneficial effects on glucose metabolism led us to posit that PAHSAs may alter the gut microbiota in a manner that contributes to their beneficial metabolic effects in diet-induced-obese mice.

In this study, researchers report that the gut microbiota is essential for, and can transmit, some of the beneficial metabolic effects of PAHSA treatment in male HFD-fed mice.

Functional profiling of the cecal metagenome and metabolome from PAHSA-treated chow-fed mice revealed that specific bacterial species including Bacteroides thetaiotaomicron (Bt) and unique signatures of lipid metabolites are altered with PAHSA treatment.

Subsequent studies in diet-induced-obese mice demonstrate sex specific responses to Bt supplementation resulting in distinct effects on mucus-producing Goblet cells that line the gut epithelium, intestinal immune phenotypes, and host metabolism.
These studies further elucidate the mechanism of action of PAHSAs. They also demonstrate the therapeutic utility of modulating the gut microbiota for the prevention and treatment of obesity and associated metabolic disease and highlight the major role of sex as a biological variable when studying host-microbiome interactions.


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