Effects of Gliadin consumption on the Intestinal Microbiota and Metabolic Homeostasis in Mice Fed a High-fat Diet

Dietary gluten causes severe disorders like celiac disease in gluten-intolerant humans. However, currently understanding of its impact in tolerant individuals is limited. Our objective was to test whether gliadin, one of the detrimental parts of gluten, would impact the metabolic effects of an obesogenic diet. Mice were fed either a defined high-fat diet (HFD) containing 4% gliadin (n = 20), or a gliadin-free, isocaloric HFD (n = 20) for 23 weeks. Combined analysis of several parameters including insulin resistance, histology of liver and adipose tissue, intestinal microbiota in three gut compartments, gut barrier function, gene expression, urinary metabolites and immune profiles in intestinal, lymphoid, liver and adipose tissues was performed. Mice fed the gliadin-containing HFD displayed higher glycated hemoglobin and higher insulin resistance as evaluated by the homeostasis model assessment, more hepatic lipid accumulation and smaller adipocytes than mice fed the gliadin-free HFD. This was accompanied by alterations in the composition and activity of the gut microbiota, gut barrier function, urine metabolome, and immune phenotypes within liver and adipose tissue. Our results reveal that gliadin disturbs the intestinal environment and affects metabolic homeostasis in obese mice, suggesting a detrimental effect of gluten intake in gluten-tolerant subjects consuming a high-fat diet.

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Environmental spread of microbes impacts the development of metabolic phenotypes in mice transplanted with microbial communities from humans

Microbiota transplantation to germ-free animals is a powerful method to study involvement of gut microbes in the aetiology of metabolic syndrome. Owing to large interpersonal variability in gut microbiota, studies with broad coverage of donors are needed to elucidate the establishment of human-derived microbiotas in mice, factors affecting this process and resulting impact on metabolic health. We thus transplanted faecal microbiotas from humans (16 obese and 16 controls) separately into 64 germ-free Swiss Webster mice caged in pairs within four isolators, with two isolators assigned to each phenotype, thereby allowing us to explore the extent of microbial spread between cages in a well-controlled environment. Despite high group-wise similarity between obese and control human microbiotas, transplanted mice in the four isolators developed distinct gut bacterial composition and activity, body mass gain, and insulin resistance. Spread of microbes between cages within isolators interacted with establishment of the transplanted microbiotas in mice, and contributed to the transmission of metabolic phenotypes. Our findings highlight the impact of donor variability and reveal that inter-individual spread of microbes contributes to the development of metabolic traits. This is of major importance for design of animal studies, and indicates that environmental transfer of microbes between individuals may affect host metabolic traits.

Gliadin affects glucose homeostasis and intestinal metagenome in C57BL6 mice fed a high-fat diet

Dietary gluten and its component gliadin are well-known environmental triggers of celiac disease and important actors in type-1 diabetes, and are reported to induce alterations in the intestinal microbiota. However, research on the impact of gluten on type-2 diabetes in non-celiac subjects is more limited. The aim of this study was to investigate the effect of gliadin on glucose homeostasis and intestinal ecology in the mouse.

Forty male C57BL/6 mice were fed a high-fat diet containing either 4% gliadin or no gliadin for 22 weeks. Gliadin consumption significantly increased the HbA1c level over time, with a borderline significance of higher HOMA-IR (homeostasis model assessment of insulin resistance) after 22 weeks. Sequencing of the V3 region of the bacterial 16S rRNA genes showed that gliadin altered the abundance of 81 bacterial taxa, separating the intestinal microbial profile of the gliadin consuming mice from the control mice in the principal coordinate analysis (PCoA) of weighted UniFrac distance. Moreover, gliadin reduced the ileal gene expression of tight junction protein 1, occludin, cadherin 1, mucin 2 and mucin 3, indicating an impaired intestinal barrier function. No difference was found in body weight gain, feed consumption or circulating cytokines (IL-1β, IL-6, IFN-γ, TNF-α and IL-10).

Our study is the first to show that gliadin as part of a defined synthetic feed exacerbates the glycaemia and alters the
intestinal microbiota composition. Comprehensive analyses of metabolites, histological sections and the profile of specific immune cells are in progress to elucidate the mechanism behind the observed effects.

Gliadin intake alters intestinal microbiota, glucose and lipid metabolism, and adipose tissue and liver immune cells

General information
Publication status: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Division of Food Microbiology and Immunology, University of Copenhagen
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Obesity-associated fecal microbiota from human modulates body mass and metabolites in mice

General information
Publication status: Published
Organisations: National Food Institute, Research Group for Gut Microbiology and Immunology, Department of Systems Biology, Holbæk University Hospital, University of Copenhagen
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Peer-reviewed: Yes
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Electronic versions:
Abstract_for_EMBL_conference_Obesity_associated_fecal_microbiota_from_human_modulates_body_mass_and_metabolites_in_mice_Li_Zhang_V6.pdf
The effects of gliadin on urine metabolome in mice

Gliadin, a proline-rich protein of gluten, is thought to modulate the gut microbiota and affect the intestinal permeability and immune system. However, little is known about the long-term effects of gliadin on the host and microbial metabolism. To study this, we compared the urine metabolome of two groups of mice, which were on a high fat diet with and without gliadin, respectively, for 23 weeks. Using liquid chromatography mass-spectrometry (MS) followed by multivariate analyses we were able to show a clear separation of the two groups of mice based on their urine metabolome. Discriminating urinary metabolites were identified by tandem MS and compared to MS libraries and authentic standards. Gliadin mice had higher levels of proline-containing dipeptides most likely originating from the gliadin itself. Furthermore, higher levels of tryptophan- and tyrosine-related metabolites were observed in the gliadin mice. Also, Maillard reaction products and β-oxidized tocopherols were observed in higher levels in the urine of gliadin mice, suggesting increased oxidative stress in the gliadin mice. Indisputably, gliadin affected the urine metabolome. However, the mechanisms behind the observed metabolite changes are yet to be elucidated.

Gliadin affects glucose homeostasis and intestinal metagenome in C57BL/6 mice fed a high-fat diet

Dietary gluten and its component gliadin are well-known environmental triggers of celiac disease and important actors in type-1 diabetes, and are reported to induce alterations in the intestinal microbiota. However, research on the impact of gluten on type-2 diabetes in non-celiac subjects is more limited. The aim of this study was to investigate the effect of gliadin on glucose homeostasis and intestinal ecology in the mouse. Forty male C57BL/6 mice were fed a high-fat diet containing either 4% gliadin or no gliadin for 22 weeks. Gliadin consumption significantly increased the HbA1c level over time, with a borderline significance of higher HOMA-IR (homeostasis model assessment of insulin resistance) after 22 weeks. Sequencing of the V3 region of the bacterial 16S rRNA genes showed that gliadin changed the abundance of 81 bacterial taxa, separating the intestinal microbial profile of the gliadin consuming mice from the control mice in the principal coordinate analysis (PCoA) of weighted UniFrac distance. No difference was found in body weight gain, feed consumption or circulating cytokines (IL-1β, IL-6, IFN-γ, TNF-α and IL-10). Our study is the first to show that gliadin as part of a defined synthetic feed exacerbates the glycaemia and alters the intestinal microbiota composition. Comprehensive analyses of the profile of specific immune cells, metabolites and intestinal permeability are in progress to elucidate the mechanism behind the observed effects.
Projects:

**Microbiota and Metabolic Diseases - Dietary intervention studies in animal models**
Zhang, L., PhD Student, National Food Institute
Licht, T. R., Main Supervisor
Bahl, M. I., Supervisor
Hansen, A. K., Supervisor
Pamp, S. J., Examiner
Ahrne, S., Examiner
Wichmann, A. E., Examiner
Technical University of Denmark
01/11/2012 → 02/06/2016
Award relations: Microbiota and Metabolic Diseases - Dietary intervention studies in animal models
Project: PhD

**3G Center: 3G Center: Center for Gut Microbiota, Metabolic disorders, and Grain/Fibre-based Diets (Guts, Grains and Greens)**
We hypothesize that the interplay between human host genome expression and gut microbiota (GM) affects the development of chronic metabolic disorders, and that interventions targeting the microbiome and mucosa can therefore reduce the risk of developing metabolic dysfunctions such as obesity, Type 2 Diabetes (T2D), and cardiovascular diseases (CVD).
Our intention is to develop an internationally competitive research platform to address this hypothesis. The platform builds on integration of data from human studies, animal models and in vitro studies with state-of-the-art methods for high-throughput sequencing and analysis of biomarkers of metabolic disorders. The hypothesis will be tested by intervention studies undertaken in this integrated setup. Grain/vegetable-based interventions, which are known to affect the host gut microbiota and metabolism either positively (dietary fibers/whole grain), or negatively (gluten-rich diet), will be applied. We will actively discuss and develop our research in dialogue with companies that produce foods or food ingredients that influence the GM, industries involved in prevention and/or treatment of metabolic and inflammatory diseases, as well as to public health authorities. This will form the basis for development of new functional foods, new innovative products and improved dietary advice, which in a short-term perspective will add to the value of these companies, and in the long-term perspective reduce the occurrence of lifestyle related metabolic diseases. Once developed, the research platform will be available for further intervention studies, and will provide the possibility to study other endpoints and biomarkers than the ones included in the present proposal. The success of the project will place Danish research at the absolute forefront within GM manipulation and host response.
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Danish Council for Strategic Research: DKK34,749,243.00
01/04/2012 → 31/03/2017
Collaborators: University of Copenhagen, Taconic Europe A/S, Technical University of Denmark, DuPont Nutrition and Health
Award relations: 3G Center: Center for Gut Microbiota, Metabolic disorders, and Grain/Fibre-based Diets (Guts, Grains and Greens)
Project: Research

Activities:

**Obesity-associated fecal microbiota from human modulates body mass and metabolites in mice**
Period: 11 Jun 2015
Li Zhang (Speaker)
National Food Institute
Research Group for Gut Microbiology and Immunology

Description
Oral presentation at the EMBL Conference 2015: The Human Microbiome.

Related event
EMBL Conference 2015: The Human Microbiome
10/06/2015 → 12/06/2015
Heidelberg, Germany
Activity: Talks and presentations › Conference presentations

Gliadin Affects Glucose Homeostasis and Intestinal Metagenome in C57BL/6 Mice Fed a High-Fat Diet
Period: 10 Nov 2014
Li Zhang (Speaker)
National Food Institute
Division of Food Microbiology

Related event
The Danish Microbiological Society Annual Congress 2014
10/11/2014 → …
Copenhagen, Denmark
Activity: Talks and presentations › Conference presentations