DIETARY HEME IRON INTAKE INDUCES GUT DYSBIOSIS AND LUMINAL REACTIVE ALDEHYDES PRODUCTION LEADING TO VISCERAL HYPERSENSITIVITY

Anaïs Mazenc, Valérie Tondereau, Claire Maslo, Françoise Guéraud, Fabrice H.F. Pierre, Hélène Eutamene, Vassilia Theodorou, Fabrice Pierre, Maïwenn Olier

DIETARY HEME IRON INTAKE INDUCES GUT DYSBIOSIS AND LUMINAL REACTIVE ALDEHYDES PRODUCTION LEADING TO VISCERAL HYPERSENSITIVITY

Anaïs Mazenc, Valérie Tondereau, Claire Maslo, Françoise Guéraud, Fabrice Pierre, Hélène Eutamène, Vassilia Théodorou, Maïwenn Olier

BACKGROUND:

One to three hours following a meal, two-thirds of irritable bowel syndrome (IBS) patients reported exacerbation of their symptoms (bloating, abdominal pain..). A low FODMAP diet improves IBS symptoms supporting running personalized strategic program diet to improve quality of life. According to literature, daily dietary intake in IBS patients is generally of lower overall quality compared to that of healthy subjects and reveals notably a higher consumption of processed meats. Heme iron contained in processed meats is a key contributing factor associated with higher risk to develop several chronic diseases through its ability to catalyze lipid peroxidation leading to reactive aldehydes formation in the gut lumen. Interestingly, one of such formed compounds, the 4-hydroxynonenal when directly injected into the hind paw promote pain in mice and activate pain signaling pathways *in vitro*.

Our aim was to decipher whether a heme-enriched diet alters the microbiota-gut-brain axis by promoting visceral hypersensitivity in mice in response to colorectal distension.

METHODS:

C3H/HeN mice were fed an AIN-76A diet supplemented with ferric citrate (control) or heme iron (1.5 µmol/g). After 15 days of diet, the animals were equipped with nickel-chrome electrodes implanted into the abdominal external oblique muscle in order to evaluate visceral pain in response to colorectal distensions. Fecal samples were collected for measuring i) lipid peroxidation-derived reactive aldehydes (LPRA), ii) lysozyme enzymatic activity as an indicator of Paneth cells antimicrobial activity, and iii) microbiota composition through 16S rDNA gene sequencing.

RESULTS:

Dietary heme iron increased luminal LPRA in fecal waters ($p<0.001$) and visceral hypersensitivity in response to colorectal distension at 0.06, 0.08 volumes ($p<0.01$, $p<0.05$, respectively). Luminal LPRA increase was associated with a strong decrease of fecal antimicrobial activity ($p<0.001$) and a significant remodeling in microbiota structure and composition. Indeed, the species richness of mice fed the heme-enriched diet was reduced (α diversity, $p<0.0001$) and β diversity revealed a clear difference in microbiota community according to the iron form in diet (Adonis: $p<0.0001$). This dysbiosis was characterized at diverse taxonomic levels: a decrease in the abundance of *Firmicutes* ($q<0.001$) and more particularly within the class of *Clostridia* was notably associated with an overabundance of *Gammaproteobacteria*, and more specifically an expansion of *Escherichia coli* ($q<0.001$).

CONCLUSION:

Our findings show how the dietary heme iron, as compared to ferric citrate, can markedly trigger gut homeostasis disruption through lipid peroxidation. Associated impairments consisted in a lower capacity of Paneth cells to respond to endoluminal bacterial stimulation, a microbiota reshape and an increase of visceral hypersensitivity.

Références

1. Simrén M, Månsson A, Langkilde AM, Svedlund J, Abrahamsson H, Bengtsson U, Björnsson ES. Food related gastrointestinal symptoms in the irritable bowel syndrome. Digestion 2001. 63, 108-115
2. Staudacher HM, Whelan K. The low FODMAP diet: recent advances in understanding its mechanisms and efficacy in IBS. Gut. 2017;66(8):1517-1527

3. Tigchelaar EF, Mujagic Z, Zhernakova A, Hesselink MAM, Meijboom S, Perenboom CWM, Masclee AAM, Wijmenga C, Feskens EJM, Jonkers DMAE. Habitual diet and diet quality in Irritable Bowel Syndrome: A case-control study. Neurogastroenterol Motil. 2017;29(12).

Hayes et al. 2014

4. Bastide N, Chenni F, Audebert M, Santarelli RL, Taché L, Naud N, Baradat M, Jouanin I, Surya R, Hobbs DA, Kuhnle GG, Raymond-Letron I, Gueraud F, Corpet DE, Pierre FHF. A central role for heme iron in colon carcinogenesis associated with red meat intake. Cancer Research. 2015

5. Trevisani M, Siemens J, Materazzi S, et al. 4-Hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1. Proc Natl Acad Sci 2007;104:13519–13524.