Göteborg, 2016

Microbial regulation of Insulin-like peptide 5 and its implication on metabolism and bariatric surgery

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Hjärtats aula, Vita stråket 12, Göteborg, Tisdagen den 14 Juni 2016, klockan 13.00

av Ying Shiuan Lee

Fakultetsopponent: Professor Anna Krook

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Avhandlingen baseras på följande delarbeten

I. Insulin-like peptide 5 is a microbially regulated peptide that promotes hepatic glucose production

Ying Shiuan Lee, Filipe De Vadder, Valentina Tremaroli, Anita Wichmann, Gilles Mithieux, Fredrik Bäckhed.

Mol Metab 2016; 5:263-270

II. Insulin-like peptide 5 is induced by sleeve gastrectomy in human serum but does not contribute to improved metabolism following sleeve gastrectomy in mice

Ying Shiuan Lee, Antonio Molinaro, Danila Capoccia, Carina Arvidsson, Rosie Perkins, Stefano Ginnani Corradini, Frida Leonetti, Gianfranco Silecchia, Fredrik Bäckhed.

Submitted

III. Mechanisms of sleeve gastrectomy and the role of the gut microbiota

Valentina Tremaroli, Antonio Molinaro, Lisa Olsson, Ying Shiuan Lee, Danila Capoccia, Louise Mannerås Holm, Robert Caesar, Carina Arvidsson, Jose Berger, Frida Leonetti, Stefano Ginnani Corradini, Gianfranco Silecchia, Randy Seeley, Fredrik Bäckhed.

Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

Göteborg, 2016

Microbial regulation of Insulin-like peptide 5 and its implication on metabolism and bariatric surgery

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Abstract

The microbial community in our gastrointestinal tract, the gut microbiota, has great impact on our physiology. Particularly, the role for gut microbiota in host health and disease has been associated with modulation of gut hormones which are key players in the regulation of energy homeostasis. Recently, a new gut hormone, insulin-like peptide (INSL5) has been identified. In this thesis, we have studied the microbial regulation of INSL5 and its role on metabolism.
Bariatric surgery is the most effective treatment for obesity and obesity-related diseases such as type 2 diabetes. There is increasing evidence that supports a role for gut hormones and gut microbiota in mediating the beneficial effects of bariatric surgery. Thus, in this thesis, we also investigated whether INSL5 and the gut microbiota directly contributes to the metabolic improvements following the bariatric procedure called vertical sleeve gastrectomy (VSG).

In paper I, we found that *Insl5* expression is higher in the colon of germ-free mice (mice that lack a microbiota), compared with their conventionally-raised control animals. We demonstrated that the elevated *Insl5* expression in GF mice is a response to low energy levels, which could be restored by increasing the energy availability. In addition, we found that mice lacking INSL5 have slightly impaired hepatic glucose production during fasting. Thus we speculate that INSL5 might play a role in low energy conditions.

In paper II, we observed that circulating fasting INSL5 levels were increased in human individuals following VSG. The high INSL5 levels were declined upon a meal test, suggesting a postprandial response. To test whether INSL5 contributes to the beneficial effects mediated by VSG, we performed VSG surgeries on wild-type and *Insl5*-knockout mice. The metabolic improvements in both groups of mice were similar after VSG. Therefore, we conclude that INSL5 is not required for the beneficial effects observed after VSG.

In paper III, we characterized the longitudinal changes of the human gut microbiota after VSG, and we found that VSG strongly altered the microbiota composition. We showed that by transferring the VSG-altered gut microbiota from humans to mice, we also transferred the improvements in metabolic effects of VSG patients. We also showed that VSG surgery produced greater metabolic improvements in mice having a normal microbiota compared with germ-free mice. These results indicate that the gut microbiota is directly contributing to the beneficial effects mediated by VSG.

In conclusion, INSL5 is a microbially regulated gut hormone which promotes hepatic glucose production during low energy conditions. INSL5 is also a gut hormone which increases after fasting following sleeve gastrectomy in humans, but it appears not to contribute to the beneficial effects observed after sleeve gastrectomy in mice. However, the gut microbiota plays an important role for the metabolic improvements mediated by sleeve gastrectomy.

Keywords: gut microbiota, gut hormones, INSL5, bariatric surgery, sleeve gastrectomy
ISBN: 978-91-628-9838-0 (TRYCK) http://hdl.handle.net/2077/42339
ISBN: 978-91-628-9839-7 (PDF)