Intestinal adaptation in response to Roux-en-Y Gastric Bypass Surgery

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten.

I. **Erik Elias**, Anna Casselbrant, Emma Spak, Lars Fändriks Ville Wallenius. Global proteomic analysis of proximal small intestinal mucosa before and after Roux-en-Y Gastric Bypass Surgery for obesity. (Manuscript)

II. Anna Casselbrant, **Erik Elias**, Lars Fändriks, Ville Wallenius, Expression of tight-junction proteins in human proximal small intestinal mucosa before and after Roux-en-Y gastric bypass surgery. Surgery for Obesity and Related Diseases, (2014) 11(1): 45-53

III. **E. Elias**, A. Casselbrant, M. Werling, K. Abegg, R. P. Vincent, J. Alaghband-Zadeh, T. Olbers, C. W. le Roux, L. Fändriks and V. Wallenius. Bone mineral density and expression of vitamin D receptor-dependent calcium uptake mechanisms in the proximal small intestine after bariatric surgery. British Journal of Surgery (2014); 101: 1566–1575

IV. **Erik Elias**, Anna Casselbrant, Lars Fändriks, Ville Wallenius. Altered lipid metabolism in the jejunum in obesity and after RYGBP surgery. (Manuscript)

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ABSTRACT

Background: Obesity is a condition with increasing prevalence that leads to morbidity, decreased quality of life and reduced life expectancy. The only effective evidence-based treatment is bariatric surgery. The most well documented procedure; Roux-en-Y Gastric Bypass (RYGB) results in a substantial and sustainable weight loss and an improved metabolic state. The mechanisms of action have not yet been fully elucidated but recent research has indicated that the proximal alimentary tract has a profound influence on central aspects of the body's metabolism such as appetite regulation and hepatic glucose production.

Aim: The general aim of this thesis was to explore alterations to the proximal small intestinal mucosa induced by RYGB, and thereby link functional aspects of the small intestine in the context of obesity and obesity related morbidity with the effects of RYGB surgery.

Method: Jejunal mucosal samples from patients were obtained during RYGB surgery and 6 months post-operatively via endoscopy. A proteomic analysis using 2-D gel electrophoresis and mass spectroscopy was then performed using a paired samples setting. The results from this exploratory proteomic analysis were then used as starting points for further in depth analysis of aspects of intestinal function such as barrier integrity, calcium uptake and lipid metabolism. For these studies additional human mucosal tissue samples were collected and analyzed with western blot, immunohistochemistry and in Ussing chambers. Also, previously collected bone densitometric data from a RCT comparing RYGB to vertical banded gastroplasty (VBG) were analyzed. Animal experiments using C57 bl6 mice and cell culture experiments using Caco-2 cell lines were performed as well.

Results: The proteomic analysis identified several proteins in the jejunal mucosa with markedly altered expression levels after RYGB surgery. Among these were cytokeratin (CK)8, Heat-shock protein (HSP) 90β and HMGCS2 that were considered of particular interest.

CK8 has been reported to be of importance for intestinal mucosal barrier function. Further analysis with western blot revealed profound alterations in the expression levels of several proteins involved in tight junctions that are important in maintaining barrier integrity. Ussing chamber experiments linked an increase in Claudin-3 expression after RYGB to a decrease in intestinal permeability as reflected by reduced electrical resistance.

HSP90β has been reported to be a co-activator of vitamin-D in the small intestine. Additional western blot analysis suggested a decreased vitamin D receptor (VDR) activity in the small intestine after RYGB. VDR mediates active calcium uptake in the small intestine and analysis of DEXA data from patients that had undergone RYGB or VBG show that RYGB induced a weight loss independent decrease in bone mineral density.

Finally, analyses of human mucosal samples and animal experiments indicated that the production of ketone bodies in the proximal small intestinal mucosa could be induced by diet composition, and that this effect may be reversed by RYGB surgery indicating that lipid metabolism in the proximal small intestine is altered in obesity and in response to RYGB.

Conclusion: In our study, RYGB induces several changes to the proteome of the small intestinal mucosa indicating alterations in central aspects of small intestinal function such as barrier integrity, calcium absorption and lipid metabolism. These alterations could be of importance for linking the clinical effects of RYGB surgery to the largely unexplained pathophysiological mechanisms that link obesity with morbidity.

Keywords: obesity, bariatric surgery, proteomic analysis, intestinal permeability, calcium, bone mineral density, lipid metabolism

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