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Effect of endogenous and exogenous ghrelin on gastrointestinal function in rat and human

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ABSTRACT

Background

Several peptides derived from the gastrointestinal tract (GI) have been shown to have profound effects on GI motility, food intake and metabolism. Two such peptides, derived from the same prohormone, are the peptides ghrelin and obestatin, discovered in 1999 and 2005, respectively. The ghrelin receptor (GHS-R) is distributed in a large number of central and peripheral tissues, such as, the GI tract, pancreas, kidney, fat, skeletal muscle and several parts of the brain. The obestatin receptor still remains unknown. Two major molecular forms of ghrelin, acyl and des-acyl ghrelin exist. They regulate GI motility peripherally in the local enteric nervous system, but also by activating hypothalamic peptides via the vagal nerve or the bloodstream by crossing the blood-brain barrier (BBB). Ghrelin is involved in a variety of metabolic functions by affecting the glucose homeostasis, fat metabolism, appetite and meal initiation. The role of obestatin and its interaction with ghrelin is still uncertain.

Aims

The main aims of this thesis were to investigate the role of obestatin and ghrelin in GI motility *in vitro* and *in vivo* in rodents and man.

Material and methods

Gastric emptying and small bowel motility were studied *in vivo* in rats with implanted gastric catheter and intestinal electrodes. Gastric emptying, oro-caecal transit, colonic transit and gut peptides were assessed in man. Ghrelin, obestatin or saline was infused in rats. Ghrelin or saline was infused in normal humans for 6 hours. *In vitro* studies with human GI tissue were also performed. Gastric emptying was studied in patients randomised to 3 hours saline or ghrelin infusion, before and day 2 after open colo-rectal surgery. Gastric emptying and changes in serum levels of GI peptide hormones were studied in obese subjects subjected to a liquid meal with acetaminophen before, 3 days, 2 months and 1 year after Roux-en-Y gastric bypass (RYGB) surgery.

Results

Whereas ghrelin stimulated GI motility, obestatin did not affect motility *in vitro* or *in vivo* in rats. Ghrelin increased gastric emptying in healthy humans and in patients after colo-rectal surgery. There was no effect on small bowel or colonic transit in healthy humans, but time to defecation was shorter when ghrelin was administered after colo-rectal surgery. Post-prandial elevations of glucose, insulin and GLP-1 occurred earlier and were higher with ghrelin in healthy humans. Plasma concentrations of ghrelin were unchanged after RYGB. Gastric (pouch) emptying was twice as fast after RYGB compared to before surgery. There was a progressive increase in several GI peptides after RYGB over 1 year after surgery.

Conclusions

In rodents ghrelin stimulates GI motility but obestatin has no effect. Ghrelin potently stimulates gastric emptying in healthy humans and in patients after surgery, while stimulation of intestinal motility seems more outspoken after surgery. In contrast to other studies plasma ghrelin was only significantly different on day 3 and thereafter not different after RYGB. Even if exogenous ghrelin can stimulate motility, endogenous ghrelin does not change after surgery and is less likely to modulate GI motility, transit or glucose metabolism after RYGB. However, early changes of other GI peptides (e.g. glucagon-like peptide-1) after RYGB likely contribute to the improved glucose homeostasis post surgery.