Ghrelin in the regulation of feeding and energy balance

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet
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Av

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Fakultetsopponent:
Professor Jacques Epelbaum
INSERM, Paris, France

Avhandlingen baseras på följande arbeten:

I **Ghrelin treatment reverses the reduction in weight gain and body fat in gastrectomised mice** Charlotta Dornonville de la Cour, Andreas Lindqvist, Emil Egecioglu, Loraine YC Tung, Vikas Surve, Claes Ohlsson, John-Olov Jansson, Charlotta Erlanson-Albertsson, Susanne L Dickson and Rolf Håkanson
Gut 2005; 54:907-913; originally published online 21 April 2005

II **Effects of ghrelin and a ghrelin receptor agonist on the expression of hypothalamic genes involved in energy balance following gastrectomy of mice and rats**
Emil Egecioglu, Björn Stenström, Scarlett B. Pinnock, Loraine YC Tung, Charlotta Dornonville de la Cour, Andreas Lindqvist, Rolf Håkanson, Unni Syversen, Duan Chen, Suzanne L. Dickson..
Submitted

III **Ghrelin stimulates locomotor activity and accumbal dopamine-overflow via central cholinergic systems in mice: implications for its involvement in brain reward**
Elisabet Jerlhag, Emil Egecioglu, Suzanne L. Dickson, Malin Andersson, Lennart Svensson, Jörgen A. Engel.
Addiction Biology May 2006; 11(1):45-54

IV **Growth hormone receptor deficiency results in blunted ghrelin feeding response, obesity, and hypolipidemia in mice**
Emil Egecioglu, Mikael Bjursell, Anna Ljungberg, Suzanne L. Dickson, John J Kopchick, Göran Bergström, Lennart Svensson, Jan Oscarsson, Jan Törnell and Mohammad Bohlooly-Y
Am J Physiol Endocrinol Metab 2006; 290:317-325; originally published online 20 September 2005

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Ghrelin in the regulation of feeding and energy balance

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Abstract
Ghrelin, the first identified endogenous ligand for the growth hormone secretagogue receptor 1A, is a 28 amino acid peptide produced mainly by the stomach. Pharmacological studies indicate a role for ghrelin in the regulation of growth hormone secretion from the pituitary and also in the regulation of body weight, fat accumulation and food intake.

Using a classical endocrine deletion/replacement approach we found support for the notion that endogenous ghrelin is required for the maintenance of normal body weight and adiposity. Gastrectomy (Gx) surgery, that depleted animals of ~80% of circulating ghrelin, caused a reduction in body weight, fat mass and lean mass in adult mice. Ghrelin replacement (at a dose that restores circulating ghrelin levels in Gx mice and that is without effect on body weight in sham animals) fully or partially reversed the decrease in body weight, fat mass and lean mass following Gx. To further investigate the central mechanism behind these effects on body weight and fat mass following Gx-surgery and ghrelin treatment key hypothalamic genes involved in energy homeostasis were analysed by *in situ* hybridisation. Surprisingly the marked changes in body composition following Gx did not effect expression of the hypothalamic genes studied, to any large extent. By contrast ghrelin treatment increased mRNA expression of NPY and AgRP and decreased POMC mRNA expression in accordance with ghrelin's effects to increase fat mass and body weight.
Using growth hormone receptor (GHR) knockout animals we investigated the importance of a functional GHR signalling system for the acute effects of ghrelin on food intake. Ghrelin treatment increased food intake in wild type animals but not in GHR knockouts indicating that a functional GHR signalling system is needed for the acute effects of ghrelin on food intake.
In addition to impacting upon the hypothalamic circuits controlling energy balance, ghrelin was found to interact with the mesolimbic reward circuits (reflected by increased locomotor activity and dopamine release after ghrelin injection to the brain ventricles).
In conclusion, endogenous ghrelin from the stomach is important for maintaining normal body weight and body composition. Long term treatment with ghrelin increases body fat by a mechanism that appears to be independent of its acute affects on food intake. Long term ghrelin treatment still impacts upon hypothalamic genes regulating energy balance. Ghrelin's acute effect on food intake is dependant on a functional GHR signalling system. Moreover, this effect may be linked to dopamine release in areas of the brain intimately associated with reward-seeking activities.

Key words: Ghrelin, obesity, food intake gastrectomy, fat mass, growth hormone, GHR, dopamine, reward

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