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Ghrelin in feeding: new insights into its role and the neurocircuits involved

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal **Arvid Carlsson**, Medicinaregatan 3, **fredagen den 20 mars 2020**, klockan **9.00**

av Marie Le May

Fakultetsopponent:
Julie A Chowen, Senior Investigator
Hospital Infantil Universitario Niño Jesús, Spain

Avhandlingen baseras på följande delarbeten

I. Central administration of ghrelin induces conditioned avoidance in rodents. Schéle E, Cook C, Le May M, Bake T, Luckman SM, Dickson SL. *European Neuropsychopharmacology*, 2017; 27: 809-815.

II. Activation of the rat hypothalamic supramammillary nucleus by food anticipation, food restriction or ghrelin administration. Le May MV*, Hume C*, Sabatier N, Schéle E, Bake T, Bergström U, Menzies J, Dickson SL. *Journal of Neuroendocrinology, 2019; e12676.* *Le May MV and Hume C contributed equally to this work.

III. Ghrelin receptor stimulation of the lateral parabrachial nucleus in rats increases food intake but not food motivation. Bake T, Le May MV, Edvardsson CE, Vogel H, Bergström U, Albers MN, Skibicka KP, Farkas I, Liposits Z, Dickson SL. *Submitted.*

IV. Silencing the GHSR neurones of the lateral parabrachial nucleus in mice protects against diet-induced weight gain and alters food choice. Le May MV, Peris-Sampedro F, Iris Stoltenborg, Adan RAH, Dickson SL. *Manuscript.*

SAHLGRENSKA AKADEMIN
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Ghrelin in feeding: new insights into its role and the neurocircuits involved

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Abstract

Appetite, originally evolved to ensure we consume enough of diverse nutrients to survive famines, has lost its survival advantage in our modern society, where food is plentiful. The hedonic aspect of appetite can indeed induce over-consumption of food, a major cause for the obesity pandemic. In this context, ghrelin, the only hormone known to promote feeding, is of particular interest because studying it helps us understand how food consumption is regulated and provides potential targets for the treatment of obesity. With the aim to further our understanding of the effects of ghrelin within the brain, we sought to investigate, first, the valence/emotion signal carried by ghrelin signalling in the brain and, second, novel central regions that mediate ghrelin's feeding effects.

Firstly, using simple behavioural tests measuring preference/avoidance in rats and mice, we demonstrate that ghrelin injection into the brain carries a negative valence signal, which leads to the animals avoiding situations paired with this injection. Secondly, our results show the hypothalamic supramammillary nucleus (SuM) to be a brain area activated by peripheral ghrelin injection as well as by anticipation of chow and palatable food, two physiological states associated with elevated ghrelin blood levels. Moreover, ghrelin delivery directly into the SuM could drive a feeding response. Thirdly, we found the lateral parabrachial nucleus (lPBN) of the brainstem, an area rich in ghrelin receptor (GHSR), to be a novel target for the effects of ghrelin on food intake and dietary choice, whereby intra-lPBN ghrelin injection increased consumption of both standard chow and high-fat diet when presented separately and induced an increase in only chow intake when the rats were offered a choice diet consisting of chow, lard and sucrose. This ghrelin treatment did not alter food motivation or reward as tested by sucrose-induced operant responding and conditioned place preference for chocolate, respectively. Fourthly, using *Ghsr-IRES-Cre* mice and a Cre-inducible viral vector, we provide evidence that the GHSR-expressing cells of the lPBN are necessary for the development of diet-induced body weight gain via a role in the regulation of energy intake (as opposed to energy expenditure) and dietary choice (notably sucrose intake). The lPBN GHSR-expressing cells were identified as a distinct population from the well-described anorexigenic lPBN cells containing the calcitonin gene-related peptide.

In summary, the work presented in this thesis determines the reinforcing properties of central ghrelin administration as being negative and identifies the SuM and lPBN as novel brain targets for ghrelin's effects on feeding. Furthermore, the GHSR-expressing cells of the lPBN are introduced as a neuronal population of importance in feeding and body weight control, thus providing a novel potential target for pharmacological therapies against obesity and other eating disorders.

Keywords: ghrelin, feeding, supramammillary nucleus, parabrachial nucleus

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