

Addressing knowledge gaps in the brain ghrelin signalling system - its neural circuitry and role in food-linked behaviours

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i hörsal 2119, hus 2, Arvid Wallgrens backe, fredag den 12 september 2025, klockan 13.00

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Avhandlingen baseras på följande delarbeten

- I. Intranasal delivery of a ghrelin mimetic engages the brain ghrelin signalling system in mice. Poelman R, Le May MV, Schéle E, Stoltenborg I, Dickson SL. *Endocrinology*, 2025; 5:166
- II. Activation of a ghrelin-responsive hunger ensemble in the dorsomedial hypothalamus is sufficient to drive food-related behaviours in male and female mice. Stoltenborg I, Poelman R, Vecchi E, Schéle E, Dickson SL. *Manuscript*
- III. Impact of chemogenetic activation of a ghrelin-responsive neuronal ensemble in the arcuate nucleus on food intake, hunger valence evaluation and food motivation in mice. Stoltenborg I, Poelman R, Vecchi E, Schéle E, Dickson SL. *Manuscript*
- IV. Impact of ghrelin on behavioural outcomes linked to attentiveness to a conditioned food cue. Poelman R, Le May MV, Stoltenborg I, Vecchi E, Schéle E, Adan RAH, Dickson SL. *Manuscript*

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Abstract

The drive to seek out and consume food is a fundamental survival mechanism, orchestrated by the brain through a range of behaviours in response to both intrinsic signals of energy status and external food-related cues. Disruption or faulty processing of these signals can lead to disordered eating behaviour across the body weight spectrum. For example, the availability of high-calorie, palatable foods and abundance of environmental cues are thought to stimulate overconsumption and contribute to the global obesity epidemic or, in contrast to this, loss of appetite in conditions such as anorexia nervosa, cancer cachexia or frailty can be detrimental. A better understanding of the brain mechanisms controlling food-linked behaviours is essential for developing effective, non-invasive therapies. Among the many signalling molecules that modulate networks controlling feeding behaviour, the hormone ghrelin stands alone as the only circulating orexigenic (pro-feeding) hormone and represents a powerful tool to access and modulate brain networks involved in feeding control. This thesis addresses important gaps in our understanding of the brain ghrelin signalling system, focussing on its neural circuitry and its role in food-linked behaviours, using advanced neural circuit mapping techniques to explore both mechanistic and translational aspects.

First, we demonstrate that the ghrelin mimetic GHRP-6 can stimulate the brain ghrelin signalling system through non-invasive intranasal application, reproducing many of the known effects of peripheral ghrelin administration in mice, including increased food intake, growth hormone release and activation of cells in the arcuate nucleus (Arc) including AgRP and GHRH neurones. In the second and third studies of this thesis, we used chemogenetic re-activation to functionally characterize hunger-responsive neuronal ensembles in the dor-somedial hypothalamus and Arc, demonstrating that re-activation of these ensembles stimulated food intake, and was able to drive food motivated behaviour. In the fourth and final study, we show that ghrelin's role in hunger extends to increase attention-linked behaviours and food intake in the presence of a food cue in a novel behavioural task adapted for mice.

Together, the studies in this thesis expand our understanding of the brain ghrelin signalling system. They identify novel functional circuits involved in hunger and food-motivated behaviour and obtained new insights into how ghrelin modulates behaviour towards environmental cues. Finally, a new, non-invasive strategy to stimulate the brain ghrelin signalling system has been proposed, which holds translational value.

Keywords: ghrelin, feeding, food motivation, food-cue, arcuate nucleus, dorsomedial hypothalamus, GHRP-6, growth hormone, intranasal administration, chemogenetics