

# **Appetite-regulating peptides and natural rewards: emphasis on ghrelin and glucagon-like peptide-1**

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, fredagen den 25 september 2020, klockan 13:00

av Jesper Vestlund

Fakultetsopponent:

Alfonso Abizaid, Associate professor  
Carleton University, Canada

## **Avhandlingen baseras på följande delarbeten**

- I. **Vestlund J**, Bergquist F, Eckernäs D, Licheri V, Adermark L, Jerlhag E. Ghrelin signalling within the rat nucleus accumbens and skilled reach foraging. *Psychoneuroendocrinology*. 2019; 106: 183-194.
- II. **Vestlund J**, Bergquist F, Licheri V, Adermark L, Jerlhag E. Activation of glucagon-like peptide-1 receptors and skilled reach foraging. *Addiction Biology*. 2020: e12953. DOI: 10.1111/adb.12953.
- III. **Vestlund J** and Jerlhag E. Glucagon-like peptide-1 receptors and sexual behaviors in male mice. *Psychoneuroendocrinology*. 2020; 117: 104687.
- IV. **Vestlund J** and Jerlhag E. The glucagon-like peptide-1 receptor agonist, exendin-4, reduces sexual interaction behaviors in a brain site-specific manner in sexually naïve male mice. *Hormones and Behavior*. 2020; 124: 104778.

# **Appetite-regulating peptides and natural rewards: emphasis on ghrelin and glucagon-like peptide-1**

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## **Abstract**

Evolutionary conserved natural behaviors, such as foraging and sexual behaviors, are strongly associated with reward processes. Brain areas important for reward processes include, but are not limited to, the nucleus accumbens (NAc) shell, the ventral tegmental area (VTA), the laterodorsal tegmental area (LDTg) and the nucleus of the solitary tract (NTS). The mechanisms that control natural rewards are complex, and appetite-regulating peptides, such as ghrelin and glucagon-like peptide-1 (GLP-1), have recently been identified as substrates involved in reward processes. The aim of the present thesis is therefore to elucidate the involvement of ghrelin and GLP-1 in natural rewards, by assessing how they mediate two different natural rewards, i.e. skilled reach foraging from the feeding-related domain and sexual behaviors from the social behavior domain, in preclinical behavioral models.

We showed in **paper I** that repeated treatment with a ghrelin receptor antagonist decreases the motivation of skilled reach foraging in rats with an acquired skilled reach performance tentatively through suppression of ghrelin receptors within the NAc shell. Repeated ghrelin increases, whereas a ghrelin receptor antagonist reduces, the motivation and learning of skilled reach foraging in rats during acquisition of this behavior. In **paper II**, we further established that GLP-1, as ghrelin, modulates the motivation and learning of skilled reach foraging. Indeed, the GLP-1 receptor (GLP-1R) agonists, exendin-4 and liraglutide, decrease the motivation of skilled reach foraging in rats with an acquired skilled reach performance whereas another GLP-1R agonist, dulaglutide, increases the learning of this complex behavior. When it comes to GLP-1 and sexual behaviors we demonstrated in **paper III** that a systemic exendin-4 injection decreases social behaviors, mounting behaviors and self-grooming behaviors but does not influence preference for females or female odors in sexually naïve male mice. We also identified that activation of GLP-1R within the NTS suppresses social behaviors, mounting behaviors and self-grooming behaviors in sexually naïve male mice. In addition, in **paper IV** we further identified that activation of GLP-1R within the LDTg or the posterior VTA suppresses social behaviors and mounting behaviors whereas activation of GLP-1R within the NAc shell only reduces social behaviors, but not mounting behaviors, in sexually naïve male mice.

Collectively, these data support the emerging literature suggesting that ghrelin increases whereas GLP-1 decreases natural rewards, by showing that these peptides via reward-related areas modulate natural rewards from both the feeding-related and the social behavior domains of natural rewards.

**Keywords:** Reward, Gut-brain axis, Sexual behaviors, Skilled reach foraging

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