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Central actions of glucagon-like peptide-1 on food intake and reward: Novel neurological targets and sex divergent effects

Akademisk avhandling

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av Jennifer Richard.

Fakultetsopponent:

Alfonso Abizaid, Associate professor

Carleton University, Canada

Avhandlingen baseras på följande delarbeten

I. Activation of the GLP-1 receptors in the nucleus of the solitary tract reduces food reward behavior and targets the mesolimbic system. Richard JE, Anderberg RH, Göteson A, Gribble FM, Reimann F, Skibicka KP. PloS One. 2015.

II. GLP-1 receptor stimulation of the lateral parabrachial nucleus reduces food intake: Neuroanatomical, electrophysiological, and behavioral evidence. Richard JE, Farkas I, Anesten F, Anderberg RH, Dickson SL, Gribble FM, Reimann F, Jansson JO, Liposits Z, Skibicka KP. Endocrinology. 2014.

III. Sex and estrogens alter the action of glucagon-like peptide-1 on reward. Richard JE, Anderberg RH, López-Ferreras L, Olandersson K, Skibicka KP. Biology of sex Differences 2016.

IV. Lateral hypothalamic GLP-1 receptors are critical for the control of food reinforcement, ingestive behavior and body weight. López-Ferreras L, Richard JE, Noble EE, Eerola K, Anderberg RH, Olandersson K, Taing L, Kanoski SE, Hayes MR, Skibicka KP. Molecular Psychiatry. 2018.

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Central actions of glucagon-like peptide-1 on food intake and reward: Novel neurological targets and sex divergent effects

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Abstract

Obesity is one of the biggest health risks of our society; however, treatment options are sparse and often result in suboptimal weight-loss. The glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonist liraglutide was recently approved for treatment of obesity in the US. GLP-1, and synthetic analogues, reduce body weight by suppressing food intake and food reward through actions on GLP-1Rs in the CNS. Regulation of homeostatic and hedonic feeding, by GLP-1, was previously attributed to actions specifically within the hypothalamus or limbic system, respectively. Our studies challenge this view and demonstrate novel central areas mediating the effects of GLP-1R stimulation on food intake and reward.

Using standard food intake and body weight measurements, and reward behavior tests, we demonstrate that GLP-1R stimulation, using GLP-1R agonist exendin-4 (Ex4), reduces food intake and food reward behavior through actions in the nucleus of the solitary tract (NTS) and lateral hypothalamus (LH). In addition, NTS GLP-1 neurons were found in close proximity to noradrenergic neurons, and intra-NTS Ex4 injection increased dopamine-related genes in the ventral tegmental area, suggesting a link between the NTS and the reward system. Furthermore, the parabrachial nucleus (PBN) was identified as a novel area mediating the anorexic effects of GLP-1R stimulation. This thesis also demonstrates potential sex differences in the effects of GLP-1, and its agonists, as central GLP-1R stimulation suppresses food-motivated behavior to a larger degree in females compared to males. In addition, central estrogen, and estrogen receptor-α (ERα), blockade attenuate the effects of Ex4 on food reward, but not food intake. However, specifically within the LH, GLP-1R stimulation is sufficient to reduce food-motivated behavior in both sexes, while it is only necessary in males.

In conclusion, effects of GLP-1R stimulation on food intake and food reward are not bound to actions on GLP-1Rs exclusively within homeostatic or hedonic feeding centers. Furthermore, GLP-1-mediated food reward, but not food intake, suppression is dependent on estrogen signaling. However, GLP-1 may also act differently within specific brain nuclei, as LH GLP-1R stimulation is sufficient to reduce food-reward in both sexes, while it is only necessary for its actions in males.

Keywords: Glucagon-like peptide-1, Food reward, Food intake, Sex differences.

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