IL-6 and GLP-1 in body fat regulating parts of the CNS in healthy mice

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Europa, Medicinaregatan 20, Göteborg, fredagen den 19 februari 2016 kl 9.00

av

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Avhandlingen baseras på förljande delarbeten:

Paper 1. **Glucagon-like peptide 1 receptor induced suppression of food intake, and body weight is mediated by central IL-1 and IL-6**
Rozita Shirazi, Vilborg Pálsdóttir, Jim Collander, Fredrik Anesten, Heike Vogel, Fanny Langlet, Alexander Jaschke, Annette Schürmann, Vincent Prévot, Ruijin Shao, John-Olov Jansson, and Karolina P. Skibicka
Proc Natl Acad Sci U S A. 2013 Oct 1;110(40):16199-204. doi: 10.1073/pnas.1306799110. Epub 2013 Sep 18

Paper 2. **Preproglucagon (PPG) neurons in the hindbrain have IL-6 Receptor α (IL-6Rα) and show Ca2+ influx in response to IL-6**
Fredrik Anesten, Marie K. Holt, Erik Schéle, Vilborg Pálsdóttir, Frank Reimann, Fiona M. Gribble,Cecilia Safari, Karolina P. Skibicka, Stefan Trapp, John-Olov Jansson
Manuscript

Paper 3. **GLP-1 Receptor Stimulation of the Lateral Parabrachial Nucleus Reduces Food Intake: Neuroanatomical, Electrophysiological, and Behavioral Evidence**
Jennifer E. Richard,* Imre Farkas,* Fredrik Anesten,* Rozita H. Anderberg, Suzanne L. Dickson, Fiona M. Gribble, Frank Reimann, John-Olov Jansson, Zsolt Liposits, and Karolina P. Skibicka
* J.E.R., I.F., and F.A. contributed equally to this work.
Endocrinology. 2014 Nov;155(11):4356-67. doi: 10.1210/en.2014-1248. Epub 2014 Aug 13.

Paper 4. **Functional interleukin-6 receptor-α is localized on tanycytes at the base of the third ventricle**
Fredrik Anesten, Tina Bake, Erik Schéle, Vilborg Pálsdóttir, Teodor Swedung-Wettervik, Björn Meister, Karolina P. Skibicka, Julian Mercer, John-Olov Jansson
Manuscript

GÖTEBORGS UNIVERSITET

IL-6 and GLP-1 in body fat regulating parts of the CNS in healthy mice

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Abstract

It has previously been shown that mice lacking interleukin-6 (IL-6) develop mature onset obesity. The weight-suppressing effects of IL-6 have been assumed to be exerted at a central level, as supported by the fact that ICV- injections, but not peripheral injections of IL-6, increases energy expenditure and decreases body fat in rodents.

Glucagon-like peptide-1 (GLP-1) is an incretin derived from the transcription product of the pro-glucagon gene. It is rapidly degraded by the enzyme dipeptidyl peptidase-4 (dpp-4) and has a very short half-life in serum. Consequently, to study the effects of GLP-1 on obesity and other metabolic parameters, GLP-1 analogues that are less easily degraded by dpp-4 with have been useful. One such analogue is Exendin-4 (Ex-4), first found in the saliva of the gila monster, a lizard. Ex4 has been used clinically as a treatment for diabetes type 2. In some patients Ex-4 and other long-acting GLP-1 analogues also promotes moderate weight loss, but the mechanisms for this action has been essentially unknown.

Tanycytes are specialized glial cells located mainly at the bottom of the third ventricle wall. They have processes that reach deep into the parenchyma of the hypothalamus, reaching into the ARN and the median eminence. These cells have been proposed to act as gatekeepers, regulating which substances that passes into the brain parenchyma and which that do not. It has recently been shown that tanycytes regulate the transport of leptin into the brain.

The aim of this thesis has been to investigate possible interactions between IL-6 and GLP-1 in the CNS. Using immunohistochemistry, we aimed to map the location of the IL-6 receptor-α (IL-6R α) in the brainstem as well as investigate its possible co-localization with GLP-1. Furthermore, we aimed to elucidate whether the weight-suppressing effects of Ex4 are dependent on IL-6. We also aimed to find out whether GLP-1 can act as an anti-obesity agent in the parabrachial nucleus (PBN). Finally, we sought to determine whether tanycytes express IL-6Rα, making them candidate cells for transport of IL-6 from cerebrospinal fluid further into the brain.

We found that IL-6 as well as interleukin-1 (IL-1) appears to act as downstream mediators of GLP-1 in the hypothalamus and brainstem. Aministration of blocking antibodies against the receptors of these cytokines lead to an attenuation of the effect of Ex4 on food intake and body weight. To expand upon these findings, we also show that the GLP-1 neurons present in the nucleus of the solitary tract (NTS) of the brainstem contain IL-6Rα. By using electrophysiology, we were able to show that this population of cells responds to IL-6 by and influx of Ca^{2+}.

Our studies of the PBN showed that direct GLP-1 receptor stimulation with Ex4 led to a decrease in food intake and body weight of rats. We also found that projections from GLP-1 neurons in the NTS reach cells in the PBN. A sizeable portion of these cells in the lateral PBN (lPBN) stain positively for calcitonin gene-related peptide (CGRP). In mice, studies have shown that stimulation of the CGRP neurons leads to a reduction in food intake. It is thus possible that GLP-1 and CGRP influence each other.

Finally, using immunohistochemistry we found that IL-6Rα is indeed present on tanycytes. This leads to a possible way for CSF-IL-6 to influence appetite-regulating centers in the brain, such as the arcuate nucleus.

Taken together, our findings show that IL-6 and GLP-1 influence each other in some of the important appetite-regulating centers of the brain.

Keywords: IL-6, IL-6Rα, GLP-1, obesity, hypothalamus, brainstem, tanycytes, immunohistochemistry

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