Body fat regulating neuropeptides: relation to interleukines and gut microbiota

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13 A, Göteborg, tisdagen den 5 juni 2012 kl 13.00

av
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Avhandlingen baseras på följande delarbeten:

Paper 1. **Interrelation between interleukin-1 (IL-1), IL-6 and body fat regulating circuits of the hypothalamic arcuate nucleus**
Erik Schéle, Anna Benrick, Louise Grahnemo, Emil Egecioglu, John-Olov Jansson
Manuscript

Paper 2. **Interleukin-6 gene knockout influences energy balance regulating peptides in the hypothalamic paraventricular and supraoptic nuclei**
Anna Benrick, Erik Schéle, Scarlett Pinnock,
Ingrid Wernstedt-Asterholm, Suzanne Dickson, Linda Karlsson-Lindahl,
John-Olov Jansson
Journal of Neuroendocrinology. 2009 Jul;21(7):620-8. Epub 2009 Apr 13.

Paper 3. **Interleukin-6 receptor α is co-localised with melanin-concentrating hormone in human and mouse hypothalamus**
Erik Schéle, Csaba Fekete, Péter Egri, Tamás Füzesi, Miklós Palkovits, Éva Keller,
Zsolt Liposits, Balázs Gereben, Linda Karlsson-Lindahl, Ruijin Shao, John-Olov Jansson
Journal of Neuroendocrinology. Epub 2012 Feb 1.

Paper 4. **The gut microbiota inhibits the expression of the obesity suppressing neuropeptides brain-derived neurotrophic factor (BDNF) and proglucagon in the hypothalamus and the brainstem**
Erik Schéle, Louise Grahnemo, Fredrik Anesten, Anna Hallén, Fredrik Bäckhed,
John-Olov Jansson
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Abstract

Previous studies have shown that mice lacking interleukin-6 (IL-6), an important cytokine in the immune system, develop obesity, and that central, but not peripheral, administration of IL-6 induces energy expenditure. These findings suggest that IL-6 suppresses fat mass through the central nervous system. The mechanism behind this, however, is not understood.

The aim of this thesis was to investigate possible neurobiological mechanisms, by which IL-6, during health, could exert its fat suppressing effect. Using immunohistochemistry, we aimed to map the distribution of the IL-6 receptor α (IL-6Rα) in human and mouse hypothalamus. In IL-6 knockout mice, we measured the gene expression of key hypothalamic neuropeptides known to regulate energy homeostasis.

In mice, IL-6Rα was present mainly on neurons, and was widely distributed throughout the hypothalamus. IL-6Rα was found in a large number of neurons in the fat suppressing arcuate nucleus (ARC) and paraventricular nucleus (PVN), as well as in the fat promoting lateral hypothalamic area (LHA). We also found the IL-6Rα to be co-localized with several energy balance regulating neuropeptides in these hypothalamic sites, for instance with orexin and melanin concentrating hormone (MCH) in the LHA. In humans, IL-6Rα was only found in MCH neurons, but virtually all MCH neurons contained IL-6Rα.

Depletion of IL-6 reduced the expression of the fat suppressing neuropeptides corticotrophin-releasing hormone (CRH) and oxytocin, as well as of arginine-vasopressin (AVP). In addition, we found IL-6Rα on neurons that produce these neuropeptides. This indicates that IL-6 could directly act on these neurons to increase the expression of CRH, oxytocin and AVP.

Depletion of IL-6 induced the expression of the fat suppressing cytokine IL-1. In addition, IL-6 expression was reduced in mice with IL-1 receptor 1 knockout. This indicates that, in the hypothalamus, IL-1 receptor 1 signaling increase IL-6 expression, while IL-6 decreases IL-1 expression.

Based on our findings in this thesis we speculate that IL-6 could act on several hypothalamic neurons and sites involved in energy homeostasis to increase energy expenditure and eventually weight loss in mice, while a similar effect could by exerted via the pro-obesity neuropeptide MCH in humans.

Previous studies show that gut microbiota contributes to obesity, in part by facilitating nutritional uptake, but probably also through other mechanisms. We aimed to investigate possible effects of gut microbiota on central energy balance regulation. We measured the gene expression of several important energy balance regulating neuropeptides in the hypothalamus and brainstem of germ free mice.

The fat suppressing neuropeptides glucagon-like peptide-1(GLP-1) and brain-derived neurotrophic factor (BDNF) was downregulated in the presence of gut microbiota, which could explain the elevated fat mass. In addition, we found that mice with gut microbiota were less sensitive to leptin, providing another mechanism by which gut microbiota could increase fat mass.

In conclution, our findings are in line the assumption that components of the immune system and the commensal gut microbiota can affect fat mass in part via energy balance-regulating circuits in the brain.

Keywords: IL-6, IL-6 receptor α, obesity, hypothalamus, brainstem, immunohistochemistry

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