Growth Hormone and Melanin-Concentrating Hormone receptor in the regulation of energy balance and metabolism

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Abstract
Energy homeostasis – the balance of energy intake, expenditure, and storage – is controlled by autonomic regulation originating in the hypothalamus and the brain stem, which receive input from the periphery. Upon receiving signals from the periphery, centres in the central nervous system (CNS) react through endocrine or neuronal responses to maintain a steady balance. Growth hormone (GH) and melanin-concentrating hormone (MCH) act in the CNS to influence the energy balance and may be connected to the peripheral signals ghrelin and leptin. The overall aim of this thesis was to investigate how these different hormonal systems interact.

To investigate the metabolic role of GH in the CNS, transgenic mice that overexpress bovine GH in the CNS (GFAP-bGH) were studied. GFAP-bGH mice have higher food intake and body weight and are obese compared with wild-type (WT) mice. Moreover, GFAP-bGH mice had hyperinsulinemia, pancreas islet hyperplasia, and dyslipidemia, but no changes in energy expenditure were observed. Thus, GH is an orexigenic signal in the CNS that leads to obesity and alters insulin and blood lipid profiles.

Mice deficient in the gene encoding GHr (GHr KO) were injected in the CNS with ghrelin to study whether the orexigenic signal from ghrelin is dependent on functional GH signalling. The stimulatory effect of ghrelin on food intake was blunted in GHr KO mice, which suggests that the effects of ghrelin on food intake involve the central GH/GHr system. Furthermore, GHr KO mice were growth retarded and obese with higher leptin and corticosterone levels, low insulin and glucose levels and altered circulating lipids. Functional GH signalling is thus required for normal carbohydrate metabolism and lipid biology.

The orexigenic neuropeptide MCH may also be involved in ghrelin-induced food intake and GH secretion. Food intake of mice that were deficient in the gene encoding MCHr (MCHr KO) and were injected in the CNS with ghrelin was similar to that of ghrelin injected WT mice, which suggests that MCHr is not required for the stimulating effect of ghrelin on food intake. But ghrelin had no effect on pituitary GH expression in MCHr KO mice, which suggests that MCHr is involved in ghrelin-mediated GH expression. Furthermore, MCHr is important for the acute effect of intracerebroventricular ghrelin on serum insulin but not on corticosterone levels. Thus, functional MCHr is required for the effects of ghrelin on GH expression and insulin secretion.

Since leptin and MCH act in common pathways in the hypothalamus to regulate energy balance, leptin-deficient MCHr KO (MCHr KO ob/ob) mice were studied to investigate the importance of MCHr on the phenotype of ob/ob mice. MCHr KO ob/ob mice were similar to ob/ob mice concerning body weight, food intake, hepatic steatosis, blood lipid profile, and energy expenditure. But normal glucose tolerance and markedly reduced insulin levels were observed in MCHr KO ob/ob mice, indicating improved insulin sensitivity. MCHr KO ob/ob mice had higher locomotor activity, improved core body temperature regulation, and reduced corticosterone levels. Thus, MCHr may be involved in direct or secondary signalling cascades that lead to changes in insulin sensitivity, locomotor activity, and blood serum parameters.

In conclusion, GH and MCHr play important roles in the CNS in regulating energy balance, including effects on food intake, body weight, obesity, and circulating endocrine signals.

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Avhandlingen baseras på följande delarbeten:

I **Growth hormone overexpression in the central nervous system results in hyperphagia-induced obesity associated with insulin resistance and dyslipidemia.**
Bohlooly-Y M, Olsson B, Bruder CEG, Lindén D, Sjögren K, Bjursell M, Egecioglu E, Svensson L, Brodin P, Waterton JC, Isaksson OGP, Sundler F, Ahrén B, Ohlsson C, Oscarsson J and Törnell J.
Diabetes, 2005 Jan; 54(1):51-62

II **Growth hormone receptor deficiency results in blunted ghrelin feeding response, obesity, and hypolipidemia in mice.**
Egecioglu E, Bjursell M, Ljungberg A, Dickson SL, Kopchick JJ, Bergstrom G, Svensson L, Oscarsson J, Törnell J and Bohlooly-Y M.
Am. J. Physiol. Endocrinol. Metab. 2006 Feb; 290(2):E317-25

III **Importance of melanin-concentrating hormone receptor for the acute effects of ghrelin.**
Bjursell M, Egecioglu E, Gerdin AK, Svensson L, Oscarsson J, Morgan D, Snaith M, Törnell J and Bohlooly-Y M.
Biochem. Biophys. Res. Commun. 2005 Jan 28;326(4):759-65

IV **Melanin-concentrating hormone receptor 1 deficiency increases insulin sensitivity in obese leptin-deficient mice without affecting body weight.**
Bjursell M, Gerdin AK, Ploj K, Svensson D, Svensson L, Oscarsson J, Snaith M, Törnell J and Bohlooly-Y M.
Diabetes, 2006 Mar;55(3):725-33