PROJECT REVIEW

"A Newly Discovered Growth Hormone Stimulating Peptide"

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Growth hormone secretagogues (GHS) are small synthetic molecules that stimulate the release of growth hormone (GH) from the pituitary. In 1996 the GHS-receptor was cloned', and in 1999 Kojima et al. discovered Ghrelin, the endogenous ligand of the GHS-receptor.
Ghrelin is a peptide hormone that is synthesized in the stomach. It strongly stimulates the production and release of GH from the pituitary, with only minor effects on other pituitary hormones. The regulation and physiological significance of ghrelin is only gradually being revealed. It appears, that the hormone plays a major role in the regulation of the growth hormone axis and in the central regulation of appetite, but so far data on plasma levels of ghrelin have only been reported in the original paper by Kojima[2].

The International Olympic Committee bans administration of GH by athletes to enhance performance, but there is currently no approved method of detection. Measurement of serum GH itself is of limited use because recombinant GH and endogenous GH have identical amino acid sequences, and therefore markers of GH action are being investigated as potential tests for GH abuse.
The rationale for the abuse of GH by athletes to enhance performance is that GH, at least in studies of GH-deficient adults, has been shown to reduce fat mass and to increase lean body mass, skeletal muscle mass, muscle force and aerobic performance. The abuse is limited by the high cost of recombinant GH and by the need of parenteral administration. However, in the near future relatively cheap growth hormone secretagogues for oral administration might become widely available, leading to a new type of indirect GH doping.

The assesment of circulating ghrelin is difficult due to the fragility of the molecule as well as to a high level of protein binding, and so far no generally accepted assay has been develloped. However, we have recently established collaboration with Dr. Kojima and his group on the measurements of ghrelin, and we have preliminary data indicating that circulating levels of ghrelin are strongly supressed by GH. **Thus measurements of plasma ghrelin may by a usefull tool in the detection of both direct and indirect GH doping.**
Our department has a longstanding tradition in development and optimization of hormone assays, and from our involvement in the IOC sponsored GH2000 project we have thorough know-how in conducting exercise related clinical trials.

Ghrelin - A newly discovered growth hormone stimulating peptide

Results and Conclusions

Ghrelin is the newly discovered endogenous ligand for the GH secretagogue receptor. Exogenous Ghrelin and its synthetic analogues are powerfull stimulators of GH release from the pituitary gland. In addition ghrelin also stimulates appetite and food intake. We hypothesised that administration of exogenous GH would suppress endogenous ghrelin levels in serum and that this could be used as a means to detect GH abuse in the future. Before such a paradigm translates into a feasible test several issues need to be scrutinised. We have reported that ghrelin levels depend on energy balance and is increased by weight loss (1). Surprisingly, ghrelin levels are unaltered during an acute exercise bout despite a concomintant increase in GH (2). Administration of GH in healthy subjects induces a moderate decline in ghrelin concentrations (3). In addition, our studies have uncovered new and complex associations between energy status and ghrelin secretion (3, 4, 5, 7, 8). More recently, a large study in fit non-elite athletes have documented that exercise is associated with a subsequent suppression of ghrelin secretion and the study also showed that GH administration lowered ghrelin in serum (presented as an abstract at the European Congress of Endocrinology 2005). Our studies are ongoing, but it remains a possible option that ghrelin measurements can be factored into a GH doping test.
Our studies are extremely well publicised; the first paper (1) has been cited 110 times in less than 3 years (effective impact factor 37 !), and the most recent publication has been selected as a hot topic by the journal in its forthcoming issue ("What's hot in European Journal of Endocrinology?") (8).

Publications

1. Hansen TK, Dall R, Hosoda H, Kojima M, Kangawa K, Christiansen JS, Jorgensen JO. Weight loss increases circulating levels of ghrelin in human obesity. Clin Endocrinol 2002;56:203-6
2. Dall R, Kanaley J, Hansen TK, Moller N, Christiansen JS, Hosoda H, Kangawa K, Jorgensen JO. Plasma ghrelin levels during exercise in healthy subjects and in growth hormone-deficient patients. Eur J Endocrinol 2002;147:65-70
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4. Riis AL, Hansen TK, Moller N, Weeke J, Jorgensen JO. Hyperthyroidism is associated with suppressed circulating ghrelin levels. J Clin Endocrinol Metab 2003;88:853-7
5. Djurhuus CB, Hansen TK, Gravholt C, Orskov L, Hosoda H, Kangawa K, Jorgensen JO, Holst JJ, Schmitz O. Circulating levels of ghrelin and GLP-1 are inversely related during glucose ingestion. Horm Metab Res 2002;34:411-3
6. Jorgensen JO, Krag M, Kanaley J, Moller J, Hansen TK, Moller N, Christiansen JS, Orskov H. Exercise, hormones, and body temperature. regulation and action of GH during exercise. J Endocrinol Invest 2003;26:838-42
7. Espelund U, Hansen TK, Hojlund K, Beck-Nielsen H, Clausen JT, Hansen BS, Orskov H, Jorgensen JO, Frystyk J. Fasting unmasks a strong inverse association between ghrelin and cortisol in serum: studies in obese and normal-weight subjects. J Clin Endocrinol Metab 2005;90:741-6
8. E T Vestergaard, T K Hansen, S Nielsen, N Møller, J S Christiansen and J O L Jorgensen. Effects of growth hormone replacement therapy in adults on serum levels of leptin and ghrelin: The role of lipolysis. European Journal of Endocrinology 2005;153:545-549

Abstracts

“Normalization of Insulin Sensitivity Through Pharmacological Antilipolysis Unmasks a Direct Suppressive Effect of GH on Circulating Ghrelin Levels”. Fifth International Symposium On GHS: Ghrelin And Its Analogues Across The Lifespan conducted in Portofino Vetta, Italia, 2004

“Normalization of Insulin Sensitivity Through Pharmacological Antilipolysis Unmasks a Direct Suppressive Effect of GH on Circulating Ghrelin Levels”. Second Joint Meeting of the GH and IGF Society. Cairns, Australia, 2004

“The Ghrelin Response to Exercise Before and After GH Administration”. European Congress of Endocrinology, Göteborg, Sweden 2005.