Clinical aspects of ghrelin

Pharmacokinetics and metabolic effects

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ABSTRACT

Ghrelin is a gastrointestinal peptide hormone. Peripheral ghrelin levels correlate inversely with body mass index (BMI). Administration of ghrelin induces appetite but ghrelin is also a potent growth hormone (GH) secretagogue. It has therefore been difficult to dissect direct peripheral effects from indirect GH-mediated effects. In view of the potential therapeutic applications of ghrelin the overall aim of this PhD study was to investigate clinical pharmacokinetics and acute metabolic effects of ghrelin in detail.

The PhD dissertation consists of three original papers based on three randomized, placebo-controlled cross-over clinical protocols comprising both healthy subjects and hypopituitary patients.

In the first protocol, acylated ghrelin was infused into healthy subjects. By measurements of ghrelin levels and pharmacokinetic modeling an extensive list of pharmacokinetic parameters was calculated and correlated with central parameters of individual characteristics. In addition, muscle biopsies were sampled to study pertinent ghrelin signaling pathways.

In the second protocol comprising healthy subjects receiving ghrelin and placebo infusion on two different occasions, the aim was to suppress the ghrelin-induced GH and cortisol secretion by concomitant somatostatin infusion in order to measure the direct effects of ghrelin on glucose and lipid metabolism. Insulin sensitivity was measured by a hyperinsulinemic euglycemic clamp and substrate metabolism was measured by tracer and microdialysis technique. The somatostatin study revealed a moderate but detectable GH and cortisol breakthrough.

To circumvent the effects of endogenous GH and cortisol on glucose and lipid metabolism, a third study comprising hypopituitary adults was performed. In this protocol we also used the pharmacokinetic parameters to calculate a ghrelin bolus dose to rapidly achieve steady state concentrations.

The pharmacokinetic results showed that ghrelin infusion followed a two-compartment model. The mean residence time of exogenous ghrelin correlated positively with both HDL cholesterol levels and BMI. The pharmacokinetic parameters are useful for designing future clinical ghrelin infusion studies. Concomitant somatostatin infusion attenuated ghrelin-induced GH secretion, but GH levels were significantly increased as compared to GH levels during placebo administration. In the third study it was demonstrated that ghrelin infusion per se caused insulin resistance and increments in levels of systemic glucose and FFA levels. These effects were not attributed to direct detectable effects on AMPK signaling. No aberrations in putative ghrelin signaling pathways were detected. In addition, our studies demonstrated that ghrelin-induced endogenous GH release translated into GH receptor signaling in skeletal muscle.