

UNACYLATED GHRELIN (UAG) ENHANCES THE EARLY INSULIN RESPONSE TO MEAL, IMPROVES GLUCOSE METABOLISM AND DECREASE FREE FATTY ACIDS LEVELS IN HEALTHY VOLUNTEERS



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Introduction

Ghrelin circulates in two different forms. Acylated ghrelin, a natural ligand of the GH Secretagogue receptor (GHS-R) type 1a, exerts several biological central and peripheral actions including stimulation of GH secretion, but also modulation of insulin secretion, glucose and lipid metabolism. Unacylated ghrelin (UAG), despite unable to bind the GHS-R1a, is biologically active showing some influence in vitro and in vivo on glucose and lipid metabolism likely mediated by still unknown receptors.

Based on these data, the aim of this study was to investigate the endocrine and metabolic effects of prolonged UAG administration in humans in physiological conditions.

Subjects and methods

We evaluated the effects of UAG (1.0 µg/Kg/h infused iv from 21.00 to 13.00 h) or saline in 8 healthy males (age mean±SEM:29.6±2.4yrs; BMI:22.4±1.7kg/m²) who had isocaloric balanced fixed meals at 21.20 and 09.00 h. Glucose, insulin, glucagon, free fatty acids (FFA), GH, and cortisol were measured every 20 minutes.

Results

UAG infusion significant modified the profile of all parameters, except glucagon. Compared to saline, UAG decreased FFA and glucose AUCs (p<0.01) [Fig. 1,2]. The FFA profile was reduced both post-prandially (p<0.01) and at fasting (p<0.01), while glucose decrease during UAG was particularly relevant at fasting during nighttime (p<0.01) [Fig. 1,2]. UAG did not modify total insulin AUC; however the early insulin response to both dinner (p<0.01) and breakfast (p<0.05) was enhanced by UAG [Fig.3]. During UAG, cortisol and GH AUCs were lower (p<0.01) than those during saline, but cortisol remained within physiological levels [Fig.4].

Conclusions

The intravenous infusion of UAG in normal subjects enhances the early insulin response to meals, improves glucose metabolism and insulin sensitivity, and inhibits lipolysis. Thus, UAG displays a remarkable metabolic impact suggesting a promising anti-diabetogenic action through an original mechanism of action.

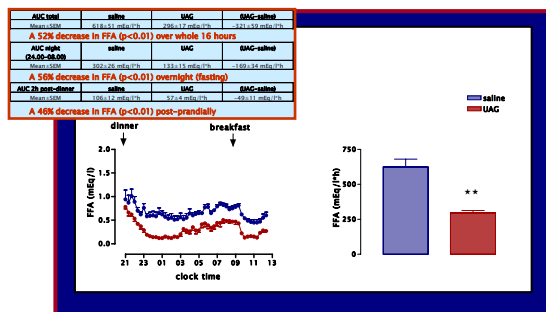


Fig. 1. FFA profile and AUC during SALINE or UAG infusion (from 21.00 to 13.00h) in healthy subjects

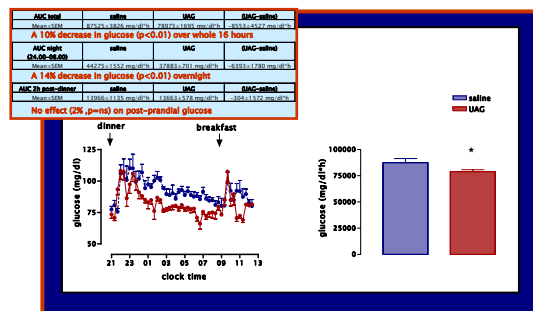


Fig. 2. Glucose profile and AUC during SALINE or UAG infusion (1.0 µg/Kg/h, from 21.00 to 13.00h) in healthy subjects

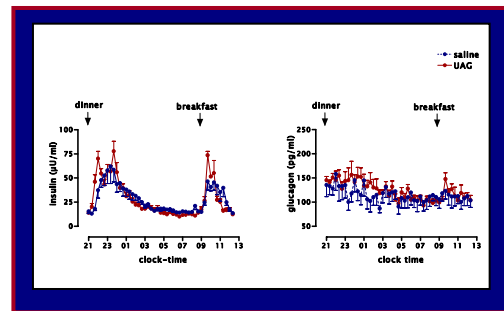


Fig. 3. Insulin and glucagon profile during SALINE or UAG infusion (1.0 µg/Kg/h, from 21.00 to 13.00h) in healthy subjects

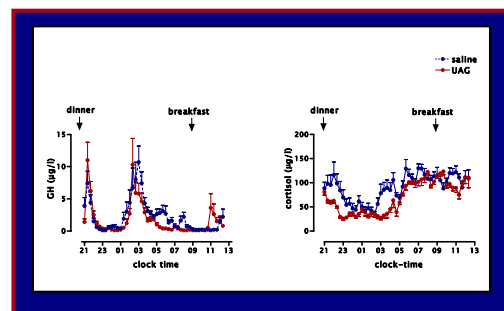


Fig. 4. GH and cortisol profile during SALINE or UAG infusion (1.0 µg/Kg/h, from 21.00 to 13.00h) in healthy subjects