EXAGGERATED AND ADDITIVE ACTH RESPONSES TO COMBINED ADMINISTRATION OF GHRELIN + CRH IN PATIENTS WITH CUSHING'S DISEASE

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INTRODUCTION

ACTH secretion is stimulated at hypothalamic level by CRH and vasopressin. Ghrelin, the gut-brain neuropeptide, is also able to stimulate hypothylamo-pituitary-adrenal axis. Over expression of ghrelin receptors on corticotroph adenoma cells can at least in part account for exaggerated ACTH and cortisol responses to ghrelin found in patients with Cushing's disease (CD).

We studied the role of ghrelin alone or in combination with CRH in the regulation of ACTH secretion in patients with CD and healthy subjects.

PATIENTS AND METHODS

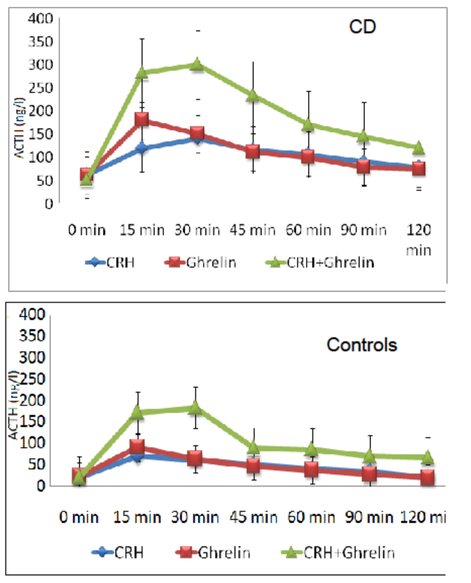
Table 1. Clinical characteristics of investigated subjects
(Values are presented as mean SEM)

Parameter	CD		Controls		p value
Number	21		8		
Age (yrs)	49.8	10.2	40.6	5.3	NS
Sex	18 F / 3 M		7 F / 1 M		
BMI (kg/m2)	29.8	0.8	29.9	1.2	NS
Micro/Macro	11 micro / 10 macro				

- CRH 100 µg iv bolus
- Acylated ghrelin 100 µg iv bolus
- CRH+ghrelin iv bolus
- Randome order, week apart
- ACTH, cortisol, PRL, GH responses at 0,15,30, 45, 60, 90, 120 min
- Peak and AUC responses were analyzed
- Clinical setting

Table 2. Protocol of investigation

RESULTS



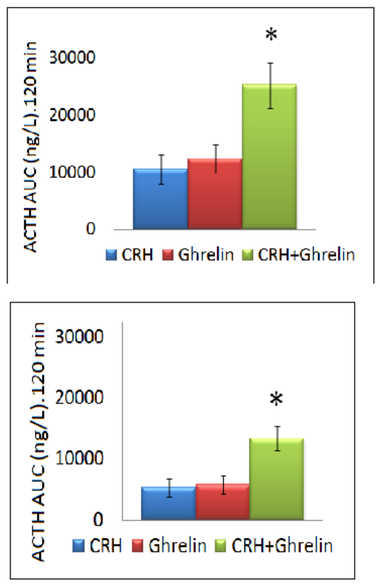


Fig.1. ACTH responses in patients with CD and controls. ACTH responses to ghrelin and CRH are exaggerated in CD patients compared to healthy controls. Mean values of peak and AUC ACTH responses to co-administration of ghrelin+CRH are additive in both groups, but higher in CD.

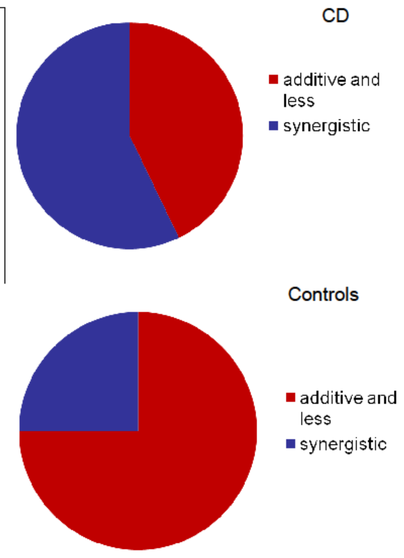
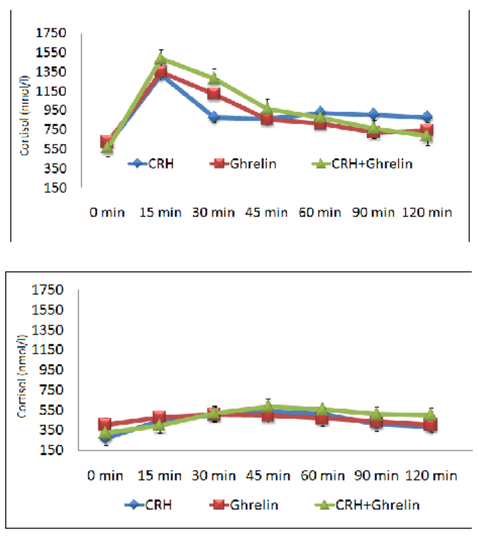
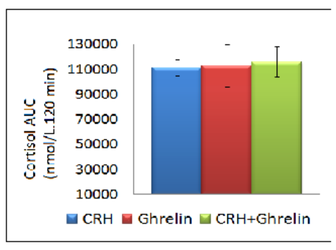


Fig.2. Individual patterns of ACTH responses to ghrelin+CRH in CD and controls. Synergism was more common in patients with CD.





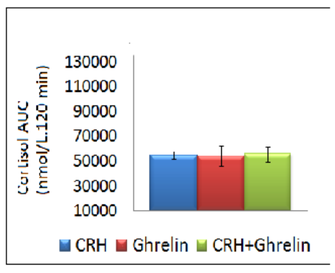


Fig.3. Cortisol responses in CD patients and controls.
Cortisol responses to ghrelin and CRH are exaggerated in CD patients compared to healthy controls, but not additive after ghrelin+CRH co-administration.

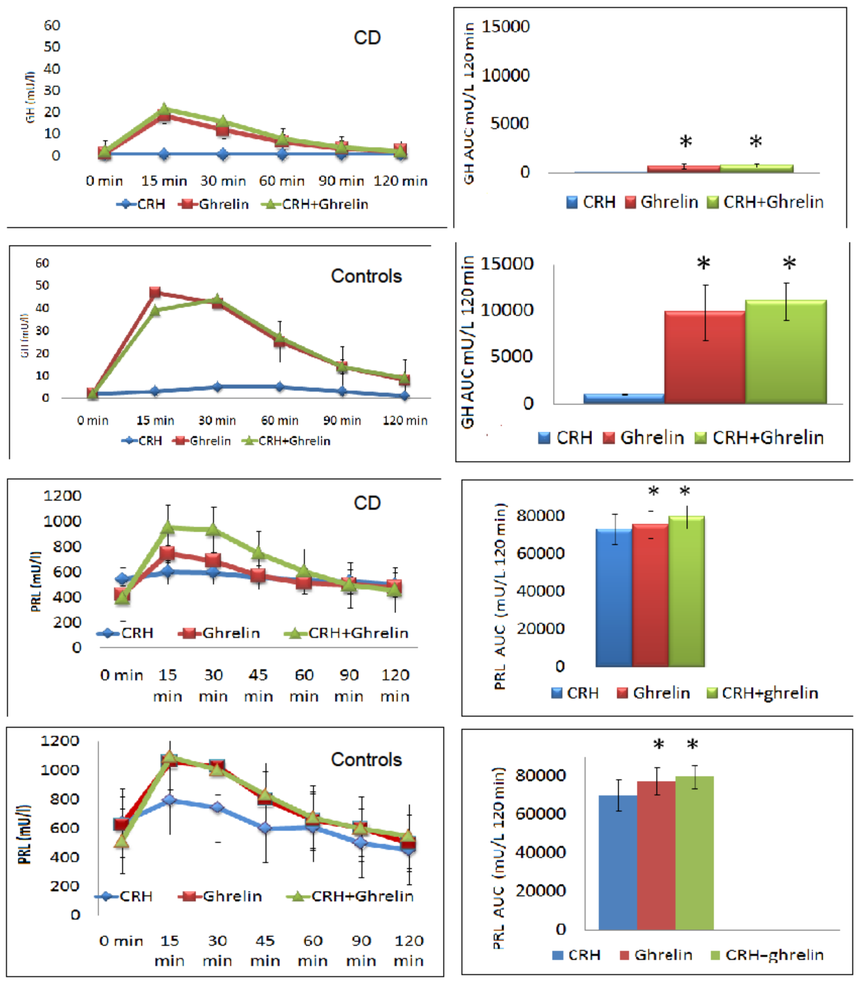


Fig. 4. GH responses in CD and controls.

GH responses to ghrelin are decreased in CD compared to control subjects

Fig. 5. PRL responses in CD and controls.

PRL responses to ghrelin are simillar in CD and control subjects.

CONCLUSION

ACTH and cortisol secretion remains regulated and responsive to trophic stimuli in patients with CD. Patterns of additive and synergistic ACTH responses after co-administration of CRH+ghrelin, suggest:

1) individual HPA axis tuning
2) combination of pituitary and hypothalamic mechanisms in the regulation of ACTH secretion in both health and CD.

17 ECE 4--GP-21
Pituitary basic and neuroendocrinology
Dragana Miljic
DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY