Towards a greater understanding of the pathophysiology of obesity: hypothalamic obesity as a model of dysregulation of appetite and metabolic homeostasis

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INTRODUCTION

- Hypothalamic obesity (HyOb) is a rare syndrome of intractable morbid obesity associated with congenital or acquired hypothalamic damage.
- It is commonly associated with the hypothalamic syndrome (panhypopituitarism, autism, sleep & temperature disturbances).
- Its pathophysiology has been attributed to hyperphagia and hyperinsulinaemia but is still poorly understood.
- To date, no successful treatments which have led to prolonged weight loss have been identified.
- We sought to compare the physiology of appetite-regulating hormones in HyOb versus "simple" obesity to identify novel therapeutic targets.

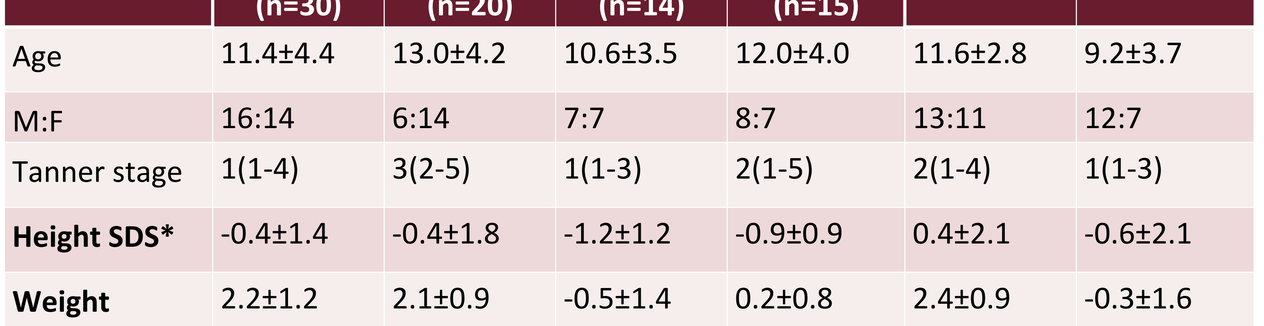
METHODS

- Multiway case-control study, 4 subcohorts:
  - Hypothalamic obese (HyOb, BMI >+2SDS) – congenital (SOD) vs. acquired (suprasellar tumour)
  - Hypothalamic lean (HyLean, BMI ≤+2SDS) – congenital vs. acquired
  - Common obese (Ob)
  - Lean controls (Lean)
- Independent variables: Age, height/ weight/ BMI SDS, Tanner stage, endocrine morbidity score (EMS)
- Dependent variables: Dykens' Hyperphagia Questionnaire Score (DHQS)[2], fasting concentrations of insulin, leptin, α-melanocyte-stimulating hormone (αMSH), oxytocin (OXT), brain derived neurotrophic factor (BDNF), acylated ghrelin, agouti-related peptide (AgRP) and copeptin
- Statistical analyses using SPSS v22 with normalised data

RESULTS

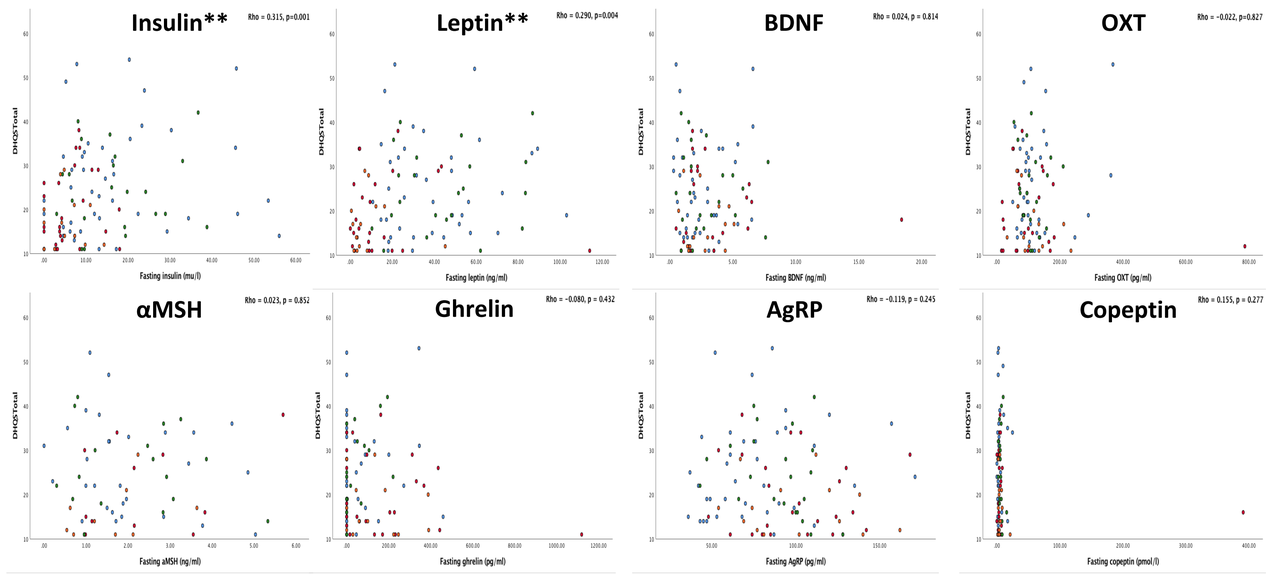
	HyOb		HyLean		Ob (n=24)	Lean (n=19)
	SOD (n=30)	Tumour (n=20)	SOD (n=14)	Tumour (n=15)		
Age	11.4±4.4	13.0±4.2	10.6±3.5	12.0±4.0	11.6±2.8	9.2±3.7
M:F	16:14	6:14	7:7	8:7	13:11	12:7
Tanner stage	1(1-4)	3(2-5)	1(1-3)	2(1-5)	2(1-4)	1(1-3)
Height SDS*	-0.4±1.4	-0.4±1.8	-1.2±1.2	-0.9±0.9	0.4±2.1	-0.6±2.1
Weight SDS***	2.2±1.2	2.1±0.9	-0.5±1.4	0.2±0.8	2.4±0.9	-0.3±1.6
BMI SDS***	2.9±0.8	2.6±0.4	0.1±1.7	0.9±0.8	2.8±0.5	0.1±1.5
Autism*	12 (42.9%)	1 (5.0%)	9 (64.3%)	1 (6.7%)	1 (4.2%)	1 (5.3%)
Learning difficulty***	20 (66.7%)	10 (50.0%)	11 (78.6%)	5 (33.3%)	4 (16.7%)	4 (21.1%)
Sleep problems**	16 (53.3%)	5 (25.0%)	8 (57.1%)	3 (20.0%)	2 (8.3%)	1 (5.3%)
Temperature disturbance	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (4.2%)	2 (10.5%)
EMS***	3 (3-4)	3 (2-5)	3 (1-3)	2 (0-4)	0 (0-2)	0 (0-2)

- **Hyperphagia is not unique to HyOb and is correlated with BMI SDS**



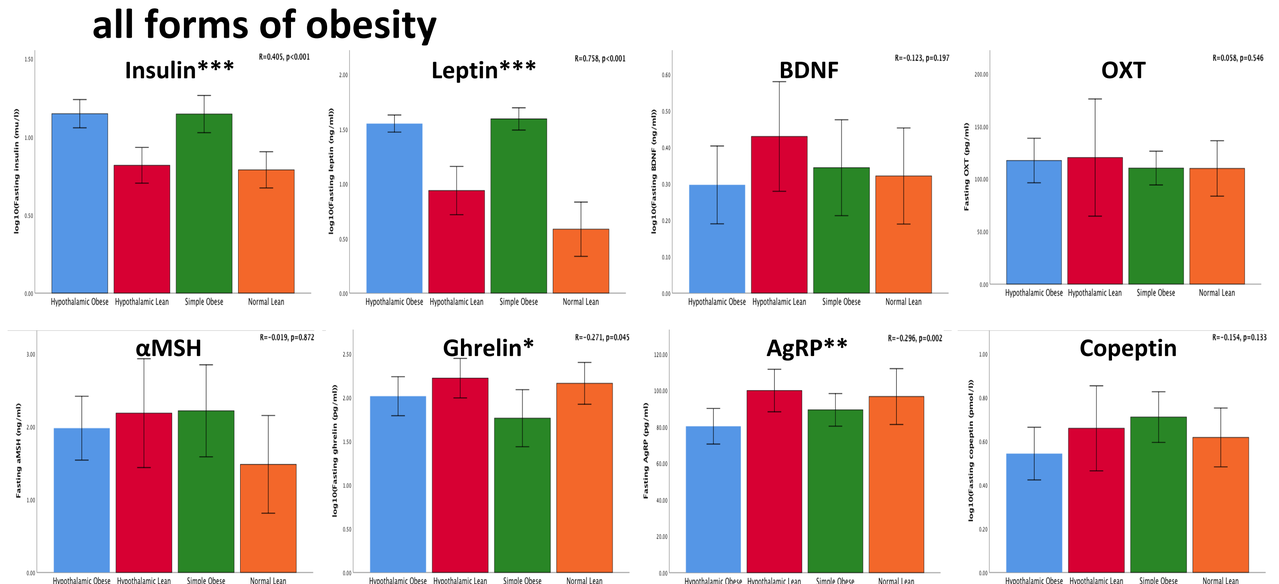
**p<0.05, **p<0.01, ***p<0.001* HyOb HyLean Ob Lean

- **Hyperphagia is associated with a compensatory increase in peripheral (insulin, leptin) anorexigens**



**p<0.05, **p<0.01, ***p<0.001* HyOb HyLean Ob Lean

- **Peripheral anorexigens (insulin, leptin) are increased, whilst peripheral (ghrelin) and central (AgRP) orexigens are suppressed in all forms of obesity**



**p<0.05, **p<0.01, ***p<0.001* HyOb HyLean Ob Lean

- **Lower αMSH and ghrelin concentrations are independently associated with a greater rate of BMI SDS gain at 1 year**

Parameter	Univariate β (95% CI)	Multivariate β (95% CI)
Age at testing (years)	-0.048 (-0.086--0.010)	**-0.086 (-0.168--0.005)***
Height SDS at testing	0.011 (-0.074-0.097)	-0.038 (-0.145-0.069)
BMI SDS at testing	**-0.233 (-0.339-0.127)*****	-0.107 (-0.294-0.081)
Tanner stage at testing	-0.083 (-0.186-0.020)	0.091 (-0.103-0.285)
Total DHQS	-0.009 (-0.023-0.004)	-0.010 (-0.028-0.008)
Insulin (mU/l)	-0.011 (-0.023-0.001)	-0.003 (-0.019-0.013)
Leptin (ng/ml)	-0.004 (-0.010-0.002)	0.005 (-0.003-0.014)
BDNF (ng/ml)	0.026 (-0.058-0.110)	0.022 (-0.076-0.120)
αMSH (ng/ml)	**-0.140 (-0.263--0.018)***	**-0.171 (-0.302--0.040)***
OXT (pg/ml)	-0.001 (-0.004-0.002)	-0.002 (-0.005-0.001)
Ghrelin (pg/ml)	-0.001 (-0.003-0.000)	**-0.003 (-0.006--0.001)****
AgRP (pg/ml)	0.003 (-0.003-0.008)	-0.002 (-0.004-0.009)
Copeptin (pmol/l)	-0.013 (-0.047-0.022)	-0.016 (-0.055-0.022)

CONCLUSIONS

- There is no difference in appetite-regulating hormone concentrations or the degree of hyperphagia in HyOb versus simple obesity, with peripheral anorexigens being increased and peripheral and central orexigens being suppressed.
- Higher αMSH concentrations at baseline seem protective against future rapid weight gain, and requires further investigation.
- HyLean patients seem to exhibit intermediary metabolism, but the risk of HyOb remains high (20% at 1 year).

References: 1. *et al.* J Clin Endocrinol Metab 2003; 88:2586-92. 2. Dykens EM *et al.* Obesity (Silver Spring) 2007; 15:1816-2Lustig RH 6.

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