Hypothalamic obesity, Hyperphagia & Hyperinsulinaemia: time for a paradigm shift in assumptions?

Hoong-Wei Gan[a,b], Clare Leeson[c], Helen Aitkenhead[c], Helen Spoudeas[b], Mehul Dattani[a,b]

Great Ormond Street Hospital for Children NHS Trust

[a]Genetics & Genomic Medicine Programme, UCL Institute of Child Health, UK | [b]The London Centre for Paediatric Endocrinology & Diabetes, Great Ormond Street Hospital for Children NHS Foundation Trust, UK | [c]Department of Chemical Pathology, Great Ormond Street Hospital for Children NHS Foundation Trust

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Background

- Hypothalamic obesity (HyOb) is a syndrome of inexorable, treatment-resistant, morbid obesity seen after congenital (e.g. septo-optic dysplasia (SOD)) and acquired (e.g. suprasellar tumours) hypothalamic damage.
- HyOb is commonly associated with other features of the hypothalamic syndrome (panhypopituitarism, autism, sleep disturbances, temperature dysregulation).
- Its pathophysiology is poorly understood but often attributed to hyperphagia and increased caloric intake.
- Unclear whether hyperinsulinaemia is the cause or effect in HyOb.
- Objectives
  - To determine the frequency of hyperphagia in HyOb in comparison to simple obesity
  - To examine the associations between hyperphagia and hyperinsulinaemia in HyOb and simple obese patients

Methods

- Multi-way case-control study of four subcohorts:
  - Hypothalamic obese (HyOb, BMI > +2 SDS) – congenital (SOD) vs. acquired (suprasellar tumour)
  - Hypothalamic lean (HyLean, BMI ≤ +2 SDS) – congenital (SOD) vs. acquired (suprasellar tumour)
  - Simple obese
  - Lean controls
- Dependent variables: Dykens' Hyperphagia Questionnaire Scores (DHQS), fasting and 2-hour oral glucose tolerance test (OGTT)-stimulated glucose and insulin indices
- Statistical analyses (SPSS v 22): Non-parametric Mann Whitney-U, Kruskal Wallis one-way ANOVA and χ^2 tests

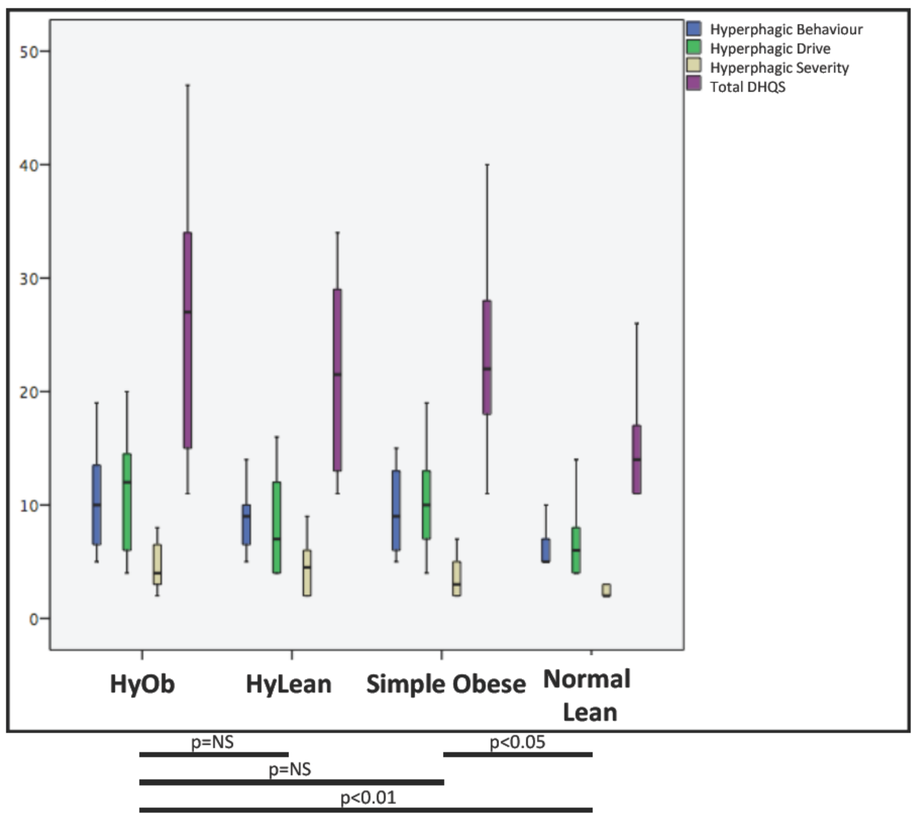
Results

- Baseline characteristics

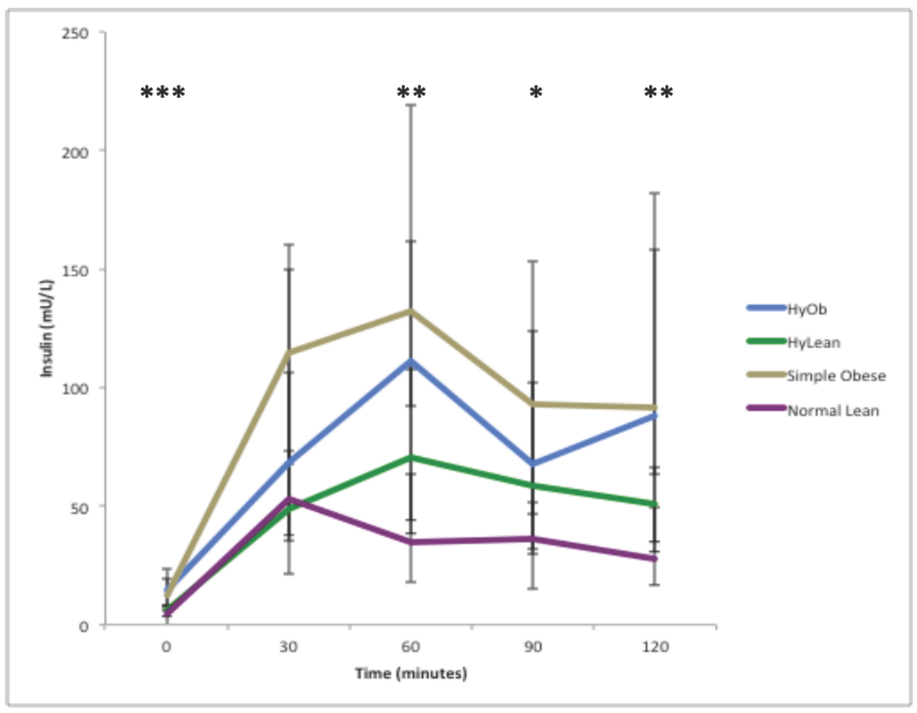
	HyOb		HyLean		Simple obese (20)	Lean control (14)
	SOD (14)	Tumour (17)	SOD (13)	Tumour (3)		
Age**	14.5 (10.2-16.3)	14.2 (9.1-18.0)	11.7 (7.3-12.3)	14.5 (8.1-14.5)	11.7 (8.9-13.8)	10.0 (6.1-12.8)
Female	6 (42.9%)	12 (70.6%)	7 (53.8%)	2 (66.7%)	10 (50.0%)	3 (21.4%)
Tanner stage*	2 (1-4)	3 (2-5)	1 (1-3)	1 (1-2)	2 (1-3)	1 (1-3)
Height SDS	-0.4 (-0.9-0.8)	-0.9 (-1.9-1.5)	-1.8 (-2.0--0.9)	-0.9 (-2.6--0.4)	0.8 (-1.2-1.1)	-1.0 (-2.4-2.0)
Weight SDS***	2.2 (1.9-2.7)	1.8 (1.4-2.6)	0.0 (-1.0-0.5)	0.9 (-1.1-1.3)	2.5 (1.6-3.5)	0.0 (-1.3-1.1)
BMI SDS***	2.8 (2.6-3.2)	2.6 (2.4-3.0)	1.0 (0.6-1.8)	1.6 (0.7-1.9)	2.8 (2.4-3.2)	0.3 (-1.0-1.3)
	NS		NS			

*p<0.05, **p<0.01, ***p<0.001

- **Hyperphagia is not unique to hypothalamic obesity**



- **Hyperinsulinaemia is not more severe in hypothalamic obesity compared to simple obesity**



	HyOb	HyLean	Simple Obese	Normal Lean
HOMA-IR***	2.8 (1.3-4.9)	1.1 (0.6-1.6)	2.5 (1.4-4.0)	0.8 (0.0-1.0)
Matsuda-ISI***	3.6 (1.8-4.9)	6.3 (4.0-11.8)	3.1 (2.0-4.9)	8.7 (6.8-58.8)
AUC/BMI	3.5 (2.6-6.6)	3.5 (2.2-5.1)	4.3 (3.4-6.0)	2.4 (1.1-3.4)

**p<0.05, **p<0.01, **p<0.001*

- Fasting insulin, HOMA-IR and Matsuda-ISI positively correlated with DHQS and subscores (all p<0.05) but not when corrected for BMI
- Autism (p<0.05), learning difficulties (p<0.05) and sleep disturbances (p<0.01) associated with hypothalamic damage but not HyOb
- 6 (11.8%) and 1 (2.0%) of 51 obese patients had impaired glucose tolerance (IGT) and frank type 2 diabetes respectively

Conclusions

- Hyperphagia not unique to HyOb and present in simple obesity
- Hyperinsulinaemia is a function of BMI and therefore unlikely to be primary driver of weight gain in HyOb
- The significant prevalence of IGT and type 2 diabetes in all obese children may indicate need for routine screening

References 1. Lustig RH *et al.* J Clin Endocrinol Metab 2003; 88:2586-92. 2. Dykens EM *et al.* Obesity (Silver Spring) 2007; 15:1816-26. 3. Matsuda M *et al.* Diab Care 1999; 22:1462-70.

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Hoong-Wei Gan

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