

# Oxytocin deficiency is associated with hyperphagia & weight gain in hypothalamic & common obesity: a first-in-humans proof-of-concept study

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## INTRODUCTION

- Hypothalamic obesity (HyOb) is a syndrome of intractable morbid obesity seen in congenital (e.g. septo-optic dysplasia (SOD)) and acquired (e.g. suprasellar tumours) hypothalamic damage.
- It is commonly associated with the hypothalamic syndrome (panhypopituitarism, autism, sleep & temperature disturbances).
- Its pathophysiology has been attributed to hyperphagia and hyperinsulinaemia.
- More recently the wider role of oxytocin (OXT) in regulating appetite and weight has emerged from animal studies and pilot trials of intranasal OXT in humans with common obesity.
- We aimed to determine if hypooxytocinaemia and hyperinsulinaemia were more prevalent in HyOb compared to common obesity and to examine the relationship between OXT concentrations, appetite and weight.

## 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, sex, height/ weight/ BMI SDS, Tanner stage, endocrine morbidity score (EMS), frequency of hypothalamic syndrome features (autism, temperature dysregulation, sleep disturbances)
- Dependent variables:** Dykens' Hyperphagia Questionnaire Score (DHQS), fasting and 2-hour oral glucose tolerance test-stimulated Insulin and OXT concentrations using internally validated ELISA
- Statistical analyses using SPSS v22

## RESULTS

	HyOb		HyLean		Common Obese (n=21)	Lean controls (n=15)
	SOD (n=25)	Tumour (n=17)	SOD (n=11)	Tumour (n=4)		
Age	12.9 (8.9-14.9)	14.2 (9.1-18.0)	10.2 (7.3-12.3)	14.1 (10.9-14.5)	11.5 (9.1-13.8)	10.3 (6.1-13.3)
Female	11 (44%)	12 (71%)	6 (55%)	2 (50%)	9 (43%)	4 (27%)
Tanner stage	2 (1-4)	3 (2-5)	1 (1-3)	2 (1-3)	2 (1-4)	1 (1-3)
Height SDS	-0.4 (-1.2-0.8)	-0.9 (-1.8-1.0)	-1.8 (-2.0--0.9)	-0.7 (-1.8--0.4)	0.4 (-1.2-1.1)	0.0 (-2.4-1.7)
Weight SDS***	2.2 (1.5-2.7)	2.0 (1.4-2.8)	0.0 (-1.0-0.5)	1.0 (-0.1-1.2)	2.3 (1.6-3.1)	0.8 (-0.9-1.5)
BMI SDS***	2.8 (2.4-3.2)	2.6 (2.4-2.9)	1.0 (0.6-1.8)	1.7 (1.1-1.8)	2.7 (2.4-3.2)	0.8 (-0.8-1.7)
Autism***	7 (36.8%)	1 (6.3%)	5 (55.6%)	0 (0.0%)	1 (5.0%)	0 (0.0%)
Learning difficulty***	15 (71.4%)	8 (50.0%)	1 (11.1%)	4 (100.0%)	16 (80.0%)	12 (80.0%)
Sleep problems***	9 (42.9%)	4 (25.0%)	7 (70.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)
Temperature dysregulation	0 (0.0%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	1 (6.7%)

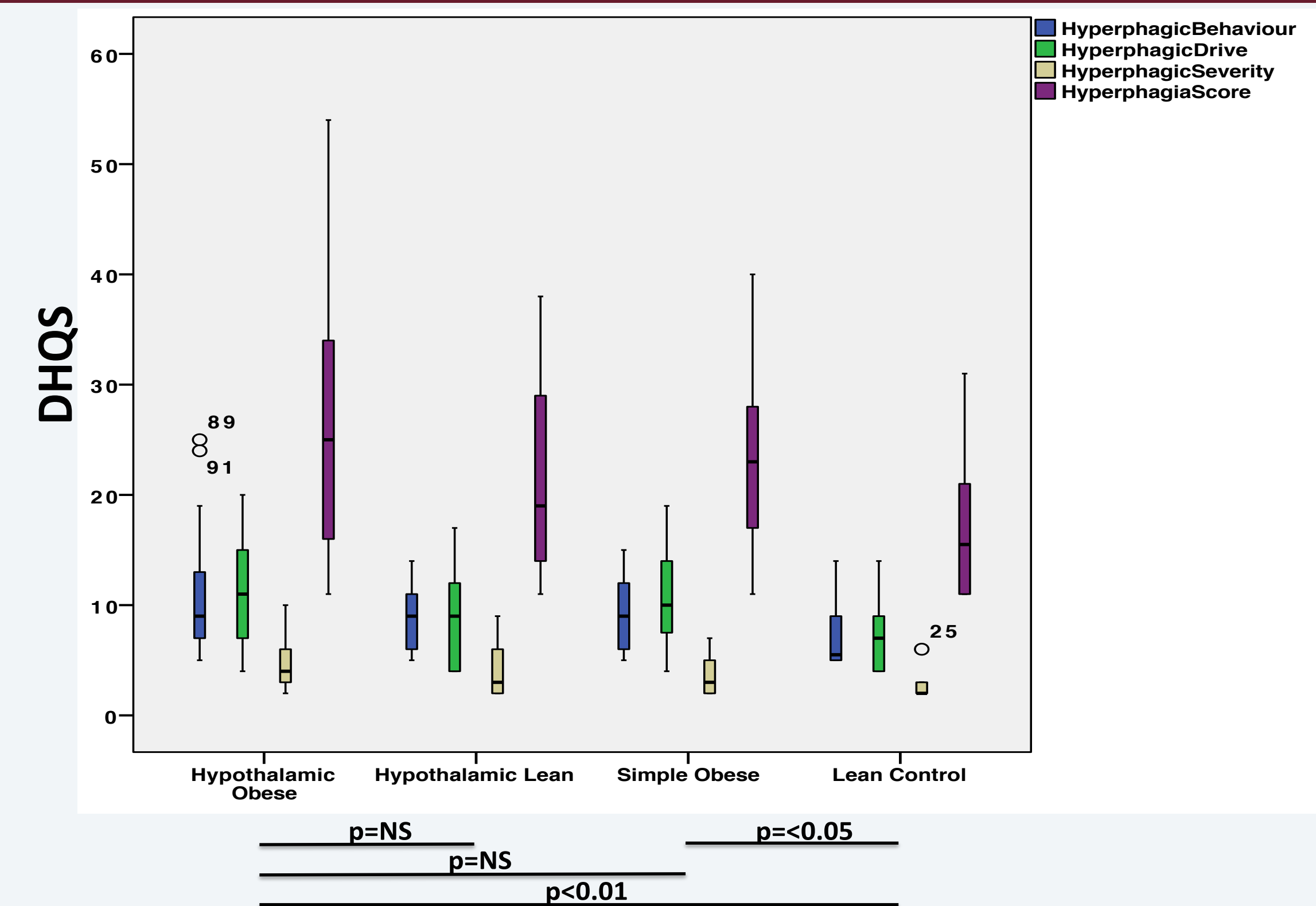
\*\*\*p<0.001

## CONCLUSIONS

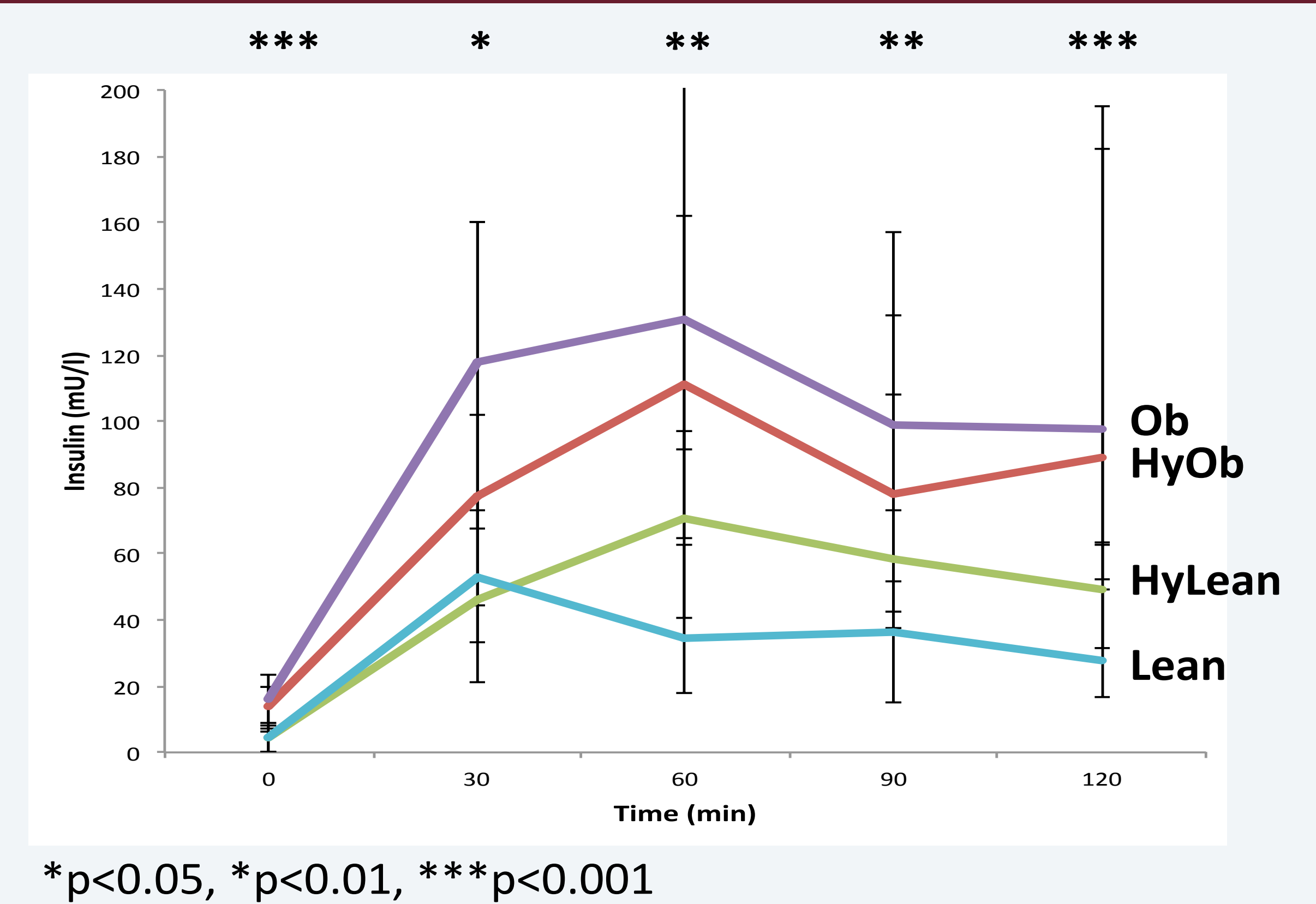
- Hyperphagia and hyperinsulinaemia are common to both HyOb and common obesity, and therefore unlikely to be primary drivers of HyOb.
- First-in-humans study supporting the role of OXT as an anorexigen with additional possible effects on weight & BMI.
- No correlation between OXT concentrations and other features of the hypothalamic syndrome or diabetes insipidus
- 6.5% had impaired glucose tolerance and 1 patient (1.1%) had frank type 2 diabetes.
- Further recruitment needed to power study sufficiently, with possible need for OXT trials in HyOb and common obesity.

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. Deblon *et al.* PLoS ONE 2011; 6:e25565. 4. Lawson EA *et al.* Obesity (Silver Spring) 2015; 23:950-6.

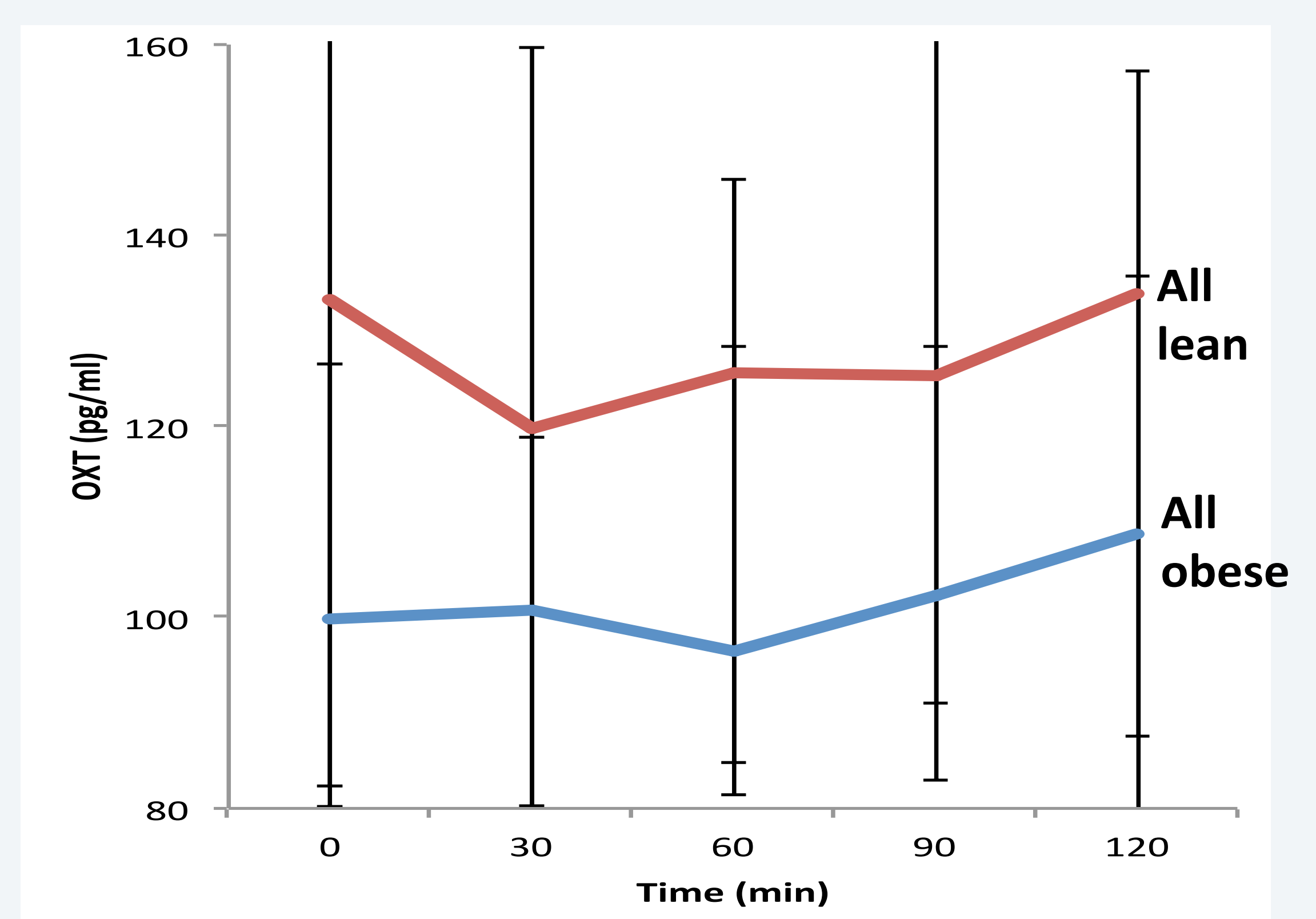
## Hyperphagia is not unique to HyOb



## Hyperinsulinaemia is not more severe in HyOb



## OXT is decreased in all forms of obesity



## OXT is associated with an increased appetite

