

# Olanzapine-induced weight gain is associated with increased hypothalamic ghrelin receptor (GHS-R1a) expression

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### Introduction

Atypical antipsychotics display increased efficacy and reduced side-effects in the treatment of schizophrenia compared to typical antipsychotics. However, they are also associated with marked metabolic adverse effects [1]. Weight gain is the most commonly reported side effects of atypical antipsychotic drugs, with clozapine and olanzapine having the highest risk of weight gain resulting in increased non-compliance in patients. Leptin and ghrelin are peptides which play key roles in the regulation of energy balance and both are affected by chronic olanzapine treatment. This study aims to investigate central expression of the growth hormone secretagogue receptor (GHS-R1a) [2] following chronic olanzapine treatment in rats as well as circulating levels of ghrelin and leptin.

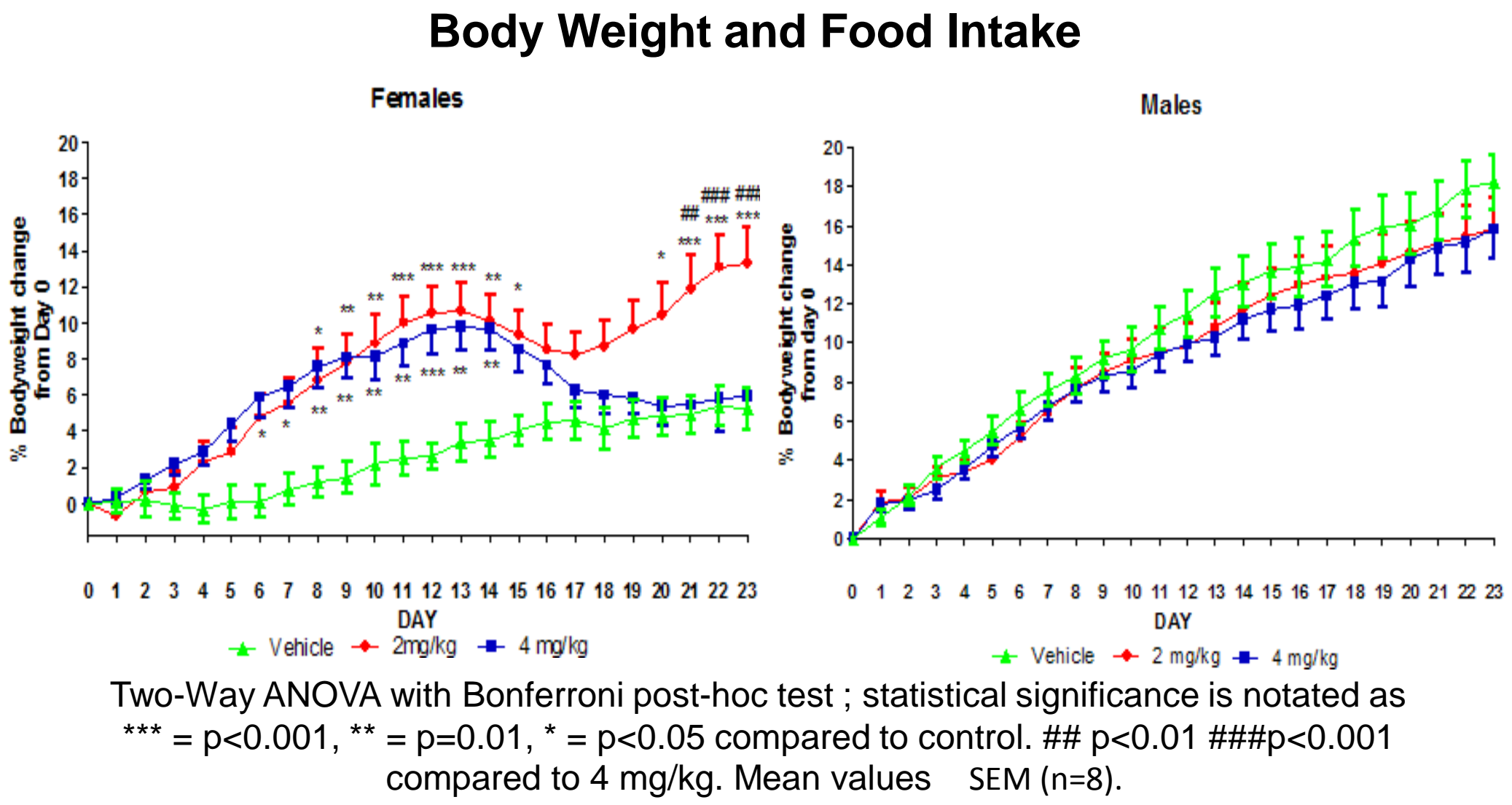
### Methods

Female and male Sprague-Dawley rats were injected twice daily with two doses of olanzapine (2mg/kg and 4mg/kg) or vehicle (acidified dH<sub>2</sub>O; ph adjusted to 6 with NaOH) for 3 weeks. Food intake and body weight were monitored and circulating leptin levels were determined using commercially available radioimmunoassays. Fat deposits, gonadal fat (epididymal for male/uterine for females), the mesenteric and the subcutaneous fat deposits were carefully excised and weighed (within 0.1mg). In addition, mRNA expression of the GHS-R1a receptor in the hypothalamus was analysed using quantitative real-time PCR.

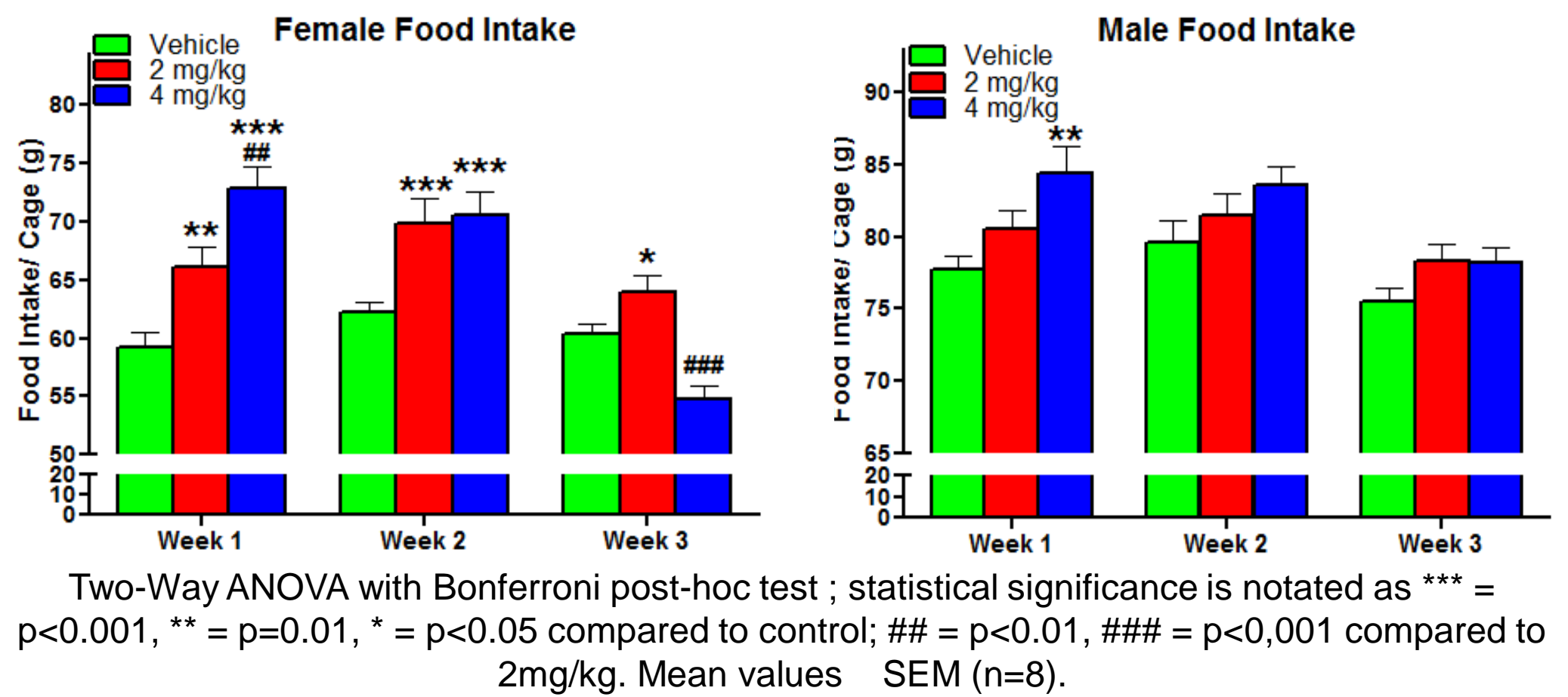
### Aim

This study aims to examine the hypothalamic mRNA expression of the GHS-R1a receptor after chronic olanzapine treatment and the potential correlation with olanzapine-induced body weight gain.

### Results

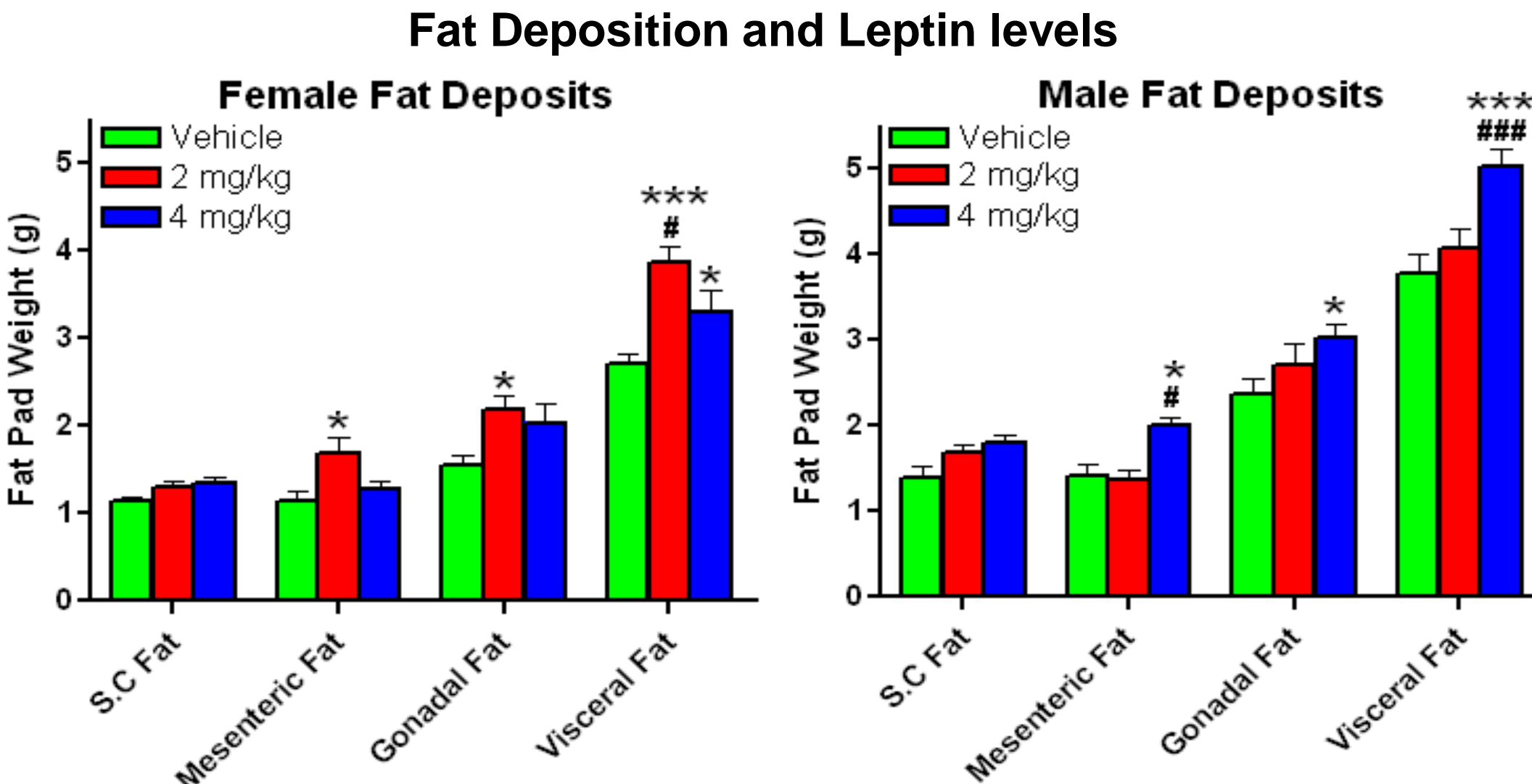


➤ Olanzapine ↑ weight gain in female rats only, which is a consistent finding in pre-clinical models.

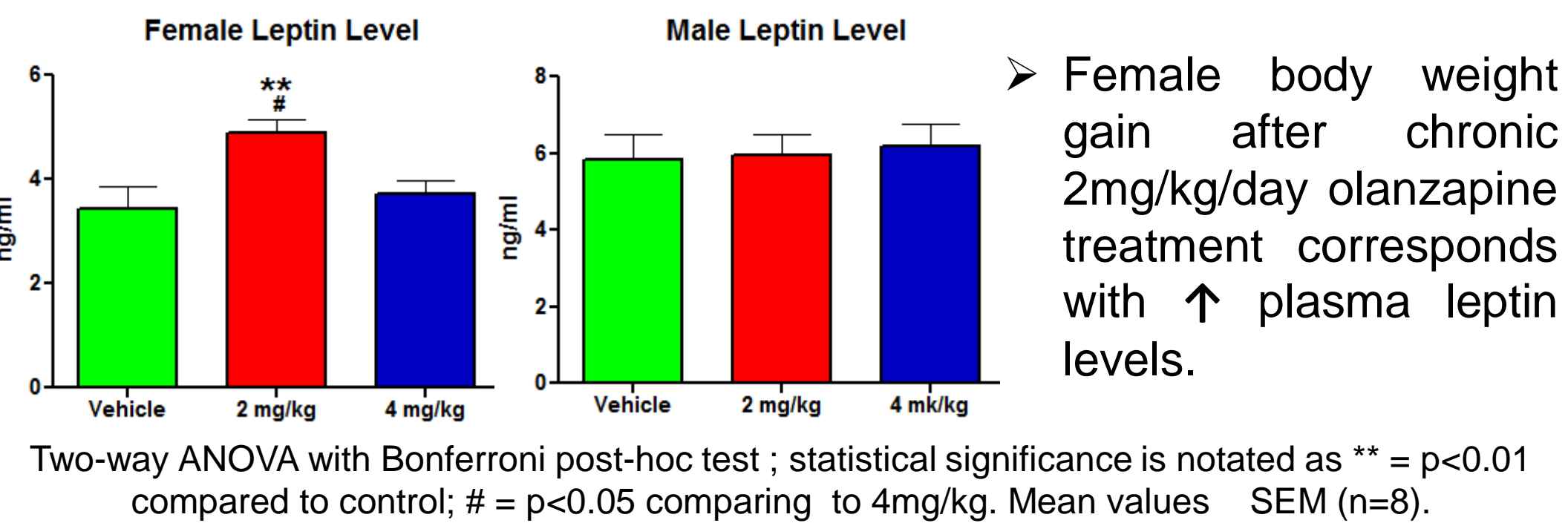


➤ Olanzapine-induced modulation of food intake correlates with body weight gain in female Sprague-Dawley rats.

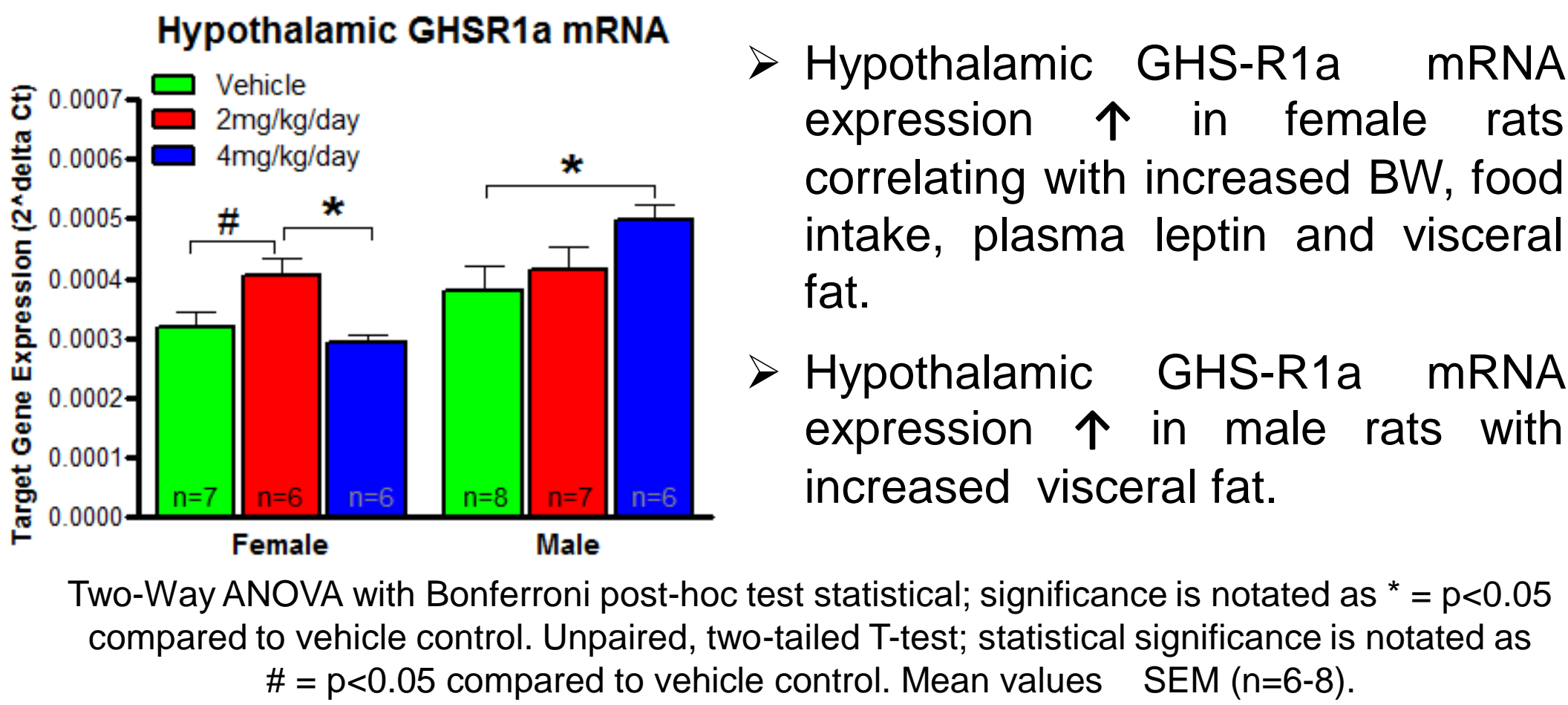
### Results



➤ Chronic olanzapine treatment ↑ visceral fat deposits in both female and male Sprague-Dawley rats.



### GHS-R1a Receptor mRNA Expression



➤ No difference in ghrelin mRNA levels in other brain regions assessed (data not shown).

### Conclusion

- Olanzapine-induced BW ↑ correlates with increased food intake, fat deposition and plasma leptin levels in female Sprague-Dawley rats.
- Enhanced adiposity does not correlate with body weight gain and food intake in male rats chronically treated with olanzapine .
- Hypothalamic GHS-R1a receptor significantly ↑ in female rats after chronic treatment with 2mg/kg olanzapine and in male rats with 4mg/kg olanzapine.
- Enhanced adiposity in the absence of antipsychotic-induced weight gain and hyperphagia may potentially involve a GHS-R1a receptor mediated effect on adipocyte function.
- To our knowledge this is the first time that chronic olanzapine treatment is linked to central GHS-R1a expression and this may underlie the molecular mechanism by which chronic olanzapine enhances fat deposition and induces weight gain.

### Acknowledgements

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### References

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