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Katrina Weston-Green

University of Wollongong, kweston@uow.edu.au

Xu-Feng Huang

University of Wollongong, xhuang@uow.edu.au

Chao Deng

University of Wollongong, chao@uow.edu.au

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Recommended Citation

Weston-Green, Katrina; Huang, Xu-Feng; and Deng, Chao, "Sensitivity of the female rat to olanzapine-induced weight gain - far from the clinic?" (2010). *Faculty of Science, Medicine and Health - Papers: part A*. 1390.

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Sensitivity of the female rat to olanzapine-induced weight gain - far from the clinic?

Abstract

Dear Editor, The recent paper by Chintoh and colleagues (2008) reporting olanzapine-induced dysfunction in glucose metabolism, enhanced visceral fat and reduced locomotor activity in female rats was highly interesting as it illustrated olanzapine's ability to replicate aspects of metabolic dysfunction in the rodent model in a similar manner to the human scenario. However, contrary to previous reports in the rat and the clinic, the authors reported no change in body weight or food intake following olanzapine treatment, questioning the validity of the rat model.....

Keywords

CMMB

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

Weston-Green, K., Huang, X. & Deng, C. (2010). Sensitivity of the female rat to olanzapine-induced weight gain - far from the clinic?. *Schizophrenia Research*, 116 (2-3), 299-300.

Letter to the editor:

Sensitivity of the Female Rat to Olanzapine-Induced Weight Gain – Far From the Clinic?

Authors: Katrina Weston-Green^{1,2}, Xu-Feng Huang^{1,2}, Chao Deng^{1,2,*}

1: Centre for Translational Neuroscience, School of Health Sciences, University of Wollongong, Wollongong, 2522, NSW, Australia

2: Schizophrenia Research Institute, 384 Victoria Street, Darlinghurst, 2010, NSW, Australia

*** Corresponding author:**

Dr Chao Deng, School of Health Sciences, University of Wollongong, Wollongong, 2522, NSW, Australia

E-mail: chao@uow.edu.au, Tel: (+61 2) 4221 4934, Fax: (+61 2) 4221 4096

Dear Editor,

The recent paper by Chintoh and colleagues (2008) reporting olanzapine-induced dysfunction in glucose metabolism, enhanced visceral fat and reduced locomotor activity in female rats was highly interesting as it illustrated olanzapine's ability to replicate aspects of metabolic dysfunction in the rodent model in a similar manner to the human scenario. However, contrary to previous reports in the rat and the clinic, the authors reported no change in body weight or food intake following olanzapine treatment, questioning the validity of the rat model. For the past decade scientists have worked to establish a rodent model that mimics the side-effect of metabolic dysfunction induced by some atypical antipsychotic drugs in the clinic, and some important experimental considerations have surfaced as a result. In particular, the issue of animal gender identified in previous animal model studies of olanzapine-induced weight gain (Minet-Ringuet et al., 2006; Pouzet et al., 2003) shadows the legitimacy of the rodent model in

its ability to mimic the human scenario. Indeed, reports indicate that male rats are less sensitive to olanzapine-induced weight gain than females. For example, contrary to female rats, male Sprague Dawley, Wistar and Mol:Wistar Hannover rats treated with olanzapine at a dosage range of 1 – 20mg/kg/day failed to exhibit increased food intake or weight gain (Albaugh et al., 2006; Pouzet et al., 2003). However, Minet-Ringuet et al. (2006) found that olanzapine (1mg/kg) treatment for 6-weeks increased adiposity and circulating leptin levels in male rats, indicating that olanzapine's enhancement of adiposity and leptin can be replicated in the rat model for both sexes.

Based on clinical data, we suggest that the rodent model of olanzapine-induced weight gain mimics aspects of the human situation as studies have revealed gender-related differences in the human response to olanzapine treatment. Evidence shows that females with psychotic disorder have a 3.6-fold increased risk of weight gain than males (Hakko et al., 2006) and previous studies have identified female gender as a risk factor and predictor for weight gain associated with olanzapine and other atypical antipsychotics (Gebhardt et al., 2009). In fact, Wu and colleagues (2007) reported that female first-episode schizophrenia patients had a higher hip to waist ratio, increased insulin-resistance and higher plasma triglycerides than males following treatment with olanzapine and clozapine. Kluge and others (2009) found that olanzapine significantly increased the BMI of female patients after 1-week treatment, however male patients took longer to reach significance, and females exhibited increased skin-fold thickness but not males. Females also showed a 2-4 times higher level of plasma leptin than males following olanzapine treatment, and this increase was observed earlier in females than in male patients (Kluge et al., 2009). Furthermore, female schizophrenia patients are more responsive to olanzapine treatment than male patients, regardless of illness chronicity (Usall et al., 2007). Female patients also exhibit higher plasma concentrations of the drug than males

(Kelly et al., 1999), possibly due to their generally lower lean body mass and increased adipose tissue, allowing greater drug storage and leading to higher plasma levels over time (Yonkers et al., 1992). Gonadal steroids such as oestrogen, progesterone and testosterone can influence food intake and metabolism. Fitzgerald and colleagues (2003) identified significant positive correlations between changes in oestrogen levels and alterations in leptin and NPY levels as well as BMI and weight gain in female schizophrenia patients treated with olanzapine or risperidone. These results suggested that fluctuating gonadal steroid levels may play a role in the weight-gain side-effect of atypical antipsychotic drugs and may explain the higher sensitivity of females to antipsychotic-induced weight gain, though the exact mechanism is unknown (Fitzgerald et al., 2003). Finally, based on waist circumference measurements, olanzapine-treated male patients are more responsive to nutritional intervention than females (Skouroliahou et al., 2009).

Indeed, human studies have shown that atypical antipsychotic-induced weight gain does not occur in all patients, and findings from the large-scale Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed an increase of 7% weight gain from baseline in 30% of patients treated with olanzapine (Allison et al., 2009).

Taken together, the rodent model olanzapine-induced weight gain cannot completely replicate human weight gain side-effect, particularly in male rats. However, the sensitivity of female rodents to this side-effect over males appears to be a common observation in the clinic. Future studies on sex differences in the rodent model may improve our understanding of the mechanisms underlying gender response to antipsychotic effects.

Role of Funding Source

This study was supported by the University of Wollongong and the Schizophrenia Research Institute, Australia, utilising infrastructure funding from NSW Health; these sources had no further role in writing or the decision to submit the paper for publication.

Contributors:

Weston-Green prepared the first draft of manuscript, with Deng and Huang providing important input in discussion and preparation of this manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest:

All authors declare that they have no conflicts of interest.

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