REGULAR RESEARCH ARTICLE

Lack of Ovarian Secretions Reverts the Anabolic Action of Olanzapine in Female Rats

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Abstract

Background: Olanzapine is an orexigenic antipsychotic drug associated with serious metabolic adverse effects in humans. Development of valid rodent models for antipsychotic-induced metabolic adverse effects is hampered by the fact that such effects occur in females only. Estradiol is a predominant female hormone that regulates energy balance. We hypothesized that the female-specific hyperphagia and weight gain induced by olanzapine in the rat are dependent on the presence of estrogens. Methods: Female sham-operated or ovariectomized rats were treated with a single injection of olanzapine depot formulation. Food intake, body weight, plasma lipids, lipogenic gene expression, energy expenditure, and thermogenic markers including brown adipose tissue uncoupling protein 1 protein levels were measured. Olanzapine was also administered to ovariectomized rats receiving estradiol replacement via the subcutaneous (peripheral) or intracerebroventricular route. Results: Orexigenic effects of olanzapine were lost in ovariectomized female rats. Ovariectomized rats treated with olanzapine had less pronounced weight gain than expected from their food intake. Accordingly, brown adipose tissue temperature and protein levels of uncoupling protein 1 were elevated. Replacement in ovariectomized rats with either peripherally or centrally
administered estradiol reduced food intake and body weight. Cotreatment with olanzapine blocked the anorexigenic effect of peripheral, but not central estradiol.

Conclusions: Our results indicate that the ovarian hormone estradiol plays an important role in olanzapine-induced hyperphagia in female rats and pinpoint the complex effects of olanzapine on the balance between energy intake and thermogenesis.

Keywords: antipsychotics, weight gain, energy expenditure, estradiol

Introduction

Schizophrenia, a debilitating mental disorder with a lifetime prevalence approximating 0.7%, constitutes a significant socioeconomic burden globally (McGrath et al., 2008). Antipsychotic agents are indispensable in the treatment of schizophrenia. Unfortunately, some antipsychotic agents, particularly the atypical antipsychotics olanzapine (OLZ) and clozapine, have widely recognized metabolic adverse effects such as weight gain, dyslipidemia, and type 2 diabetes (Leucht et al., 2013). In addition, while antipsychotics provide relief from positive symptoms such as hallucinations and delusions, effects on negative symptoms, such as affective flattening and anhedonia as well as cognitive impairment, are limited (Remington et al., 2016).

The therapeutic effect of antipsychotic drugs is mediated via blockage of dopamine D2 receptors, but other mechanisms may also be of relevance. The molecular underpinnings for both therapeutic and metabolic effects of antipsychotic agents remain elusive. Rodents are frequently used in preclinical experiments designed to shed light on these matters, in particular on drug-induced metabolic disturbances. In the rat, unlike in humans, some aspects of antipsychotic-induced metabolic adverse effects are sex specific (Boyda et al., 2010). In female rats, the effect of OLZ mimics the clinical situation, with hyperphagia, weight gain, increased plasma lipids, and activated transcription of lipid biosynthesis genes after treatment (Albaugh et al., 2006; Vik-Mo et al., 2009; Skrede et al., 2012). In male rats, on the other hand, antipsychotic drug treatment does not lead to weight gain, although OLZ has been shown to increase several plasma lipid species, accompanied by elevated hepatic transcription of lipogenic genes (Ferno et al., 2015).

The lifetime incidence of schizophrenia is 40% higher in males than in females (McGrath et al., 2008), with onset of the disorder peaking significantly later in women (Markham, 2012). Based on these and other data, the ovarian steroids, such as estrogens, have been suggested to contribute to the lower incidence of schizophrenia in females through its neuroprotective properties (Crider and Pillai, 2017). As part of the search for improved pharmacological treatment strategies for schizophrenia, several clinical studies have pointed towards beneficial effects of estrogen/estrogen-modulating agents in female patients suffering from schizophrenia (Heringa et al., 2015). In this context, estradiol (E2), the physiologically most potent estrogen, is highly relevant in the control of energy homeostasis (Mauvais-Jarvis et al., 2013; Lopez and Tena-Sempere, 2015). Decreased E2 levels due to menopause in humans or ovariectomy (OVX) in rodents are associated with hyperphagia, reduced energy expenditure, and weight gain, effects that are reversed by administration of exogenous E2 to OVX rats (Mauvais-Jarvis et al., 2013; Martinez de Morentin et al., 2014, 2015) and hormonal replacement therapy in postmenopausal women (Mauvais-Jarvis et al., 2013).

To address whether physiological E2 milieu is required in the rat model of antipsychotic-induced weight gain, we first administered a depot injection of OLZ to OVX female rats. We then explored how E2 replacement at physiological levels (Martinez de Morentin et al., 2015) affected the OLZ-induced effects. Our data show that OLZ treatment leads to hyperphagia and weight gain in sham-operated (gonadal-intact), but not in OVX rats. The s.c. E2 replacement in OVX rats seems to partially rescue the OLZ-induced hyperphagia, but this partial reversion was not observed when E2 replacement was central. Our findings support the suggestion that E2 is a relevant hormone for the orexigenic effects of OLZ in female rats.

Experimental Procedures

Animals

All experiments were approved by the USC Ethical Committee (project license 15010/14/006). Adult female Sprague-Dawley rats (2–3 months old) were kept under standard conditions with an artificial 12-hour-light/-dark cycle (lights on 8:00 AM) and constant 48% humidity. Animals were housed individually and allowed access to tap water and free (ad libitum) access to
standard laboratory chow (Special Diets Services) during the experimental period.

Surgical Procedures

Bilateral OVX or sham surgery was performed on female Sprague-Dawley rats under ketamine/xylazine anesthesia (50 mg/kg i.p.) as previously described (Martinez de Morentin et al., 2014, 2015). All treatment schemes in OVX rats were started 2 weeks after surgery to ensure a total washout of endogenous ovarian hormones (Martinez de Morentin et al., 2014, 2015). In the intracerebroventricular (ICV) experiment, ICV cannulas were surgically implanted as previously reported (Lopez et al., 2004). Animals were left to recover for 2 days before the initiation of treatment (see below).

Treatment Schedules

Two weeks after sham surgery or OVX, rats (n=9 in each treatment group) received one intramuscular injection of either OLZ pamoate depot formulation (100 mg/kg; ZypAdhera, Eli Lilly) or vehicle (VEH) solution (injection volume 160 µL/250 g body weight) (Skerde et al., 2014). A subgroup of the OVX rats (n=8) received daily s.c. injections of E2 (25 µg) and olanzapine (1 mg/kg) or vehicle (0 µg). Rats were sacrificed 30 minutes after the first ICV E2 dose, animals received a single intramuscular dose of OLZ pamoate 100 mg/kg. Animals and chow were weighed daily. Rats treated with SC E2 were sacrificed after 8 days of treatment, that is, on day 22 after surgical procedures (OVX or sham). Tissue and blood samples were harvested and stored at −80°C until further analysis. Due to limited durability of ICV cannulas, rats treated with ICV E2 were killed after 6 days of treatment, that is, on day 20 after OVX or sham surgery.

Calorimetric System and Nuclear Magnetic Resonance

In a separate experiment, OVX rats (n=6 in each treatment group) received an intramuscular injection of either OLZ pamoate depot formulation (100 mg/kg) or VEH. During the first 6 days after injection, energy expenditure (EE), food intake, body weight, and locomotor activity (LA) were measured using a calorimetric system (LabMaster, TSE Systems). Animals were placed in a temperature-controlled (24°C) box through which air was pumped. After calibrating the system with the reference gases (20.9% O₂, 0.05% CO₂, and 79.05% N₂), the metabolic rate was measured as previously shown (Imbernon et al., 2013; Martinez de Morentin et al., 2014). EE, respiratory quotient (VCO₂/VO₂), food intake (FI), and LA were recorded every 30 minutes. Animals were placed for adaptation for 1 week before starting the measurements. To adjust for body composition, lean mass was measured using nuclear magnetic resonance (Whole Body Composition Analyzer, EchoMRI). EchoMRI is a body composition analyzer for live subjects measuring body fat and lean masses with short scan times to ensure the comfort of the animals. Animals do not need to be anesthetized or subjected to other special preparation before measurement. They are placed in a holder of custom-defined size during the measurement (measuring time: 0.5–3.2 minutes). Two measurements were done for each animal, as previously shown (Imbernon et al., 2013; Martinez de Morentin et al., 2014).

RNA Extraction, cDNA Synthesis, and Real-Time PCR

RNA extraction, cDNA synthesis, and real-time PCR were performed as previously described (Ferno et al., 2005; Martinez de Morentin et al., 2014, 2015). Relative gene expression levels were determined using the comparative ΔCt method using β-actin (Actβ) and ribosomal protein, large, (Rplp0) as endogenous controls. For primer sequences, see Table 1.

Western Blotting

Tissue homogenization and western blotting were performed as previously described (Martinez de Morentin et al., 2014, 2015). The primary antibodies used were: Uncoupling protein 1 (UCP1) (ab10983; RRID: AB_2241462, polyclonal, lot #GR249119-1, Abcam; dilution 1:10000) and α-tubulin (T5168; RRID: AB_477579, mouse clone B-5-1-2, ascites fluid. Lot#035M4878V, Sigma; dilution 1:5000). Signal intensity measurements were performed using the ImageJ software (National Institutes of Health).

Biochemical Parameters

Glucose and lipids (total cholesterol [tot-CHOL], free cholesterol, HDL cholesterol [HDL-CHOL], LDL cholesterol [LDL-CHOL], free fatty acids [FFA], phospholipids [PLIP], and triglycerides [TG]) were measured enzymatically in plasma samples obtained from fasted rats using the Hitachi 917 system (Roche Diagnostics) as previously described (Jassim et al., 2012).

Statistical Analysis

Food intake and weight gain were analyzed using 2-way ANOVA repeated measures. For all other comparisons, we used 2-sided Student’s t test. P ≤.05 was considered statistically significant. PASW Statistics Version 18 (PASW Statistics, IBM) was used for all calculations. Data are presented as mean ± SEM.

Table 1. Primer Sequences Used for Real-Time PCR

| Gene                        | Main function       | Accession number | Fwd primer       | Rev primer       |
|-----------------------------|---------------------|------------------|------------------|------------------|
| Fatty acid synthase (Fasn)  | Fatty acid synthesis| NM_017332        | CCATCATCCCCCTTGGATGAA GA | GTTGATGTCGATGGCCTGTGAG |
| Stearoyl-CoA 9-desaturase;  | Fatty acid          | NM_139192        | TCAATCTCCGGAGAACATCC | CATGCGATGTCGATGAAACG |
| stearoyl-CoA desaturase 1   | desaturation         |                  |                  |                  |
| β-Actin (Actβ)              | Endogenous control  | NM_031144        | TACAGCTTCACCACCAAGC | CTTTCACCAGGAGAGAGG |
| Rattus norvegicus ribosomal | Endogenous control  | NM_022402.2      | CATTGAATATCTGGACCTGTGAG | AGATGGTACAACATGGTCCAGC |
Results

OLZ Reduces Weight Gain in OVX Female Rats

As expected, OLZ treatment in sham-operated female rats resulted in significant increases in both daily and cumulative food intake (Figure 1a) as well as body weight gain (Figure 1b). Also in agreement with our previously published data (Martinez de Morentin et al., 2014, 2015), OVX resulted in marked hyperphagia (Figure 1c) and elevated weight gain (Figure 1d) to levels that were in the range of the OLZ-induced effects in gonad-intact rats. OLZ administration to OVX rats did not stimulate food intake further, and interestingly, body weight gain was in fact reduced by OLZ relative to VEH-treated rats (Figure 1d).

OLZ Does Not Impact Plasma Lipids in OVX Female Rats

In sham-operated female rats (Figure 1e, white bars), OLZ treatment caused significant increases in plasma TGs, PLIPs, Tot-CHOL, and HDL-CHOL, but not in LDL-CHOL and FFAs. In line with the effect of OVX on food intake and body weight gain, all plasma lipid parameters were higher in OVX vs sham-operated rats, with the exception of FFA, where levels remained unaltered (Figure 1e). In OVX rats (Figure 1b, grey bars), OLZ did not further increase plasma lipid levels. OLZ had no effect on fasting glucose levels in either OVX or sham-operated rats (Figure 1e).
OLZ Does Not Impact Adipose Tissue Lipogenic Gene Expression in OVX Female Rats

As expected (Skrede et al., 2012), in gonadal white adipose tissue from gonadal-intact rats, OLZ induced a significant upregulation of genes involved in fatty acid biosynthesis, such as acetyl-CoA carboxylase 1, fatty acid synthase, and stearoyl-CoA desaturase 1 (Figure 1f, white bars). In OVX rats (Figure 1f, grey bars), the expression levels of all these genes were markedly lower than in sham rats, and notably, OLZ failed to induce significant transcriptional changes for any of the genes in the absence of ovarian secretions.

Peripheral E2 Replacement Partially Recovers OLZ-Induced Orexigenic Effect in OVX Rats

To investigate whether estrogen replacement in OVX rats could restore the orexigenic action of OLZ, OVX rats received daily s.c. injections of E2 while co-administered with either OLZ or VEH as single intramuscular depot injections. As expected, E2 decreased food intake and body weight gain in OVX rats (Figure 2a; compare open circles with open triangles). However, when E2 rats were co-treated with OLZ (Figure 2a), an interaction effect was observed, with daily and cumulative food intake significantly higher in E2+OLZ than in E2+VEH rats and body weight displaying a slight trend towards elevation (Figure 2b). On the contrary, in OVX rats without E2 (Figure 2b), OLZ significantly reduced body weight vs VEH-treated OVX rats, which occurred independent of changes in food intake.

OLZ Increases UCP1 Expression in BAT

The fact that OLZ decreased body weight gain in OVX female rats without concomitant reduction in food intake suggested that OLZ stimulates EE in this setting. We therefore measured UCP1 protein levels in BAT. In agreement with the phenotype, we found increased levels of BAT UCP1 in OVX female rats treated with OLZ relative to VEH (Figure 2c). Treatment of OVX female rats with E2 did not change this effect, as UCP1 levels were still increased to a similar magnitude in OVX rats cotreated with E2+OLZ vs rats treated with VEH+E2 (Figure 2c).

Central E2 Replacement in OVX Rats Does Not Recover OLZ-Induced Orexigenic Effect

To address whether the observed interactive effect of E2 and OLZ on food intake was centrally mediated, the effect of OLZ in OVX rats treated ICV with E2 was investigated. As expected, ICV E2 markedly reduced the hyperphagia and weight gain in OVX rats relative to ICV VEH (Figure 3a-b). Surprisingly, however, an intramuscular injection of OLZ did not counteract the anorexigenic effect of E2 in this setting, with no significant difference between ICV E2 and ICV E2+OLZ on either food intake or body weight (Figure 3a-b). In line with these data, we observed a significant increase in BAT temperature in all animals treated with E2 (Figure 3c), whereas there was no difference in BAT temperature between ICV E2 and ICV E2+OLZ (Figure 3c). In an additional experiment, we investigated the isolated effect of an OLZ on BAT temperature in OVX rats, without ICV E2 cotreatment. In agreement with the observed OLZ-induced increase in BAT UCP1 levels (Figure 2c), an intramuscular injection of OLZ significantly increased BAT temperature (Figure 3d). This effect occurred without any significant changes in food intake (OLZ: 20.9 ± 2.5 g/d vs VEH: 17.5 ± 1.3) or body weight (OLZ: -8.0 ± 8.6 g vs VEH: -5.3 ± 7.8 g). Of note, during this short observation period of 3 days, total EE or the respiratory quotient were not significantly elevated by the OLZ treatment (supplementary Figure S1a-b). This may, at least in part, be explained by the concomitant reduced LA (supplementary Figure S1d-e), which was expected from the sedative effect of OLZ.

Discussion

Conditions of suppressed or lacking ovarian estrogen secretions are associated with a positive energy balance (Mauvais-Jarvis et al., 2013; Lopez and Tena-Sempere, 2015). Hence, in the OVX rats we found the expected elevation of food intake, body weight, and plasma lipids. Interestingly, treatment with OLZ yielded strikingly different results in ovarian-intact and OVX rats. In sham rats, OLZ led to elevation of food intake, body weight, plasma lipids, and lipogenic gene expression in white adipose tissue, as previously shown (Ferno et al., 2011; McNamara et al., 2011; Skrede et al., 2012). In contrast, OLZ had no effect on food intake, plasma lipids, or lipogenic gene expression in OVX rats in which body weight gain was actually reduced by OLZ.

A possible explanation for the lack of orexigenic and dysmetabolic effects of OLZ in OVX rats is that the anabolic effects of OLZ were masked by OVX-induced hyperphagia and elevated plasma

Figure 2. (A) Daily and cumulative food intake and (B) cumulative body weight gain in female ovariectomized (OVX) rats treated with single depot injections of olanzapine (OLZ) (100 mg/kg) or vehicle (VEH), with (open circles) or without (triangles) cotreatment with daily s.c. injections of vehicle or E2 (2 μg/d) for 8 days. *P ≤ .05, **P ≤ .01, ***P ≤ .001, E2+OLZ compared with E2+VEH, +P ≤ .05, †P ≤ .01, ‡P ≤ .001, OLZ compared with VEH. (C) Uncoupling protein 1 (UCP1) western blots in brown adipose tissue (BAT) from female sham or OVX rats treated with a single injection of VEH, OLZ (100 mg/kg), or OLZ+E2 (2 μg) for 8 days. *P ≤ .05, **P ≤ .01, OLZ compared with VEH and OLZ+E2 compared with VEH+E2.
lipids. However, the fact that lipogenic gene expression levels were lower in OVX than in sham rats argues against the validity of this explanation, at least with regard to the whole set of metabolic alterations of OLZ. Notably, the effect of OLZ in OVX rats has been examined previously, but contrary to our findings, OLZ treatment was reported to induce hyperphagia and weight gain in OVX rats (Park et al., 2010). However, the previous study was carried out on a diabetic background (90% pancreatectomy) in rats fed a high-fat diet, whereas here we used nondiabetic Sprague-Dawley rats fed standard chow. Furthermore, in our study, OLZ was administered as a depot formulation, which yields high and stable OLZ serum concentrations (Skrede et al., 2014).

The observation that OLZ reduced body weight in OVX female rats without concomitant changes in food intake suggests that in the absence of ovarian secretions OLZ stimulates thermogenesis. While findings of increased BAT temperature and UCP1 protein levels supported this theory, net EE was unaltered in OVX rats treated with OLZ, possibly due to sedation and subsequent reduced LA. Interestingly, BAT UCP1 levels were also elevated by OLZ in sham-operated rats despite that both food intake and weight gain were increased by the drug in this situation. Thus, the marked hyperphagia observed in sham-operated rats treated with OLZ seems to overshadow the increase in thermogenesis, with a net increase in body weight as the observed phenotype. In OVX rats, OLZ does not induce hyperphagia but increases thermogenesis, as demonstrated by the augmentation of BAT temperature and UCP1 protein levels, potentially explaining the lack of body weight gain.

We further examined the effect of E2 substitution on the OLZ-induced phenotype. Daily injections of SC or ICV E2 to OVX female rats led to reversal of hyperphagia and weight gain, as expected (Martinez de Morentin et al., 2014, 2015). This anorexigenic effect was blunted by OLZ in rats receiving peripheral, but not central, E2. OVX rats treated with peripheral E2 and OLZ displayed markedly higher food intake than OLZ-treated OVX rats without E2 replacement. These data show that when OVX rats are substituted with E2 via the peripheral route, OLZ regains its orexigenic potential. However, these data should be interpreted with caution, since the orexigenic effect of OLZ during cotreatment with E2 may be a result of its action as an inhibitor of E2’s anorexigenic effect rather than a direct stimulator of food intake. Of note, the elevated food intake did not translate into significantly higher body weight gain in the group of OVX rats treated s.c. with E2 and OLZ. In keeping with this observation and the results discussed above, BAT UCP1 levels were elevated by OLZ also when cotreated with E2. In rats receiving central E2, we also showed that BAT temperature was increased, again indicative of increased thermogenesis. Nevertheless, OLZ did not further affect BAT temperature in these rats.

Taken together, the findings support our hypothesis that the presence of estradiol is important for the hyperphagia and weight gain associated with the antipsychotic agent OLZ in the rat. Notably, the thermogenic effects of OLZ seem to occur independent of estradiol.

The molecular underpinnings of our results should be further evaluated in future studies. OLZ is believed to mediate its
orexigenic effects via its antagonistic effects on serotonin 5HT2C and histamine H1 receptors (Reynolds and Kirk, 2010). We have previously demonstrated that OLZ-induced hyperphagia is associated with upregulation of the orexigenic neuropeptides NPY and AgRP and downregulation of the anorexigenic neuropeptide SOMC in the hypothalamus (Ferno et al., 2011). Furthermore, we and others have suggested that activation of AMPK in the arcuate nucleus of the hypothalamus is important (Kim et al., 2007; He et al., 2014; Skrede et al., 2014). The impact of OLZ treatment on AMPK activation and neuropeptide levels in OVX rats could be a topic of targeted investigations. Considering that NPY is likely to mediate OVX-induced hyperphagia, this neuropeptide would be of particular interest to investigate the E2 OLZ interaction effect.

Direct translation of our rodent data should be done with caution. While some clinical trials have documented that female gender is a risk factor for antipsychotic-induced weight gain, gender differences seem to be far less pronounced in patients than in rodents. It must be stressed, though, that gender aspects are often overlooked in clinical trials; this issue requires more attention through targeted clinical studies. Furthermore, the involvement of EE in antipsychotic-induced weight gain remains under-investigated in humans. It is possible that OLZ stimulates EE also in humans, and the balance between orexigenic and energy dissipation effects may contribute to the large inter-individual variation observed among patients during treatment with antipsychotic agents. Correspondingly, studies in healthy volunteers and patients treated with antipsychotic agents have yielded conflicting results with regard to resting EE (Cuerda et al., 2014). All in all, further research is warranted to determine the role of EE in antipsychotic-induced metabolic dysfunction.

As part of the search for improved pharmacological strategies to treat schizophrenia, several clinical studies have pointed toward beneficial effects of treatment with estrogen/estrogen-modulating agents in female patients suffering from schizophrenia (Heringa et al., 2015). The present study documents that in the rat, key features of the metabolic impact of OLZ are dependent on ovarian secretion. The results highlight important aspects that need to be considered in clinical trials, both involving antipsychotic monotherapy and add-on treatment with estrogen and its related pharmacological agents.

Acknowledgments

The authors thank Marianne S. Nævdal and Liv Kristine Øysæd for excellent technical assistance.

Funding

This work was supported by the Research Council of Norway (V.M.S.: CoE grant to Norwegian Centre for Mental Disorders Research, project number 223273), Stiftelsen Kristen Gerhard Jebsen (V.M.S.), Dr. Einar Martens Foundation (V.M.S., S.S., J.F.), Helse Vest RHF (J.F. and G.M.: the Western Norway Regional Health Authority), the European Community’s Seventh Framework Programme (FP7/2007–2013) under grant agreement no. 281854, the ObEStress European Research Council Project (M.L.), Junta de Andalucía (M.T.-S.: P12-FQM-01943), Xunta de Galicia (R.N.: 2015-CP080 and 2016-PG057; M.L.: 2015-CP079), Instituto de Salud Carlos III and Fondo Europeo de Desarrollo Regional (ISCIII, FEDER; M.L.: PIE13/00024), MINECO co-funded by the FEDER Program of EU (R.N.: BFU2015-70664; M.T.S.: BFU2014-2502157581-R; M.L.: SAF2015-71026-R and BFU2015-70454-REDT/Adipoplast). I.G.-G. is a recipient of a fellowship from Ministerio de Educación, Cultura y Deporte (FP12/01827).

Statement of Interest

None.

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