Effects of naltrexone on food intake and body weight gain in olanzapine-treated rats

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Abstract

Blockade of opioidergic neurotransmission contributes to reduction in body weight. However, how such blockade affects body weight gain (BWG) attributed to second generation antipsychotic agents (SGAs) has not yet been established. Here we examined the effects of an opioid receptor antagonist, naltrexone (NTX), on food intake and BWG associated with an SGA, olanzapine (OL). Four groups of Wistar Han IGS rats were treated for 28 days with either OL (2 mg/kg twice daily, intraperitoneal (IP)), a combination of OL (2 mg/kg twice daily, IP) + extended-release NTX (50 mg/kg, one-time, intramuscular (IM)), extended-release NTX (50 mg/kg, one-time, IM) or vehicle and their food intake and body weight were measured daily for the first nine days and every other day thereafter. Food intake and BWG that were increased by OL were decreased by the added NTX while NTX alone had no significant effects on food intake or on BWG. Plasma leptin concentrations were significantly elevated in the three groups receiving pharmacological agents, but did not differ among each other, suggesting that changes in leptin secretion and/or clearance alone would not explain the food intake and the body weight findings. Our results extend prior reports on anorexigenic effects of opioid antagonists by demonstrating that such effects may generalize to food intake increases and BWG arising in the context of OL pharmacotherapy.

Keywords

Opioid, water intake, second generation antipsychotic drugs, metabolism, leptin, orexigenic pathways, obesity

Introduction

Excessive body weight gain (BWG) is a broad allostatic phenomenon (McEwen, 2004), integrating complex systems of interrelated neurochemical, endocrine, environmental and behavioral factors, each of which exhibits a unique role within the context of eating behavior. Iatrogenic causes, including pharmacotherapy with second-generation antipsychotic agents (SGAs) are also quite prevalent (Muench and Hamer, 2010), afflicting over 50% of the exposed patients (Mahendran et al., 2010). While precise mechanisms underlying SGA-induced BWG remain a target of an intensive preclinical and clinical investigation, increases in food intake have consistently been implicated (Treuer et al., 2009).

Orexigenic opioid pathways are critically involved in the regulation of food intake (Elman et al., 2006). To begin with, the rewarding features of food are conveyed to the frontotemporal cortical regions (Berridge, 2003; Kelley, 2004) via μ-opioid neurotransmission within the dispersed network of subcortical and brainstem nuclei (Berridge, 2009). Thus, opioids enhance food pleasantness (Pecina, 2008) and contribute to excessive food consumption (Olszewski and Levine, 2007) with resultant BWG (Erlanson-Albertsson, 2005; Johnson and Kenny, 2010). In addition to enhancing food reward, opioids respectively boost orexigenic neuropeptides such as orexin (Kreek, 2007) and suppress anorexigenic peptides like proopiomelanocortin (Greenway et al., 2009). Together with central effects on appetite and food intake, opioids also decrease peripheral secretion of hormones including leptin (Houshyar et al., 2003) and insulin (Fulghesu et al., 1998; Garcia-Barrado et al., 2002) and desensitize insulin receptors (Li et al., 2003).

Among the complex mix of their pharmacological properties, some SGAs may also be associated with enhancements in opioidergic activity. Olanzapine (OL) is one of the most commonly prescribed SGAs and it is approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia, acute mania, agitation in schizophrenia and in bipolar disorder, as well as for maintenance therapy in bipolar disorder and (in combination with fluoxetine) for refractory depression. Several lines of evidence support the opioidergic mechanism of action of OL including clinical presentation of OL overdose, which is similar to opioid intoxication (O'Malley et al., 1999; Kochhar et al., 2002; Palenzona et al., 2004) and analgesic and antinociceptive properties of OL observed in human (Kiser et al., 2001; Silberstein et al., 2002; Khojainova et al., 2002; Gorski and Willis, 2003; Fishbain

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et al., 2004) and in rodent models and partially ascribed to opioid mechanisms (Schreiber et al., 1999; Weizman et al., 2003).

If excess opioid activity creates metabolic disturbances, it is reasonable to expect amelioration of these effects through the blockade of opioid receptors (Elman et al., 2006). In view of that, opioid antagonists block hedonic responses to sweet foods (Blass et al., 1987; Blass and Fitzgerald, 1988; Langleben et al., 2012) and suppress appetite in laboratory animals (Bodnar and Levine, 2008; Nathan et al., 2012) and humans (Yeomans and Gray, 2002; Baldo et al., 2010; Berner et al., 2011).

To our knowledge, metabolic outcomes of opioid antagonism have not yet been examined in combination with OL. To that end, we sought to determine the effects of an opioid receptor antagonist, naltrexone (NTX), administered to rats, maintained on OL. With the above considerations in mind, it was hypothesized that rats treated with a combination of OL+NTX, in comparison to OL alone, will present diminished food intake and BWG.

To gain insight into potential mechanisms of OL and NTX interactions, we also measured plasma concentrations of leptin, which is a stable endocrine marker of energy storage reflected in total body fat mass. Being released by adipocytes, it is a satiety brain signal (Korner and Leibel, 2003), which becomes inefficient in the event of chronically elevated hormonal levels (Scarpace and Zhang, 2009). Given the reported potentiation of exogenously administered leptin weight reduction properties by NTX (Yuan et al., 2009), it is reasonable to expect the same NTX effect on the naturally circulating endogenous leptin. If this is the case, diminished BWG accompanied by modest hormonal changes would strengthen the case for the 'potentiation' effect (Yuan et al., 2009). On the other hand, failure to restrain BWG, hyperleptinemia notwithstanding, as is seen in OL-treated patients (Bobo et al., 2011; Raposo et al., 2011), would be more indicative of the leptin-resistant state (Scarpace and Zhang, 2009).

Methods

Subjects

The employed research protocol was adapted from Cooper and colleagues (2005), who developed a rodent model of hyperphagia and BWG during chronic OL treatment. Twenty-eight female Wistar Han IGS rats (Charles River Laboratories; Wilmington, Massachusetts, USA) at eight weeks of age at the time of the study initiation participated in the experiment. The animals' strain and sex were chosen because human OL effects in terms of food intake and BWG are more consistently demonstrated in female rats (Cooper et al., 2005; 2007) while male rats develop under the same laboratory conditions visceral adiposity in the face of reduced BWG and unaltered food intake (Cope et al., 2005).

Rats were marked with a number on the base of their tail and maintained on a 12-hr light/dark cycle (lights on: 0600 hr; lights off: 1800 hr) in an environment controlled for temperature (21°C) and humidity (40–50%). Animals were habituated to housing for 14 days prior to treatment. They were handled daily for seven days for routine husbandry and habituated to the injection protocol with physiological saline, over two additional days. All experimental procedures were performed in the dark cycle. Food (standard rodent chow) and tap water were available ad libitum in the home cages throughout the study. Body-weight as well as food and water intake were recorded at the same time daily (1730 hr). Food and water intake was measured by weighing the containers and subtracting the difference from the previous day. Spillage amounts were overall minor and in all likelihood similar across the groups. Non-negligible amounts (e.g. a large piece of food visible in the bedding beneath the food hopper) were returned to the food hopper before weighing. Animals were treated in accordance with the National Institutes of Health principles of laboratory animal care under the supervision of the Reed College Institutional Animal Care and Use Committee.

Pharmacological agents

We adopted the methodology of Cooper et al. (2005) in dissolving OL tablets and preparing them for injection, as well as in the formulation of the vehicle solution. In short, OL (Ly170053, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1.5]) benzodiazepine; carnauba wax, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide, as excipients (Zyprexa Prescribing Information, Eli Lilly) oral tablets were crushed with mortar and pestle and dissolved in 0.1 M hydrochloric acid, buffered to pH of 5.5 using 0.1 M sodium hydroxide and diluted with distilled water. The solution was made every three days and kept refrigerated at 5°C until needed for administration at which time it was vortexed for resuspension. The OL dose, 2 mg/kg (Raskind et al., 2007), was chosen as it was demonstrated to produce rat plasma concentrations that are roughly equivalent to human therapeutic range (Gao et al., 1998). Given OL's short half-life in rats following intraperitoneal (IP) administration, it was administered twice daily IP with a 6-hr inter-injection interval (i.e. at 1800 and 2400 hr); the injection volume was 2 mL/kg per rat (Cooper et al., 2005). The vehicle was a solution of 0.1 M hydrochloric acid buffered to pH of 5.5 using 0.1 M sodium hydroxide and diluted with distilled water up to dosage volume 2 mL/kg. It was administered IP twice daily with a 6-hr inter-injection interval (i.e. at 1800 and 2400 hr).

The extended-release (approximately 30 days) properties of injectable suspension (Vivitrol®) of NTX hydrochloride (17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) are accomplished by poly-(lactide-co-glycolide) small-diameter (<100 μm) injectable microspheres along with additional proprietary active molecules (Dean, 2005). The microspheres are suspended in an aqueous solution containing 3.0% low-viscosity carboxymethylcellulose, 0.9% saline, and 0.1% Tween-20. The dosage was 50 mg/kg, administered intramuscularly as a one-time injection in a volume of 0.5 mL/kg per rat. The same dose and mode of administration effectively abolished morphine-induced analgesia and remained physiologically active in plasma and in the rats' brain for 30 days (Bartus et al., 2003; Dean, 2005).

Experimental procedure

Animals were randomly assigned to one of four 28-day treatment groups namely, OL, OL+NTX, NTX and vehicle. Food and water intake and body weight values were collected at baseline and measured daily for the first nine days and every other day for the remaining 19 days. NTX injection was administered on day 0 to the

Table 1. Effects of olanzapine (OL) and naltrexone (NTX) on food and water intake and on body weight.

Variable	Drug condition	Baseline value (g)	Maximal value (g)	Adjusted mean*	Newman-Keuls tests
Food intake	OL	18.71±0.34	43.86±0.57	29.22±0.27	OL>NTX, NTX+OL, Vehicle
	NTX	17.14±0.87	40.29±0.82	27.07±0.26	$p<0.0005$
	OL+NTX	15.29±0.70	38.14±0.55	27.04±0.31	
	Vehicle	18.71±0.37	41.14±1.19	27.09±0.28	
Water intake	OL	29.29±1.10	64.00±1.44	45.78±1.10	OL, Vehicle> NTX, NTX+OL
	NTX	25.57±0.16	59.29±1.12	41.82±1.14	$p\leq0.001$
	OL+NTX	24.71±0.94	62.142±0.20	43.12±1.22	
	Vehicle	31.29±1.48	74.86±7.32	47.78±1.28	
Weight	OL	205.00±3.68	244.71±4.78	227.10±1.39	OL>NTX, NTX+OL, Vehicle
	NTX	203.57±3.52	237.00±3.07	217.20±1.41	$p<0.001$
	OL+NTX	200.43±1.38	230.14±3.94	219.04±1.42	
	Vehicle	207.14±4.01	232.14±3.67	217.20±1.41	

*Least squares means, computed to adjust for potential outliers. Data are group mean±SEM.

OL+NTX and NTX groups. The OL and vehicle dosage were determined according to the most recent body weight measurement.

Venous blood at days 0 and 28 was collected into tubes containing heparin sodium. Samples were centrifuged and plasma aliquots were stored at -80°C. The leptin assay utilized enzyme-linked immunosorbent technique; the intra-and interassay coefficient of variation was 2.5% and 3.9% respectively. At the study completion, on day 28, animals fasted over the light cycle and were sacrificed by carbon dioxide gas inhalation.

Statistical analysis

Data were analyzed using the statistical package Statistica (StatSoft, Inc., Tulsa, Oklahoma, USA). The analyses differed with respect to the within-subjects factor i.e. the repeated measures, in the following fashion. First, to determine the effects of OL, NTX and their combination on food and water intake and on body weight, a one-way analysis of variance (ANOVA) with repeated measures design was conducted. Drug (OL, OL+NTX, NTX or vehicle) was the grouping factor and time (days: 0–8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and 28) was the within subjects factor.

Second, leptin plasma concentrations at the commencement and the completion of the study were subjected to ANOVA. Here the within-subjects factor had two levels (day 0 vs day 28). Third, area under the curve (AUC) values for food and water intakes and for body weight were computed using trapezoidal integration. Area under the curve differences among treatment groups were assessed by one-way ANOVA with drug (OL, OL+NTX, NTX, or vehicle) as the grouping factor.

To account for the marked variability, the baseline measures of food and water intake and of body weight were used as covariates in the respective analyses. Post-hoc Newman-Keuls tests were performed to determine whether and how the groups were different among each other. Multiple linear regression analysis used a model in which the dependent variable was the AUC value for body weight with the AUC for food and water intake and leptin change scores as independent variables. Group data were summarized as mean ± SEM. All analyses were two-tailed and p value<0.05 defined statistical significance.

Results

For food intake ANCOVA yielded significant group ($F(3, 23)=13.63$; $p<0.0001$) and time ($F(1,17)=8.72$; $p<0.0001$) effects and a significant group-by-time interaction ($F(3, 23)=7.68$; $p<0.0001$). The effects for water intake were also significant for group ($F(3, 23)=3.41$; $p=0.04$) and for group-by-time interaction: $F(3, 23)=2.16$; $p<0.0001$) but not for time ($F(3, 17)=1.10$; $p=0.36$). Body weight analyses revealed a significant effects for group ($F(3, 23)=11.52$, $p=0.0001$) and for group-by-time interaction ($F(3,23)=2.41$; $p=0.0001$).

Table 1 presents the baseline, maximal and adjusted mean values for each drug condition separately, along with results of post-hoc pairwise group Newman-Keuls tests. OL-treated rats displayed significantly higher food intake and body weight than rats in the three other groups. There were no significant group differences for food intake and body weight among NTX-, OL+NTX- and vehicle-treated animals. In contrast, water intake effects were mainly driven by the similarly diminished values in the two NTX -treated groups, as compared to the vehicle.

The group effect for plasma leptin concentrations was significant ($F(3,24)=4.17$, $p=0.016$), but there was no significant time ($F(1,3)=1.77$; $p=0.20$) effect or a significant group-by-time interaction ($F(3, 23)=55$; $p=0.65$). Post-hoc tests indicated greater hormonal increases in the three drug-treated groups as compared to vehicle (Table 2).

The AUC values provided a cumulative measure of drug exposure. Predictably, these results paralleled those of the raw data analyses. There was a significant group effect on food ($F(3,23)=8.93$, $p<0.001$) intake and on body weight ($F(3,23)=9.97$, $p<0.001$) (Figure 1) and a trend toward significance for water intake ($F(3,23)=2.45$, $p=0.09$). Post-hoc analyses demonstrated significantly higher AUC values for food intake and body weight in the OL than in the OL+NTX, NTX or vehicle-treated rats. The

Table 2. Effects of olanzapine (OL) and naltrexone (NTX) on plasma leptin concentrations.

Drug condition	Day 0 (ng/mL)	Day 28 (ng/mL)	Adjusted mean	Newman-Keuls tests
OL	3.71±0.17	3.89±0.48	3.80±0.31	NTX, OL, NTX+OL>Vehicle
NTX	3.52±0.41	4.01±0.41	3.77±0.31	$p<0.05$
OL+NTX	3.19±0.48	3.72±0.38	3.45±0.31	
Vehicle	2.52±0.27	2.40±0.18	2.46±0.31	

Data are group mean±SEM.

latter three groups (i.e. OL+NTX, NTX and vehicle) were not significantly different among each other with respect to both food intake and body weight (Figure 1).

Multiple linear regression was employed to determine whether dietary and/or hormonal indices predict BWG. When AUC values for food and water intake along with changes in leptin plasma concentrations were considered, only food intake was an independent predictor of body weight, accounting for approximately 32% of the variance ($F(3,24)=3.73$, $r=0.56$, $p<0.05$); (Table 3). When regression was performed using only food intake as a predictor, the effect was also significant ($F(1,26)=8.88$, $r=0.50$, $p<0.01$) (Figure 2).

Discussion

To our knowledge, this is the first study to evaluate the effects of opioid blockade on the metabolic outcomes of OL pharmacotherapy. The major finding was that rats treated with the combination of OL+NTX were similar to NTX alone or vehicle-treated animals with respect to their food intake and BWG. Olanzapine has consistently been implicated in increased appetite and BWG in both preclinical and clinical (Newcomer, 2005; Elman et al., 2006; Treuer et al., 2009) studies, while NTX has been shown to exert the opposite effect (Barbano and Cador, 2007; Kelley et al., 2005; Rada et al., 2010; Langleben et al., 2012). Hence, the present results extend prior reports on the anorexogenic properties of opioid antagonists by suggesting that such effects may generalize to OL-induced food intake and BWG.

Our data contrast with previous reports of OL-induced leptin elevations (Peña et al., 2008; Marquina et al., 2011 Raposo et al., 2011; Bobo et al., 2011) usually emerging concurrently (Melkersson and Hulting, 2001) with the BWGs. Such an effect on leptin of OL is not entirely consistent, however, with no changes (Wang et al., 2007; Brambilla et al., 2007; Peña et al., 2008) or decreases (Haupt et al., 2005; Albaugh et al., 2006) which have also been reported. Variables such as sex (Power and Schulkin, 2008), baseline metabolic parameters (Albaugh et al., 2006; Brambilla et al., 2007), duration of the trial (Albaugh et al., 2006; Brambilla et al., 2007) and body composition (Haupt et al., 2005) may potentially explain the divergent leptin results.

In the present study, leptin concentrations varied significantly across groups, with the lowest values in the vehicle group and elevated mean concentrations in the three groups receiving pharmacological agents. Opioid neurotransmission contributes to

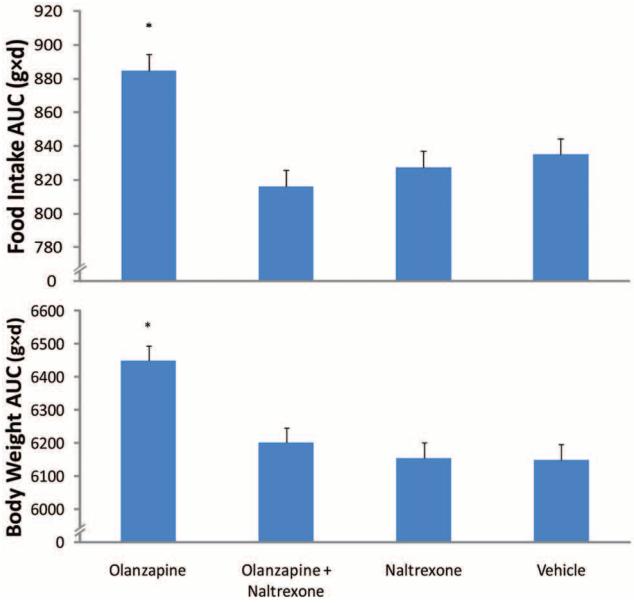

Figure 1. Area under the curve (AUC) values for food intake and body weight in rats treated with olanzapine (OL), olanzapine and naltrexone (OL+NTX), naltrexone (NTX) and vehicle (n=7, each group) expressed as grams x the number of days (g x d).
Data are presented as mean±SEM. Statistical differences were determined using a one-way analysis of covariance (ANCOVA) with drug condition (OL, OL+NTX, NTX and vehicle) as the grouping factor and post-hoc Newman-Keuls tests. *Indicates significantly higher food intake and body weight in the OL group than in the three other groups ($p<0.001$) that are not significantly different among each other.

Table 3. Results of multiple regression analysis of relationship between body weight and dietary and hormonal indices.

Variable	Coefficient	*r*	*t* (24)	*p*
AUC food intake	0.62	0.51	3.25	<0.01
AUC water intake	−0.23	0.03	−1.16	0.25
Leptin change	0.11	0.12	0.66	0.51

AUC: area under the curve. n=28, r^2 for the model=0.32.

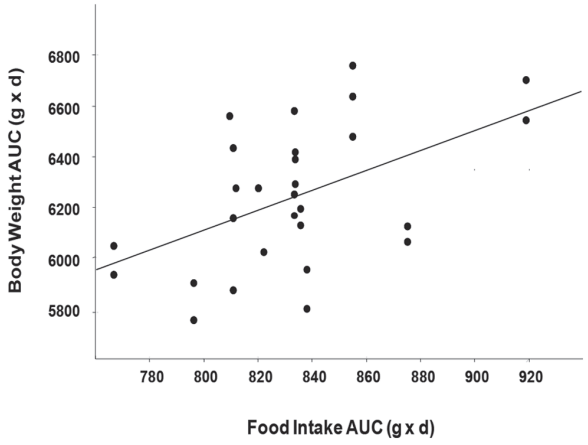

Figure 2. Scatterplot relating body weight with food intake (F(1,26)=8.88, r=0.50, p<0.01). AUC: area under the curve.

plasma leptin levels (Ferenczi et al., 2010). However, similar leptin findings in the OL vs OL+NTX groups, differing in the body weight, argue against changes in leptin secretion and/or clearance as a basis for the lower BWG in the latter group. On the other hand, NTX potentiates leptin action (Yuan et al., 2009) and thus could potentially improve hormonal sensitivity for a given amount of BWG (Fruzzetti et al., 2002). Since there were no weight differences between NTX- and vehicle-treated rats, leptin potentiation was not likely to be the sole mechanism of NTX action. In short, the question concerning the precise role of OL in modulation of leptin secretion and/or clearance still remains open and more research assessing the role of opioid mechanisms is warranted to fully address the effects of OL on plasma leptin concentrations.

Interestingly, NTX alone failed to reduce food intake and BWG. This pattern suggests that regular feeding on bland laboratory rat chow is relatively unaffected by the endogenous opiate peptides (Zhang et al., 1998; Zhang and Kelley 2000; Glass et al., 2006). On the other hand, OL therapy may add to the physiological opioidergic tone with the ensuing increase in the perceived food palatability and consequent hedonic overeating (Gosnell and Krahn, 1993; Olszewski et al., 2011) that is otherwise mainly driven by homeostatic needs (Elman et al., 2006; Lenard et al., 2010). Indirect support for this interpretation is provided by a study demonstrating the lack of NTX's significant food intake and BWG effects in rats treated with a selective dopaminergic agent, sulpiride (Baptista et al., 2000). Further study of how the opioidergic neurotransmitter system is affected by OL and by other antipsychotic drugs (Baptista et al., 2001) may be valuable in identifying pathophysiological mechanisms underlying metabolic disturbances appearing in the course of antipsychotic pharmacotherapy.

Although it is tempting to suggest that NTX blockade of the central orexigenic opioid pathways activated by OL underlies the observed effects, the procedures employed do not allow us to make such a firm conclusion. For instance, it remains unclear whether the present findings are a product of central and/or peripheral NTX action. Recent work with a peripherally acting NTX preparation, i.e. methylnaltrexone, and a nonselective opioid receptor blocker, naloxone, has demonstrated that potentiation of leptin-induced weight losses may be achieved via exclusively peripheral opioidergic mechanisms (Yuan et al., 2009). For this reason, it would be revealing to perform a follow-up study with centrally-administered NTX to examine whether the weight and leptin effects of opioid blockade would be present in this case, or some more complex pattern would transpire.

A few additional caveats should be considered in interpreting our data. First, it is unknown whether the opioidergic mechanism of action generalizes to SGAs as a class. Second, OL pharmacokinetics may play a role in the metabolic effects of the drug and their modulation by NTX. Whereas OL concentration may account for a portion of the observed group differences, the prominence of such an effect is not supported by clinical work (Citrome et al., 2009). Given the added stress for animals associated with frequent blood sampling, OL concentrations along with other plasma indices (e.g. glucose and insulin) were not measured throughout the study. Animal stress levels could have been further diminished by using an osmotic minipump that reportedly mirrors human metabolic OL processing (Remington et al., 2011). Third, the study assessed a relatively high dose of NTX and a lower dose may have yielded different results (Tempel et al., 1995). Fourth, the investigators were not 'blinded' to the group assignment. An 'unblinded' design employed on the study could have biased the findings (Bebarta et al., 2003) even if less likely with relatively objective outcomes (Heard et al., 2010). This and other factors that were not part of the present study protocol (e.g. body composition) may need to be assessed in future studies. Finally, the fact that significant food intake and body weight decreases were specific to the OLZ+NTX group argues against non-specific behavioral phenomena as a basis for our findings. Nonetheless, the paradigm employed does not allow us to firmly conclude that a non-specific behavioral disruption is not implicated in the decreased food intake and weight gain in the OL+NTX group. Answering this question would require disentangling this component via an exclusively in vivo paradigm that did not entail behavioral output.

The decrease in water intake in both NTX-treated groups suggests that opioidergic neurotransmission is involved in the maintenance of the body water content (Barney et al., 1992). Indeed, opioid antagonists have been shown to reduce all forms of fluid consumption in water-deprived and hypophysectomized rats during choice tests between saline solutions and water (Brown et al., 1980) as well as following thermal dehydration (Barney et al., 1992) and angiotensin II and hypertonic saline administration (Holtzman, 1975); the OL effects on water intake are less prominent (Bersani et al., 2007). While the extension of the NTX water intake to humans has not yet been established, its potential clinical significance may be in the form of a recommendation for NTX-treated patients to increase their fluid intake regardless of subjective thirst sensation in order to avoid dehydration, particularly during hot seasons.

Superior therapeutic properties of OL (See, 2000) frequently render a switch to a more metabolically inert antipsychotic agent a clinically undesirable endeavor. However, little is known about the specific mechanisms that lead to weight gain after SGA treatment, or whether a target pharmacologic approach might be able to specifically identify the underlying mechanism.

Current therapy for OL-associated BWG along with the glucose and lipid dysregulation has focused on dietary caloric restriction (which has limited efficacy even in patients without the psychopathology of schizophrenia), weight loss medications (many of which are contraindicated because of CNS side effects) e.g. sibutramine (Henderson et al., 2005) and the frequent use of metformin (Ehret et al., 2010; Praharaj et al., 2011) that may be superior to the other agents particularly when impaired glucose tolerance or type 2 diabetes develops (Bushe et al., 2009). Also, reboxetine (Poyurovsky et al., 2003) and topiramate (Narula et al., 2010) additions to ongoing OL treatment resulted in significant attenuation of BWG, whereas fluoxetine (Poyurovsky et al., 2002) or famotidine (Poyurovsky et al., 2004) proved to be ineffective. The clinical utility of topiramate is as yet unclear as none of the Narula et al. (2010) study participants presented clinically meaningful metabolic problems as a result of OL therapy.

In conclusion, the current findings could have important clinical implications because they suggest an inexpensive and effective treatment that specifically targets the underlying pathophysiologic mechanisms. NTX is a well-tolerated opioid antagonist lacking any abuse potential, and may even possess beneficial properties for negative symptoms of schizophrenia (Murphy et al., 2006) and for co-morbid substance abuse disorders (Roth et al., 2005; Wobrock and Soyka, 2008). Moreover, NTX is approved by the FDA for the treatment of opioid and alcohol dependence. There is considerable overlap between neural circuitries involved in food and drug reward and in homeostatic processing (Elman et al., 2006; Nair et al., 2009; Volkow et al., 2008). Thus, if the findings presented here are confirmed in clinical trials, NTX could emerge as an important part of a medically supervised program aimed at the maintenance of a healthy weight and metabolic profile in OL-treated patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

Albaugh VL, Henry CR, Bello NT, et al. (2006) Hormonal and metabolic effects of olanzapine and clozapine related to body weight in rodents. *Obesity (Silver Spring)* 14: 36–51.

Baldo BA, Pratt WE and Kelley AE (2010) Control of fat intake by striatal opioids. In: Montmayeur JP and Le Coutre J (eds) *SourceFat Detection: Taste, Texture, and Post Ingestive Effects.* Boca Raton: CRC Press, pp. 323–344.

Baptista T, Lacruz A, Acosta A, et al. (2000) Naltrexone does not prevent the weight gain and hyperphagia induced by the antipsychotic drug sulpiride in rats. *Appetite* 34: 77–86.

Baptista T, Lacruz A, Angeles F, et al. (2001) Endocrine and metabolic abnormalities involved in obesity associated with typical antipsychotic drug administration. *Pharmacopsychiatry* 4: 223–231.

Barbano MF and Cador M (2007) Opioids for hedonic experience and dopamine to get ready for it. *Psychopharmacology (Berl)* 191: 497–506.

Barney CC, Morrison CM, Renkema LA, et al. (1992) Opioid modulation of thermal dehydration-induced thirst in rats. *Pharmacol Biochem Behav* 43: 1065–1070.

Bartus R, Emerich D, Hotz J, et al. (2003) Vivitrex®, an injectable, extended-release formulation of naltrexone, provides pharmacokinetic and pharmacodynamic evidence of efficacy for I month in rats. *Neuropsychopharmacology* 28: 1973–1982.

Bebarta V, Luyten D and Heard K (2003) Emergency medicine animal research: does use of randomization and blinding affect the results? *Acad Emerg Med* 10: 684–687.

Berner LA, Bocarsly ME, Hoebel BG, et al. (2011) Pharmacological interventions for binge eating: lessons from animal models, current treatments, and future directions. *Curr Pharm Des* 17: 1180–1187.

Berridge KC (2003) Pleasures of the brain. *Brain Cogn* 52: 106–128.

Berridge KC (2009) 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. *Physiol Behav* 97: 537–550.

Bersani G, Pesaresi L, Orlandi V, et al. (2007) Atypical antipsychotics and polydipsia: a cause or a treatment? *Hum Psychopharmacol* 22: 103–107.

Blass E, Fitzgerald E and Kehoe P (1987) Interactions between sucrose, pain and isolation distress. *Pharmacol Biochem Behav* 26: 483–489.

Blass EM and Fitzgerald E (1988) Milk-induced analgesia and comforting in 10-day-old rats: opioid mediation. *Pharmacol Biochem Behav* 29: 9–13.

Bobo WV, Epstein RA Jr and Shelton RC (2011) Effects of orally disintegrating vs regular olanzapine tablets on body weight, eating behavior, glycemic and lipid indices, and gastrointestinal hormones: a randomized, open comparison in outpatients with bipolar depression. *Ann Clin Psychiatry* 23: 193–201.

Bodnar RJ and Levine AS (2008) Role of opiate peptides in regulating energy balance. In: Harvey J and Withers DJ (eds) *Neurobiology of Obesity*. Cambridge, UK: Cambridge University Press, pp. 232–265.

Brambilla F, Monteleone P and Maj M (2007) Olanzapine-induced weight gain in anorexia nervosa: involvement of leptin and ghrelin secretion? *Psychoneuroendocrinology* 32: 402–406.

Brown DR, Blank MS and Holtzman SG (1980) Suppression by naloxone of water intake induced by deprivation and hypertonic saline in intact and hypophysectomized rats. *Life Sci* 26: 1535–1542.

Bushe CJ, Bradley AJ, Doshi S, et al. (2009) Changes in weight and metabolic parameters during treatment with antipsychotics and metformin: do the data inform as to potential guideline development? A systematic review of clinical studies. *Int J Clin Pract* 63: 1743–1761.

Citrome L, Stauffer VL, Chen L, et al. (2009) Olanzapine plasma concentrations after treatment with 10, 20, and 40 mg/d in patients with schizophrenia: an analysis of correlations with efficacy, weight gain, and prolactin concentration. *J Clin Psychopharmacol* 29: 278–283.

Cooper G, Pickavance L, Wilding J, et al. (2005) A parametric analysis of olanzapine-induced weight gain in female rats. *Psychopharmacology* 181: 80–89.

Cooper GD, Pickavance LC, Wilding JP, et al. (2007) Effects of olanzapine in male rats: enhanced adiposity in the absence of hyperphagia, weight gain or metabolic abnormalities. *J Psychopharmacol* 21: 405–413.

Cope MB, Nagy TR, Fernández JR, et al. (2005) Antipsychotic drug-induced weight gain: development of an animal model. *Int J Obes (Lond)* 6: 607–614.

Dean RL (2005) The preclinical development of Medisorb Naltrexone, a once a month long acting injection, for the treatment of alcohol dependence. *Front Biosci* 10: 643–655.

Ehret M, Goethe J, Lanosa M, et al. (2010) The effect of metformin on anthropometrics and insulin resistance in patients receiving atypical antipsychotic agents: a meta-analysis. *J Clin Psychiatry* 71: 1286–1292.

Elman I, Borsook D and Lukas SE (2006) Food intake and reward mechanisms in patients with schizophrenia: implications for metabolic disturbances and treatment with second-generation antipsychotic agents. *Neuropsychopharmacology* 31: 2091–2120.

Erlanson-Albertsson C (2005) How palatable food disrupts appetite regulation. *Basic Clin Pharmacol Toxico* 97: 61–73

Ferenczi S, Nunez C, Pinter-Kubler B, et al. (2010) Changes in metabolic-related variables during chronic morphine treatment. *Neurochem Int* 57: 323–330.

Fishbain DA, Cutler RB, Lewis J, et al. (2004) Do the second-generation "atypical neuroleptics" have analgesic properties? A structured evidence-based review. *Pain Med* 5: 359–65.

Fruzzetti F, Bersi C, Parrini D, et al. (2002) Effect of long-term naltrexone treatment on endocrine profile, clinical features, and insulin sensitivity in obese women with polycystic ovary syndrome. *Fertil Steril* 77: 936–944.

Fulghesu AM, Ciampelli M, Guido M, et al. (1998) Role of opioid tone in the pathophysiology of hyperinsulinemia and insulin resistance in polycystic ovarian disease. *Metabolism* 47: 158–162.

Gao XM, Sakai K and Tamminga CA (1998) Chronic olanzapine or sertindole treatment results in reduced oral chewing movements in rats compared to haloperidol *Neuropsychopharmacology* 19: 428–433.

Garcia-Barrado MJ, Iglesias-Osma MC, Rodriguez R, et al. (2002) Role of mu-opioid receptors in insulin release in the presence of inhibitory and excitatory secretagogues. *Eur J Pharmacol* 448: 95–104.

Glass MJ, Grace M, Cleary JP, et al. (2006) Potency of naloxone's anorectic effect in rats is dependent on diet preference. *Am J Physiol* 271: R217–R221.

Gorski ED and Willis KC (2003) Report of three case studies with olanzapine for chronic pain. *J Pain* 4: 166–168.

Gosnell BA and Krahn DD (1993) Morphine-induced feeding: a comparison of the Lewis and Fischer 344 inbred rat strains. *Pharmacol Biochem Behav* 44: 919–924.

Greenway FL, Whitehouse MJ, Guttadauria M, et al. (2009) Rational design of a combination medication for the treatment of obesity. *Obesity (Silver Spring)* 17: 30–39.

Haupt DW, Luber A, Maeda J, Melson AK, Schweiger JA, Newcomer JW (2005) Plasma leptin and adiposity during antipsychotic treatment of schizophrenia. *Neuropsychopharmacology* 30: 184–191.

Heard KJ, Krier S and Cleveland NR (2010) Knowledge of treatment group does not bias assessment of time to seizure in an animal model of cocaine poisoning. *Acad Emerg Med* 17: e75–e77.

Henderson DC, Copeland PM, Daley TB, et al. (2005) A double-blind, placebo-controlled trial of sibutramine for olanzapine-associated weight gain. *Am J Psychiatry* 162: 954–962.

Holtzman SG (1975) Effects of narcotic antagonists on fluid intake in the rat. *Life Sci* 16: 1465–1470.

Houshyar H, Gomez F, Manalo S, et al. (2003) Intermittent morphine administration induces dependence and is a chronic stressor in rats. *Neuropsychopharmacology* 28: 1960–72.

Johnson PM and Kenny PJ (2010) Dopamine d2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosc* 13: 635–641.

Kelley AE (2004). Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. *Neurosci Biobehav Rev* 27: 765–776.

Kelley AE, Baldo BA, Pratt WE, et al. (2005) Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. *Physiol Behav* 86: 773–795.

Khojainova N, Santiago-Palma J, Kornick C, et al. (2002) Olanzapine in the management of cancer pain. *J Pain Symptom Manage* 23: 346–350.

Kiser RS, Cohen HM, Freedenfeld RN, et al. (2001) Olanzapine for the treatment of fibromyalgia symptoms. *J Pain Symptom Manage* 22: 704–708.

Kochhar S, Nwokike JN, Jankowitz B, et al. (2002) Olanzapine overdose: a pediatric case report. *J Child Adolesc Psychopharmacol* 12: 351–353.

Korner J and Leibel RL (2003) To eat or not to eat - how the gut talks to the brain. *N Engl J Med* 349: 926–928.

Kreek MJ (2007) Opioids, dopamine, stress, and the addictions. *Dialogues Clin Neurosci* 9: 363–378.

Langleben DD, Busch EL, O'Brien CP, et al. (2012) Depot naltrexone decreases rewarding properties of sugar in patients with opioid dependence. *Psychopharmacology (Berl)* 220: 559–564.

Lenard NR, Zheng H and Berthoud HR (2010) Chronic suppression of μ-opioid receptor signaling in the nucleus accumbens attenuates development of diet-induced obesity in rats. *Int J Obes (Lond)* 34: 1001–1010.

Li Y, Eitan S, Wu J, et al. (2003) Morphine induces desensitization of insulin receptor signaling. *Mol Cell Biol* 23: 6255–6266.

McEwen BS (2004) Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann N Y Acad Sci* 1032: 1–7.

Mahendran R, Hendricks M and Chan YH (2010) Weight gain in Asian patients on second-generation antipsychotics. *Ann Acad Med Singapore* 39: 118–121.

Marquina D, Peña R, Fernández E, et al. (2011) Abnormal correlation between serum leptin levels and body mass index may predict metabolic dysfunction irrespective of the psychopharmacological treatment *Int Clin Psychopharmacol* 26: 169–172.

Melkersson KI and Hulting AL (2001) Insulin and leptin levels in patients with schizophrenia or related psychoses--a comparison between different antipsychotic agents. *Psychopharmacology (Berl)* 154: 205–212.

Muench J and Hamer AM (2010) Adverse effects of antipsychotic medications. *Am Fam Physician* 81: 617–622.

Murphy BP, Chung YC, Park TW, et al. (2006) Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. *Schizophr Res* 88: 5–25.

Nair SG, Adams-Deutsch T, Epstein DH, et al. (2009) The neuropharmacology of relapse to food seeking: methodology, main findings, and comparison with relapse to drug seeking. *Prog Neurobiol* 89: 18–45.

Narula PK, Rehan HS, Unni KE, et al. (2010) Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: A double-blind, placebo-controlled trial. *Schizophr Res* 118: 218–23.

Nathan PJ, O'Neill BV, Bush MA, et al. (2012) Opioid receptor modulation of hedonic taste preference and food intake: a single-dose

safety, pharmacokinetic, and pharmacodynamic investigation with gsk1521498, a novel ?-opioid receptor inverse agonist. *J Clin Pharmacol* Apr 52: 464–474.

Newcomer J (2005) Second-generation atypical antipsychotics and metabolic effects. a comprehensive literature review. *CNS Drugs* 19: 1–93.

Olszewski PK, Alsiö J, Schiöth HB, et al. (2011) Opioids as facilitators of feeding: can any food be rewarding? *Physiol Behav* 104: 105–110.

Olszewski PK and Levine AS (2007) Central opioids and consumption of sweet tastants: when reward outweighs homeostasis. *Physiol Behav* 91: 506–512.

O'Malley GF, Seifert S, Heard K, et al. (1999) Olanzapine overdose mimicking opioid intoxication. *Ann Emerg Med* 34: 279–281.

Palenzona S, Meier PJ, Kupferschmidt H, et al. (2004) The clinical picture of olanzapine poisoning with special reference to fluctuating mental status. *J Toxicol Clin Toxicol* 42: 27–32.

Pecina S (2008) Opioid reward 'liking' and 'wanting' in the nucleus accumbens. *Physiol Behav* 94: 675–680.

Peña R, Marquina D, Serrano A, et al. (2008) Frequency of abnormal correlation between leptin and the body mass index during first and second generation antipsychotic drug treatment. *Schizophr Res* 106: 315–319.

Power ML and Schulkin J (2008) Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br J Nutr* 99: 931–940.

Poyurovsky M, Isaacs I, Fuchs C, et al. (2003) Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: a double-blind, placebo-controlled study. *Am J Psychiatry* 160: 297–302.

Poyurovsky M, Pashinian A, Gil-Ad I, et al. (2002) Olanzapine-induced weight gain in patients with first-episode schizophrenia: a double-blind, placebo-controlled study of fluoxetine addition. *Am J Psychiatry* 159: 1058–1060.

Poyurovsky M, Tal V, Maayan R, et al. (2004) The effect of famotidine addition on olanzapine-induced weight gain in first-episode schizophrenia patients: a double-blind placebo-controlled pilot study. *Eur Neuropsychopharmacol* 14: 332–336.

Praharaj SK, Jana AK, Goyal N, et al. (2011) Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis. *Br J Clin Pharmacol* 71: 377–382.

Rada P, Barson JR, Leibowitz SF, et al. (2010) Opioids in the hypothalamus control dopamine and acetylcholine levels in the nucleus accumbens. *Brain Res* 1312: 1–9.

Raposo NR, Ferreira AS and Gattaz WF (2011) Body mass index increase, serum leptin, adiponectin, neuropeptide Y and lipid levels during treatment with olanzapine and haloperidol. *Pharmacopsychiatry* 44: 169–172.

Raskind MA, Burke BL, Crites NJ, et al. (2007) Olanzapine-induced weight gain and increased visceral adiposity is blocked by melatonin replacement therapy in rats. *Neuropsychopharmacology* 32: 284–288.

Remington G, Mann S, McCormick P, et al. (2011) Modeling chronic olanzapine exposure using osmotic minipumps: pharmacological limitations. *Pharmacol Biochem Behav* 100: 86–89.

Roth RM, Brunette MF and Green AI (2005) Treatment of substance use disorders in schizophrenia: a unifying neurobiological mechanism? *Curr Psychiatry Rep* 7: 283–291.

Scarpace PJ and Zhang Y (2009) Leptin resistance: a prediposing factor for diet-induced obesity. *Am J Physiol Regul Integr Comp Physiol* 296: R493–R500.

Schreiber S, Getslev V, Backer MM, et al. (1999) The atypical neuroleptics clozapine and olanzapine differ regarding their antinociceptive mechanisms and potency. *Pharmacol Biochem Behav* 64: 75–80.

See R (2000) The role of neurotransmitter receptors in the adverse effects of antipsychotic drugs. In: Lidow MS (ed) *Neurotransmitter Receptors in Actions of Antipsychotic Medications. Pharmacology and Toxicology: Basic and Clinical Aspects.* London: CRC Press, pp. 221–242.

Silberstein SD, Peres MF, Hopkins MM, et al. (2002) Olanzapine in the treatment of refractory migraine and chronic daily headache. *Headache* 42: 515–518.

Tempel A, Gardner EL and Zukin RS (1995). Neurochemical and functional correlates of naltrexone-induced opiate receptor up-regulation. *J Pharmacol Exp Ther* 232: 439–444.

Treuer T, Hoffmann VP, Chen AK, et al. (2009) Factors associated with weight gain during olanzapine treatment in patients with schizophrenia or bipolar disorder: results from a six-month prospective, multinational, observational study. *World J Biol Psychiatry* 10: 729–740.

Volkow ND, Wang GJ, Fowler JS, et al. (2008) Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philos Trans R Soc Lond B Biol Sci* 363: 3191–3200.

Wang HC, Chen PS, Lee IH, et al. (2006) Rapid leptin elevation after initiation of olanzapine? *Neuropsychobiology* 54: 182–185.

Weizman T, Pick CG, Backer MM, et al. (2003) The antinociceptive effect of amisulpride in mice is mediated through opioid mechanisms. *Eur J Pharmacol* 478: 155–159.

Wobrock T and Soyka M (2008) Pharmacotherapy of schizophrenia with comorbid substance use disorder--reviewing the evidence and clinical recommendations. *Prog Neuropsychopharmacol Biol Psychiatry* 32: 1375–1385.

Yeomans MR and Gray RW (2002) Opioid peptides and the control of human ingestive behaviour. *Neurosci Biobehav Rev* 26: 713–728.

Yuan CS, Sun S, Attele A, et al. (2009) Methylnaltrexone potentiates body weight and fat reduction with leptin. *J Opioid Manag* 5: 373–378.

Zhang M, Gosnell BA and Kelley AE (2008) Intake of high-fat food is selectively enhanced by mu opioid receptor stimulation within the nucleus accumbens. J Pharmacol Exp Ther 285: 908–914.

Zhang M and Kelley AE (2000) Enhanced intake of high-fat food following striatal mu-opioid stimulation: microinjection mapping and fos expression. *Neuroscience* 99: 267–277.