CLINICAL STUDY

Short-term treatment with olanzapine does not modulate gut hormone secretion: olanzapine disintegrating versus standard tablets

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Abstract

Background: Treatment with olanzapine (atypical antipsychotic drug) is frequently associated with various metabolic anomalies, including obesity, dyslipidemia, and diabetes mellitus. Recent data suggest that olanzapine orally disintegrating tablets (ODT), which dissolve instantaneously in the mouth, might cause less weight gain than olanzapine standard oral tablets (OST).

Design and methods: Ten healthy men received olanzapine ODT (10 mg o.d., 8 days), olanzapine OST (10 mg o.d., 8 days), or no intervention in a randomized crossover design. At breakfast and dinner, blood samples were taken for measurement of pancreatic polypeptide, peptide YY, glucagon-like peptide-1, total glucagon, total ghrelin, and cholecystokinin (CCK) concentrations.

Results: With the exception of pre- and postprandial concentration of ghrelin at dinner and preprandial CCK concentrations at breakfast, which were all slightly increased (respectively $P=0.048$, $P=0.034$ and $P=0.042$), olanzapine did not affect gut hormone concentrations. Thus, olanzapine ODT and OST had similar effects on gut hormone secretion.

Conclusion: Short-term treatment with olanzapine does not have major impact on the plasma concentration of gut hormones we measured in healthy men. Moreover, despite pharmacological difference, gut hormone concentrations are similar during treatment with olanzapine ODT and OST. The capacity of olanzapine to induce weight gain and diabetes is unlikely to be caused by modulation of the secretion of gut hormones measured here. We cannot exclude the possibility that olanzapine's impact on other gut hormones, to impair insulin sensitivity and stimulate weight gain, exists.

European Journal of Endocrinology 162 75–83

Introduction

The use of atypical antipsychotic (AP) drugs is associated with obesity (1, 2) and diabetes mellitus (3). The mechanism underlying these serious metabolic side effects is unclear. Olanzapine, one of the atypical AP drugs, which is extensively used to treat schizophrenia and (more recently) bipolar disorders, has offered a valuable alternative to the older 'typical' AP drugs, which have major (CNS) side effects. Currently, two types of olanzapine tablets are available for clinical use: standard (oral standard tablets (OST)) and orally disintegrating (orally disintegrating tablets (ODT)). Two recent papers report that treatment with ODT might be less harmful in terms of weight gain than treatment with OST (4, 5); while Arranz *et al.* reported significantly less weight gain in subjects treated with ODT versus OST for 6 weeks (3.3 vs 6.6 kg respectively), de Haan reported significant weight loss after switching from OST to ODT (in 16 weeks 6.6 kg weight loss versus 3.3 kg weight gain in subjects treated with OST).

The main pharmacological difference between these compounds is that ODT dissolves instantaneously in the mouth upon administration allowing absorption through the sublingual mucosa. Administration of the ODT formulation, therefore, results in an earlier detection of the drug in the plasma than OST (6), while the maximum plasma concentration ($C_{\max}$) and the time until the maximum plasma concentration is reached ($T_{\max}$) are similar for both compounds (6, 7). Thus, it is unlikely that distinct effects on central neurotransmission explain the different effect of ODT and OST on body weight.

The gastrointestinal (GI) tract is richly innervated by the enteric nervous system (ENS), which controls and coordinates enteric behavior, including motility, blood flow, and secretion (8). In recent years, a variety of peptide hormones have been identified. They are released from the gut in response to food intake and deprivation (9). These gut peptides are involved in the regulation of energy balance (9). Some evidence suggests that the ENS modulates gut hormone synthesis

and secretion. For example, ghrelin-secreting cells express the vesicular monoamine (MA) transporter 2 (10), suggesting a role of monoaminergic neurotransmission in ghrelin secretion. Also, secretion of glucagon-like peptide-1 (GLP-1) (11, 12) and peptide YY (PYY) (13) is stimulated by cholinergic muscarinic receptor agonists and blocked by atropine (11, 13). Since many of the small MA neurotransmitter receptors in the CNS have also been identified in the ENS, it is conceivable that olanzapine, which blocks many of these receptors, also affects neural circuits in the ENS.

We hypothesized that olanzapine impacts on gut hormone release to explain its characteristic to induce obesity and type 2 diabetes. We also proposed that treatment with ODT, which is absorbed through the sublingual mucosa and therefore presumably exerts less influence on MA receptors in the GI tract, would have less impact on gut hormone secretion than treatment with OST to explain their distinct impact on body weight. Here, we compare the early effects of the two forms of olanzapine tablets on pre- and postprandial gut hormone concentrations in healthy men.

Method

Twelve healthy men between 20 and 40 years were recruited through advertisements in local newspapers. The subjects were required to have a stable body mass index (BMI) between 20 and 27 kg/m² and a normal fasting plasma glucose concentration (<6.0 mmol/l). Subjects who had ever used AP medication, and subjects who were currently smoking or using medication affecting the CNS were excluded. All subjects provided written informed consent after explanation of the study procedures and possible adverse effects of the treatment. The protocol was approved by the medical ethics committee of the Leiden University Medical Center and registered by www.controlled-trials.com (ISRCTN17632637).

Drugs

All subjects received olanzapine standard tablets (OST; 10 mg o.d. for 8 days), olanzapine ODT (10 mg o.d. for 8 days), or no intervention in a randomized crossover design. The drugs were taken at 0800 h except on day 8 when they were taken at 0700 h. The minimum plasma concentration ($C_{\min}$) of olanzapine was determined on day 8 at 0700 h by HPLC with u.v. ($\lambda=270$ nm) detection. The detection limit of olanzapine was 5 µg/l.

Diet

To limit confounding by nutritional factors, subjects received a standard diet containing 2400 kcal/day on days 7 and 8 of each intervention period. The diet

consisted of bread, fillings, and drinks, prepared by the research center. The macronutrient composition of the diet was exactly the same on all occasions: 48% of total ingested calories from carbohydrates, 17% from proteins and 35% from fat. Intake of alcohol and caffeine/theine containing beverages was not allowed the day before and during all study occasions.

Clinical protocol

Subjects were studied thrice in random order; without an intervention (control) and after treatment with olanzapine OST (10 mg o.d., 8 days) and ODT (10 mg o.d., 8 days). There was a time interval of at least 6 weeks between each study occasion. On day 7, after a 10-h overnight fast, body fat percentage was determined by bioelectrical impedance analysis (BIA; Bodystat 1500 MDD, Bodystat LTD, Douglas, Isle of Man, UK). At this time point, the subjects were prescribed the standard diet delineated earlier. Subjects were re-admitted to the research center at 1700 h. A cannula for blood sampling was inserted into an antecubital vein. Blood samples were collected with S-monovette (Sarstedt, Etten-Leur, The Netherlands) from a three-way stopcock that was attached to a 0.9% NaCl infusion (20 ml/h; with 100 U heparin/500 ml) to keep the cannula from clotting. Blood samples were taken at 20 min intervals as from 1 h prior to until 2 h after each meal, and after that every 30 min until 4 h after each meal (dinner on day 7; breakfast on day 8) for measurement of pancreatic polypeptide (PP), PYY, GLP-1, total glucagon, total ghrelin, and cholecystokinin (CCK) concentrations. Total glucagon was measured in order to estimate oxyntomodulin (and glicentin) concentrations in response to meals. At 0700 h, the drug was taken. Dinner and breakfast were served at 1830 and 0800 h respectively. Subjects remained sedentary except for bathroom visits; at 2300 h, lights were switched off.

Assays

Blood was sampled in EDTA tubes to which Trasylol had been added (40 µl/ml blood). Each tube was immediately chilled on ice. Samples were centrifuged at 2630 *g* at 4 °C for 20 min. Subsequently, plasma was divided into separate aliquots and frozen at −80 °C until assays were performed. One mmol/l HCl (50 µl/ml) was added to the plasma for measurement of total ghrelin.

PYY_{3–36} and PP concentrations in plasma were measured by in-house RIA with a detection limit of 1 pmol/l. Total ghrelin concentration in plasma was measured by RIA (Linco Research, St Charles, Missouri, USA) with a detection limit of 0.93 pg/ml. The intra- and interassay coefficients of variation (CV) were 3.3–10 and 14.7–17.8% respectively. GLP-1 concentrations in plasma were measured by RIA after extraction of plasma

with 70% ethanol (vol/vol, final concentration). Carboxy-terminal GLP-1 immunoreactivity was determined using antiserum 89 390 (14), which has an absolute requirement for the intact amidated carboxy-terminus of GLP-1 7–36 amide, and cross-reacts <0.01% with carboxy-terminally truncated fragments and 89% with GLP-1 9–36 amide, the primary metabolite of dipeptidyl peptidase IV-mediated degradation. The sum of the two components (total GLP-1 concentration) reflects the rate of secretion of the L-cell. The detection limit was < 5 pmol/l, and intra-assay CV was < 10%. In order to estimate oxyntomodulin (and glicentin) concentrations, total glucagon concentrations were measured in plasma after extraction of plasma with 70% ethanol (vol/vol, final concentration). The glucagon RIA is directed against a mid sequence of the glucagon molecule comprising residues nos 6–15 (antibody code no. 4304) and, therefore, measures all glucagon-containing peptide moieties of pancreatic and intestinal origin (15, 16), including glicentin and oxyntomodulin. Standards were human glucagons, and tracer was monoiodinated human glucagon (both gifts from NovoNordisk, Bagsværd, Denmark). The detection limit was < 2 pmol/l, intra-assay CV < 6% at 40 pmol/l, and recovery of standard (glucagon), added to plasma before extraction, about 100% when corrected for losses inherent in the plasma extraction procedure. Plasma CCK concentrations were measured by CCK-specific RIA without cross-reactivity with any gastrin (17). The detection limit was 0.1 pmol/l, and the intra- and inter-assay variations at different concentrations ranged between 5 and 15% (17).

Homeostasis model assessment index

Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated as described by Matthews *et al.* (18) ($\text{HOMA-IR} = \text{fasting insulin (mU/l)} \times \text{fasting plasma glucose (mmol/l)} / 22.5$).

Statistical analysis

Results are presented as mean $\pm$ S.E.M. Data was logarithmically transformed before analysis when appropriate and statistically analyzed using paired Student's *t*-test. When the distribution of the data was not normal after logarithmic transformation, they were analyzed using Wilcoxon signed-rank test. Significance level was set at 0.05. First, the effect of treatment with olanzapine ODT was compared with olanzapine OST. Secondly, to evaluate the effect of treatment with olanzapine, the mean of values in response to treatment with olanzapine OST and olanzapine ODT was calculated and compared with values measured in the control group. All analysis was performed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Subjects

Twelve subjects (age: 25.1 ± 5.5 years) were enrolled in the study (19); ten subjects completed all study occasions. Two subjects did not finish their third study occasion for personal reasons, one missing treatment with olanzapine ODT, and the other treatment with olanzapine OST. The third subject who completed all study occasions was nauseous and vomited after dinner at one study occasion; at this particular occasion, the 'dinner' data were excluded from the statistical analysis. None of the subjects using olanzapine had major side effects. However, most subjects felt tired during the first days of the treatment.

Olanzapine concentration

Minimum plasma olanzapine concentration ($C_{\min}$) was 13.5 ± 1.3 and 15.4 ± 1.5 $\mu\text{g/l}$ during treatment with olanzapine ODT and OST respectively and did not differ between groups ($P=0.18$).

Anthropometric variables and metabolic profile in fasting condition

There was no difference in BMI, waist-to-hip ratio, or fat percentage between treatment conditions as we reported earlier (19). Treatment with olanzapine (ODT and OST) significantly ($P=0.005$) increased HOMA-IR (19) as compared with the control group, where the effect of ODT and OST did not differ. There was no difference in fasting glucose concentrations (control: 4.7 ± 0.1 mmol/l; olanzapine OST: 4.4 ± 0.2 mmol/l; olanzapine ODT: 4.1 ± 0.2 mmol/l) between treatment groups, while fasting insulin concentrations increased slightly (control: 7.3 ± 1.1 mU/l; olanzapine OST: 9.4 ± 1.1 mU/l; olanzapine ODT: 8.9 ± 1.2 mU/l), although not significantly ($P=0.053$). Fasting free fatty acids significantly decreased during olanzapine treatment ($P=0.013$ one tailed; control: 0.520 ± 0.065 , olanzapine OST: 0.383 ± 0.025 mmol/l, olanzapine ODT: 0.034 ± 0.038 mmol/l), while there was no difference between the effects of ODT and OST on these parameters (20).

Fasting and preprandial gut peptide concentrations

With exception of ghrelin concentrations at dinner and CCK concentrations at breakfast, which were both slightly increased in the treatment groups (respectively $P=0.048$, $P=0.042$), treatment with olanzapine did not affect preprandial gut hormone concentrations at dinner or fasting gut hormone concentrations. Gut peptide concentrations were similar during treatment with olanzapine ODT and OST (Table 1, Figs 1 and 2).

Table 1 Fasting and preprandial gut hormones at breakfast and dinner: without intervention (control), during treatment with olanzapine oral standard tablets (Ola-OST) and orally disintegrating tablets (Ola-ODT).

Parameter	Control (n=10)	Ola-OST (n=10)	Ola-ODT (n=10)	Paired t-test ODT versus OST	Paired t-test Co versus treatment
Mean PP dinner (pmol/l) ^a	34.2±8.2	37.5±8.2	39.2±10.9	NS	NS
Mean PP breakfast (pmol/l)	7.6±2.3	8.8±2.0	6.9±1.7	NS	NS
Mean PYY dinner (pmol/l) ^a	18.9±1.5	17.4±1.3	17.9±1.5	NS	NS
Mean PYY breakfast (pmol/l)	13.1±2.1	14.7±1.8	13.4±1.4	NS	NS
Mean GLP-1 dinner (pmol/l) ^a	12.6±1.5	14.2±1.8	15.0±2.7	NS	NS
Mean GLP-1 breakfast (pmol/l)	8.4±1.4	9.7±1.5	8.6±1.5	NS	NS
Mean total glucagon dinner (pmol/l) ^a	34.1±3.4	40.8±5.4	37.3±4.5	NS	NS
Mean total glucagon breakfast (pmol/l)	20.0±1.5	23.4±2.4	21.3±1.7	NS	NS
Mean ghrelin dinner (pg/ml) ^a	855±51	894±79	974±64	NS	0.048
Mean ghrelin breakfast (pg/ml)	882±61	866±71	890±67	NS	NS
Mean CCK dinner (pmol/l) ^a	0.93±0.34	1.20±0.45	1.28±0.36	NS	NS
Mean CCK breakfast (pmol/l)	0.28±0.06	0.78±0.22	0.68±0.21	NS	0.042

Data are presented as mean ± s.e.m. CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PP, pancreatic polypeptide; PYY, peptide YY.

^aData missing for one subject (ola-OST).

Postprandial gut peptide concentrations

Treatment with olanzapine did not affect postprandial gut hormone concentrations (Table 2, Figs 1 and 2) except at dinner when mean ghrelin concentrations were slightly increased in the treatment groups ($P=0.034$). Postprandial gut peptide concentrations were similar during treatment with olanzapine ODT and OST.

Discussion

This study shows that short-term treatment with either orally disintegrating or standard olanzapine formulations does not have a major impact on gut hormone concentrations in plasma in healthy men.

The mechanisms underpinning weight gain associated with AP drug use are unclear. Their affinity for central and/or peripheral MA receptors could be involved. A plethora of data suggests that gut hormones have an important physiological role in the regulation of postprandial satiety and energy homeostasis (9). The secretion of gut hormones is mainly stimulated by nutrient content of the gut. The secretion of various hormones is also modulated by monoaminergic neurotransmission, as has been demonstrated for GLP-1, PYY, PP, and ghrelin secretion (13, 21–23). Atypical AP drugs, including olanzapine, block various MA receptors in the CNS. Since the majority of these receptors are also located in the ENS, atypical AP drugs might induce weight by modulating gut hormone secretion. If so, olanzapine ODT might cause less weight gain, as it is absorbed more rapidly allowing less binding to MA receptors in the GI tract.

Ghrelin

In this study, pre- and postprandial ghrelin concentrations were slightly increased during olanzapine treatment at dinner, but not at breakfast, whereas

the effect of olanzapine ODT and OST was similar. Earlier studies have shown that long-term treatment with olanzapine is accompanied by elevated plasma ghrelin concentrations (24, 25). In contrast, ghrelin concentrations were either not affected (26, 27) or decreased (28, 29) by short-term treatment (2–10 weeks) with olanzapine. Unfortunately, in the short-term studies, the number of participants was small, participants were of both sexes, and hormonal status of premenopausal women was not taken into account. This might be of importance, since plasma ghrelin levels in humans are sexually dimorphic, with women in the late follicular phase exhibiting higher concentrations than men (30). The current study indicates that olanzapine does not have a major direct effect on plasma ghrelin levels in men. We therefore infer that ghrelin is not involved in the mechanism(s) underpinning the drug's metabolic effects. Long-term treatment with olanzapine may affect ghrelin secretion indirectly through its effects on body weight and/or composition.

CCK

Fasting CCK concentrations were slightly increased in the olanzapine-treated groups, while preprandial concentrations at dinner and postprandial concentrations at both breakfast and dinner were not affected. CCK concentrations were similar during treatment with olanzapine ODT and OST. To our knowledge, no data are available on the effect of olanzapine on plasma CCK concentrations. Weickert *et al.* recently showed that hyperinsulinemic euglycemia in healthy men resulted in up to a fivefold increase in circulating CCK concentrations that rapidly declined during lipid infusion and were negatively correlated with free fatty acids (FFA) concentrations (31). This interesting finding suggests that a negative feedback mechanism of circulating FFA on CCK concentration may exist. One might consider

Figure 1 Gut hormone concentrations at dinner. Data are presented as mean $\pm$ S.E.M. $\uparrow$, ingestion of meal. CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PP, pancreatic polypeptide; PYY, peptide YY.

whether the slight increase in fasting circulating CCK concentrations by olanzapine treatment is caused by suppression of circulating FFA concentrations.

PP and PYY

PP and PYY concentrations were not affected by olanzapine treatment. To our knowledge, no data are available on the effect of olanzapine on plasma PP and PYY concentrations in humans or animals. In rodents, long-term treatment with olanzapine significantly reduced PYY-binding densities in different parts of the brain when compared to control- and haloperidol-treated groups (32). This finding suggests that olanzapine might counteract the central effect of PYY on satiety. However, our data suggest that olanzapine does not modulate PP or PYY secretion to induce metabolic anomalies.

GLP-1

GLP-1 concentrations were similar in all treatment groups. To our knowledge, no data are available on the effect of olanzapine or other atypical AP drugs on

plasma GLP-1 concentrations. GLP-1 secretion from intestinal human L-cells is stimulated by M1 and M2 muscarinic receptor agonists and blocked by a muscarinic antagonist (12). Olanzapine is among the AP drugs with the highest affinity for muscarinic receptors, although its affinity is relatively low when compared with atropine (33), which may account for the lack of its abilities to affect plasma GLP-1 levels.

Total glucagons

Total glucagon concentrations were measured in order to estimate oxyntomodulin (and glicentin) concentrations in response to meals. The total glucagon concentrations were similar in all study groups, and the effects of olanzapine ODT and OST did not differ. There was a rather large increase in total glucagon concentrations in response to breakfast, which did not show any sign of decline 240 min after breakfast (Fig. 1). The concentrations were still high before dinner but showed a small additional increase in response to the meal (Fig. 2). These findings are similar to the (diurnal) responses to meals described by Holst

Figure 2 Gut hormone concentrations at breakfast. Data are presented as mean $\pm$ S.E.M. $\uparrow$, ingestion of meal. CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PP, pancreatic polypeptide; PYY, peptide YY.

et al. and Le Quellec *et al.* (34, 35). In humans, oxyntomodulin reduced food intake by 25% and repeated preprandial s.c. administration resulted in significant weight loss in overweight and obese subjects (36). Interestingly, oxyntomodulin (OXM) also increased activity-related energy expenditure in obese

humans (37) and prevented food induced suppression of TSH secretion in rats when administered intracerebroventricularly (38). It should be noted that it is impossible to distinguish which glucagon-containing moieties contributed to the postprandial increase in the total glucagon concentration. Glucagon from

Table 2 Postprandial gut hormones at breakfast and dinner: without intervention (control), during treatment with olanzapine standard tablets (Ola-OST) and orally disintegrating tablets (Ola-ODT).

Parameter	Control (n=10)	Ola-OST (n=10)	Ola-ODT (n=10)	Paired t-test ODT versus OST	Paired t-test Co versus treatment
Mean PP dinner (pmol/l) ^a	42.1 $\pm$ 7.8	40.8 $\pm$ 6.4	40.3 $\pm$ 7.6	NS	NS
Mean PP breakfast (pmol/l)	36.1 $\pm$ 7.0	33.9 $\pm$ 7.6	37.4 $\pm$ 7.6	NS	NS
Mean PYY dinner (pmol/l) ^a	22.2 $\pm$ 2.5	19.1 $\pm$ 1.4	21.4 $\pm$ 2.2	NS	NS
Mean PYY breakfast (pmol/l)	25.3 $\pm$ 3.9	22.0 $\pm$ 1.7	23.2 $\pm$ 2.2	NS	NS
Mean GLP-1 dinner (pmol/l) ^a	14.9 $\pm$ 1.3	16.9 $\pm$ 1.8	18.7 $\pm$ 3.3	NS	NS
Mean GLP-1 breakfast (pmol/l)	24.0 $\pm$ 3.9	23.0 $\pm$ 3.9	22.8 $\pm$ 2.5	NS	NS
Mean total glucagon dinner (pmol/l) ^a	29.4 $\pm$ 2.2	32.5 $\pm$ 3.5	30.7 $\pm$ 3.0	NS	NS
Mean total glucagon breakfast (pmol/l)	33.0 $\pm$ 4.0	32.9 $\pm$ 4.2	36.5 $\pm$ 5.5	NS	NS
Mean ghrelin dinner (pg/ml) ^a	780 $\pm$ 47	892 $\pm$ 87	862 $\pm$ 47	NS	0.034
Mean ghrelin breakfast (pg/ml)	774 $\pm$ 35	736 $\pm$ 46	788 $\pm$ 64	NS	NS
Mean CCK dinner (pmol/l) ^a	1.38 $\pm$ 0.33	1.39 $\pm$ 0.37	1.61 $\pm$ 0.28	NS	NS
Mean CCK breakfast (pmol/l)	1.38 $\pm$ 0.23	1.79 $\pm$ 0.37	1.68 $\pm$ 0.25	NS	NS

Data are presented as mean $\pm$ S.E.M. CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PP, pancreatic polypeptide; PYY, peptide YY.

^aData missing for one subject (ola-OST).

the pancreas is also likely to contribute, but would be expected to reduce food intake if anything (39). There is currently no specific analysis for oxyntomodulin available.

The results of this short-term study suggest that olanzapine-induced weight gain is not caused by modulation of the secretion of gut hormones we measured here. Obviously, we cannot exclude the possibility that olanzapine impacts on other gut peptides (e.g. bombesin, acylated ghrelin) to modulate insulin sensitivity and body weight. Alternatively, olanzapine might act as a competitive inhibitor of central gut hormone receptors preventing their physiological effects. In rodents, olanzapine reduced PYY-binding densities in different parts of the brain (32), indicating that the drug might indeed counteract the central effects of PYY. In a recent study, olanzapine exhibited a negligible affinity for a number of anorexigenic neuroreceptors, including those of CCK (40). Unfortunately, the drug's affinity for GLP-1, PYY, and OXM receptors was not studied. Furthermore, the weight gaining properties of olanzapine might either be associated with its peripheral effect on serotonin receptors in the pylorus as proposed by de Haan *et al.* (5) or with its affinity for MA receptors in the CNS, in particular the hypothalamus and the brain stem. Indeed, the distinct weight-inducing properties of olanzapine ODT and OST, which were recently confirmed in two clinical studies (41, 42), may be ascribed to their different pharmacodynamic characteristics. Arranz *et al.* (4) proposed that partial sublingual absorption of the ODT formulation, partly bypassing gastrointestinal metabolism, might alter the parent to metabolite concentration ratio. They state that two of olanzapine's metabolites would be devoid of activity at central receptors. If true, ODT and OST may differ in their effect on the CNS.

Activation of histamine H1, serotonin 5-HT (2C in particular), α -1 adrenergic, and dopamine D2 receptors are known to inhibit food intake and reduce body weight (43–47). All these MA receptors are blocked by olanzapine. Neuroendocrine effects of olanzapine might also account for its weight-inducing properties. We recently showed that short-term treatment with olanzapine shifts the temporal relationship of the acrophase of prolactin and cortisol in healthy men (19). Similar endocrine patterns are known to presage weight gain in a variety of obese animal models (48). Finally, treatment with AP is often complicated by tiredness/drowsiness, which might diminish physical activity and thereby induce weight gain. However, we did not detect differences in physical activity (by accelerometer) or resting energy expenditure (by indirect calorimetry) during short-term treatment with olanzapine (20). Notably, this study was conducted in active healthy young men and not in patients with psychiatric disorders, which might be of importance for the level of physical activity.

The small sample size is a limitation of this study; However, its crossover design increases the statistical power. Indeed, if we take fasting PYY levels as an example, the study has 85% power to detect a difference of 5.0 pmol/l with an alpha error level of 5% in a two-sided paired *t*-test, given an average baseline value of 18.2 with a s.d. of 3.9 pmol/l (s.e.m. is given in the table). As stated before, we measured the plasma concentration of a variety, but not all gut hormones in response to olanzapine treatment. Therefore, the data do not exclude the possibility that the drug impacts on one of the other hormones to affect insulin action and body weight.

In conclusion, short-term treatment with olanzapine does not have a major impact on the plasma concentrations of gut hormones we measured in healthy men. Moreover, despite the pharmacological differences of the two oral olanzapine formulations, the concentration of these hormones was similar during treatment with ODT and OST. Weight gain and diabetes during olanzapine treatment are therefore unlikely to be caused by modulation of the secretion of gut hormones measured here. We cannot exclude the possibility that olanzapine impacts on other gut hormones to impair insulin sensitivity and stimulate weight gain.

Declaration of interest

All authors declare that they have no conflict of interest.

Funding

The research described in this article was supported by the Dutch Diabetes Foundation (2002.01.005) and was partly funded by Eli Lilly (Houten, The Netherlands).

Acknowledgements

We thank the research assistants of the Clinical Research Center of the General Internal Medicine Department of Leiden University Medical Center (E J M Ladan-Eijgenraam and I A Sierat-van der Steen) for their assistance during the study.

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Received 14 August 2009

Accepted 4 September 2009