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Endocrine and metabolic effects of antipsychotic drugs

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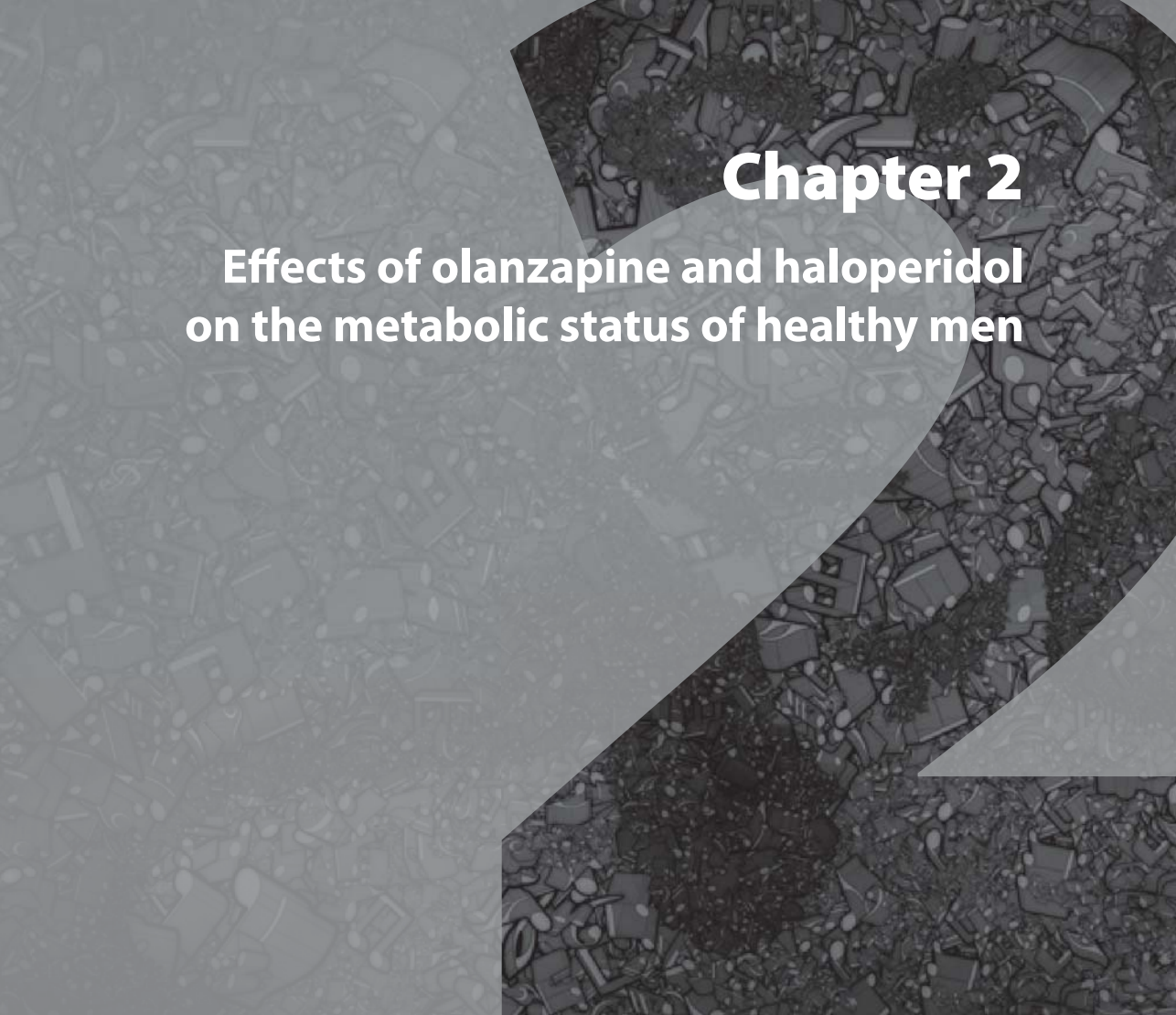
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Chapter 2

Effects of olanzapine and haloperidol on the metabolic status of healthy men

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ABSTRACT

Background: A large body of evidence suggests that antipsychotic drugs cause body weight gain and type 2 diabetes mellitus, and atypical (new generation) drugs appear to be most harmful. The aim of this study was to determine the effect of short-term olanzapine (atypical antipsychotic drug) and haloperidol (conventional antipsychotic drug) treatment on glucose and lipid metabolism.

Research Design and Methods: Healthy normal weight men were treated with olanzapine (10 mg/day, n=7) or haloperidol (3 mg/day, n=7) for 8 days. Endogenous glucose production, whole body glucose disposal (by [6,6 $^2\text{H}_2$]-glucose dilution), lipolysis (by [$^2\text{H}_3$]-glycerol dilution) and substrate oxidation rates (by indirect calorimetry) were measured before and after intervention in basal and hyperinsulinemic condition.

Results: Olanzapine hampered insulin-mediated glucose disposal (by $1.3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), whereas haloperidol did not have a significant effect. Endogenous glucose production was not affected by either drug. Also, the glycerol rate of appearance (a measure of lipolysis rate) was not affected by either drug. Olanzapine, but not haloperidol, blunted the insulin-induced decline of plasma free fatty acids and triglycerides concentrations. Fasting free fatty acid concentrations declined during olanzapine treatment, whereas they did not during treatment with haloperidol.

Conclusions: Short-term treatment with olanzapine reduces fasting plasma free fatty acid concentrations and hampers insulin action on glucose disposal in healthy men, whereas haloperidol has less clear effects. Moreover, olanzapine, but not haloperidol, blunts the insulin-induced decline of plasma free fatty acids and triglyceride concentrations. Notably, these effects come about without a measurable change of body fat mass.

INTRODUCTION

Typical antipsychotic drugs (AP) have been the cornerstone of the medical management of patients with schizophrenia for a long time. The advent of atypical AP drugs has brought clear benefits for schizophrenic patients, as these compounds have less extrapyramidal side effects and ameliorate negative symptoms (1). However, a large body of evidence suggests that the use of these drugs is associated with obesity (2,3) and diabetes mellitus (4). Several studies have looked at the metabolic effects of AP drugs in non-diabetic schizophrenic patients. The results consistently show that these drugs induce (euglycemic) hyperinsulinemia and impaired glucose tolerance (5,6). Treatment with atypical AP drugs appears to be more harmful for glucose/lipid metabolism than treatment with conventional AP drugs (5,7).

Because obesity is a major risk factor for insulin resistance and type 2 diabetes (8), it is tempting to postulate that weight gain induced by atypical AP drugs is primarily responsible for their unfavourable impact on these pathologies. However, this does not appear to be the case in studies evaluating this possibility (2,9). Moreover, in a review of case reports, diabetes often developed after a short treatment period, in some cases without significant weight gain (10). The metabolic profile often improved upon drug discontinuation, whereas rechallenge with the same drug resulted in recurrence of hyperglycemia (10). Thus, AP drugs may act directly to induce insulin resistance and diabetes. Atypical AP drugs antagonize a broad range of monoamine neurotransmitter receptors. In addition to their relatively weak affinity for dopamine D2 receptors, they have a strong affinity for serotonin 5-HT₂, histamine H₁, α ₁ adrenergic, and muscarinic M₃ receptors, whereas typical AP drugs particularly antagonize dopamine D2 receptors. Indeed, various neurotransmitters, whose signals are blocked by atypical but not typical AP drugs, are involved in the control of glucose metabolism (11-15), which could mechanistically explain direct actions of olanzapine on insulin sensitivity.

We hypothesized that short-term treatment with AP drugs induces insulin resistance through a mechanistic route that is independent of weight gain and that atypical drugs exert stronger effects than typical compounds in this respect. To evaluate this hypothesis, we treated healthy nonobese men with olanzapine (atypical AP) or haloperidol (typical AP) for 8 days and studied the impact of these interventions on glucose and lipid metabolism by hyperinsulinemic euglycemic clamp, isotope dilution technology, and indirect calorimetry.

RESEARCH DESIGN AND METHODS

Subjects

14 healthy men between 20 and 40 yr were recruited through advertisements in local newspapers. Subjects were required to have a normal weight, normal fasting plasma glucose concentration (<6.0 mmol/l), and normal physical examination. Subjects who had ever used AP

medication, and subjects who were currently smoking or using medication affecting the central nervous system were excluded. Subjects who dropped out (because of side effects) were replaced by other volunteers. All subjects provided written informed consent after the study procedures and possible adverse effects of the treatment had been explained. The protocol was approved by the medical ethics committee of the Leiden University Medical Center.

Clinical protocol

Subjects underwent a hyperinsulinemic, euglycemic clamp at baseline and on the last day (day 8) of treatment with either olanzapine (10 mg once daily) or haloperidol (3 mg once daily). The drugs were taken at 0800 h. The drug doses prescribed are in the low range of doses used for the treatment of patients with schizophrenia. On both study days, substrate oxidation was measured by indirect calorimetry (Oxycon β ; Jaeger Toennies, Breda, The Netherlands) in basal (after a 10-h overnight fast) and hyperinsulinemic conditions. Body fat percentage was determined by bioelectrical impedance analysis (BIA; Bodystat[®] 1500, Bodystat Limited, Douglas, Isle of Man, United Kingdom). Body mass index (weight/length²) and waist/hip circumference were measured according to WHO recommendations. The subjects were asked to refrain from vigorous physical exercise for one week before each clamp. When the study drug was not tolerated, treatment was discontinued. Food intake was not monitored.

Hyperinsulinemic, euglycemic clamp

[6,6-²H₂]-glucose was infused in the basal state and during a hyperinsulinemic, euglycemic clamp to determine the effect of insulin on peripheral glucose disposal and endogenous glucose production. Lipolysis was monitored by primed continuous infusion of [²H₅]-glycerol. At 07:30 h, after an overnight (10 h) fast, subjects were admitted to the clinical research unit and asked to lie down in a semi-recumbent position. An iv catheter was placed in an antecubital vein for infusions. Another catheter was placed in the contralateral hand for blood sampling. This hand was placed in a heated box (60 °C) to obtain arterialised venous blood samples. The subjects were asked to take their last drug dose at 08.00 A.M. Thereafter, basal blood samples for glucose, insulin, free fatty acids (FFA), lipid spectrum and background isotope enrichment of [6,6-²H₂]-glucose and [²H₅]-glycerol were taken. At time (t) = 0, primed (26.4 μ mol/kg) continuous (0.33 μ mol/kg per minute) infusion of [6,6-²H₂]-glucose (enrichment 99.9%; Cambridge Isotopes, Cambridge, MA) was started and continued throughout the clamp (4 h) to monitor glucose metabolism. At 09:00 h (t = 60), a primed (1.6 μ mol/kg) continuous (0.11 μ mol/kg per minute) infusion of [²H₅]-glycerol (Cambridge Isotopes) began and continued throughout the clamp (3 h) to monitor lipolysis. At t = 90-120 min, 4 blood samples were taken with 10 minutes intervals for determination of plasma glucose, insulin, glycerol, and enrichment of [6,6-²H₂]-glucose and [²H₅]-glycerol. Subsequently (t = 120), a primed continuous (40 mU·m⁻²·min⁻¹) infusion of insulin (Actrapid, Novo Nordisk Pharma BV, Alphen aan de Rijn, The Netherlands) was started. Insulin was infused for 2 h. Blood glucose concentrations were measured every 5 minutes, and a

variable infusion of 20% glucose (enriched with 3% [6,6- $^2\text{H}_2$]-glucose) was adjusted to maintain a stable blood glucose concentration (~ 5.0 mmol/l). By the end of the hyperinsulinemic clamp ($t = 210$ – 240), blood was drawn every 10 minutes for determination of plasma glucose, insulin, glycerol, and enrichment of [6,6- $^2\text{H}_2$]-glucose and [$^2\text{H}_5$]-glycerol. Indirect calorimetry was performed for determination of resting energy expenditure, respiratory quotient (RQ), glucose and fat oxidation in basal condition ($t = 60$ – 90) and during hyperinsulinemia ($t = 180$ – 210).

Assays

Each tube, except the serum tubes, was immediately chilled on ice. Samples were centrifuged at 4000 rpm at 4 C for 20 min. Subsequently, plasma was divided into separate aliquots and frozen at -80 C until assays were performed.

Serum glucose, total cholesterol and HDL-cholesterol were measured in the laboratory for Clinical Chemistry at Leiden University Medical Center, using a fully automated Hitachi Modular P800 system (Hitachi Ltd., Tokyo, Japan). LDL-cholesterol was measured with COBAS INTEGRA 800 (Roche Diagnostics, Mannheim, Germany).

Serum insulin was measured by immunoradiometric assay (INS-IRMA; BioSource Europe S.A., Nivelles, Belgium), and serum glucagon was measured by radioimmunoassay (RIA; Medgenix, Fleurus, Belgium). Serum prolactin concentrations were measured with a sensitive time-resolved fluoroimmunoassay with a detection limit of 0.04 $\mu\text{g/l}$ (Delfia, Wallac Oy, Turku, Finland).

Plasma levels of FFA and triglycerides (TG) were determined using commercially available kits (Wako Pure Chemical Industries, Osaka, Japan; Roche Diagnostics).

Glucose and [6,6- $^2\text{H}_2$]-glucose enrichment as well as glycerol and [$^2\text{H}_5$]-glycerol enrichment were determined in a single analytical run, using gas chromatography coupled to mass spectrometry (Hewlett-Packard, Palo Alto, CA) as previously described (16,17).

Calculations

In isotopic steady state condition, the rate of glucose disappearance (R_d) equals the rate of glucose appearance (R_a). R_a , which represents endogenous glucose production (EGP), was calculated by dividing the [6,6- $^2\text{H}_2$]-glucose infusion rate (mg/min) by the steady state plasma [6,6- $^2\text{H}_2$]-glucose tracer/tracee ratio. During insulin infusion, R_d was calculated by adding the rate of exogenous glucose infusion to the R_a . The R_a of glycerol was calculated by dividing the [$^2\text{H}_5$]-glycerol infusion rate ($\mu\text{mol/minute}$) by the steady-state plasma [$^2\text{H}_5$]-glycerol tracer/tracee ratio. Total lipid and carbohydrate oxidation rates were calculated as previously described (18). Data are expressed per kilogram body weight.

Statistical analysis

The study was powered to detect a difference in glucose infusion rate before and after treatment with either drug. Eight subjects per group allowed detection of a 30% difference with

80% power at a 2-sided significance level of 0.05. Data are presented as mean $\pm$ standard error of the mean. Data were logarithmically transformed when appropriate. Comparisons were made within groups with two-tailed dependent Student's *t*-test. To compare the effect of olanzapine and haloperidol treatment (between groups), an independent Student's *t*-test was used; the difference of the values before and after each intervention was compared. When the distribution of data was not normal after logarithmic transformation, they were analysed using non-parametric Wilcoxon signed-rank test. Significance level was set at 0.05. All analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc, Chicago, IL).

RESULTS

Subjects, anthropometric measures and plasma metabolites

14 subjects were included in the study. Four subjects discontinued haloperidol treatment: 1 subject because of a vasovagal reaction when basal blood samples were taken at the first study day; 3 subjects because of the occurrence of side effects. Of those subjects, 2 subjects had acute dystonia, which was treated with anticholinergic drugs (Akineton® i.m.) and 1 subject discontinued treatment because of restlessness. All of these subjects were replaced by other volunteers. None of the subjects using olanzapine had major side effects. Five were somewhat drowsy during the first day of treatment only. The father of one subject in the haloperidol group was of Mediterranean origin (ethnicity may have impact on insulin sensitivity); all other subjects were of Caucasian origin. In the haloperidol group, one subject had a father with type 2 diabetes, and in the olanzapine group one subject had a second degree family member with type 2 diabetes.

Table 1 summarizes anthropometric measurements and biochemical parameters in fasting condition on day 0 and day 8 in both groups. Baseline characteristics, including risk factors for insulin resistance (i.e. anthropometrics, ethnicity, family history of type 2 diabetes, fasting insulin and glucose levels), did not differ between the treatment groups. Body weight and waist-hip ratio did not change from day 0 to day 8 in either group. Fat percentage decreased slightly during treatment with haloperidol. Fasting plasma insulin and glucose levels did not change during treatment in either group. FFA concentrations significantly declined during olanzapine treatment ($P = 0.03$). This effect did not differ significantly from the effect of haloperidol treatment. Serum glucagon concentrations were significantly elevated by olanzapine treatment, but the difference with the effect of haloperidol did not reach statistical significance. Plasma prolactin concentrations were increased during treatment in both groups (olanzapine $P = 0.002$; haloperidol $P = 0.01$), which indicates that the drugs were properly taken.

Table 1: Subject characteristics; before and after treatment with olanzapine or haloperidol.

	Olanzapine (n=7)		Haloperidol (n=7)	
	Day 0	Day 8	Day 0	Day 8
Age (yr)	25.7 ± 1.3		23.7 ± 1.3	
Body weight (kg)	76.7 ± 3.4	77.4 ± 3.3	76.8 ± 2.2	76.6 ± 2.2
BMI (kg/m ²)	22.3 ± 0.7	22.5 ± 0.6	22.9 ± 0.8	22.8 ± 0.9
WHR	0.82 ± 0.02	0.83 ± 0.02	0.79 ± 0.02	0.80 ± 0.02
Fat percentage (%)	9.1 ± 0.7	9.3 ± 1.2	10.6 ± 1.3	8.9 ± 1.5 *
Glucose (mmol/l)	4.9 ± 0.2	5.1 ± 0.2	5.1 ± 0.1	4.9 ± 0.1
Insulin (mU/l)	10.2 ± 1.2	11.5 ± 1.9	8.3 ± 0.8	7.6 ± 0.6
Glucagon (pg/ml)	54.3 ± 4.7	68.5 ± 6.6 *	50.9 ± 5.2	53.9 ± 4.3
Prolactin (µg/l)	9.0 ± 1.9	16.3 ± 3.1 **	8.8 ± 1.5	15.2 ± 1.9 *
TG (mmol/l)	1.22 ± 0.20	1.33 ± 0.18	1.16 ± 0.12	1.32 ± 0.30
FFA (mmol/l)	0.58 ± 0.10	0.43 ± 0.10 *	0.51 ± 0.08	0.53 ± 0.08
Total cholesterol (mmol/l)	4.3 ± 0.3	4.2 ± 0.2	3.8 ± 0.3	3.9 ± 0.2

Values are expressed as mean ± S.E.M. Abbreviations: BMI, body mass index; FFA, free fatty acids; TG, triglycerides; WHR, waist hip ratio.

* $P < 0.05$ vs. baseline

** $P < 0.01$ vs. baseline

Endogenous glucose production and whole body glucose disposal

Basal condition

Serum glucose and insulin concentrations in basal condition did not change in response to either treatment (Table 1). Accordingly, endogenous glucose production (EGP) was not affected by olanzapine or haloperidol (Table 2, Figure 1).

Hyperinsulinemic clamp

Data on glucose metabolism during insulin infusion are shown in Table 2. Serum glucose concentrations were clamped at similar levels on both study days. Also, plasma insulin concentrations during insulin infusion were in the postprandial range and similar on both days (Table 2). Background enrichment of $[6,6\text{-}^2\text{H}_2]$ -glucose (% of total glucose) was similar on both study occasions (olanzapine: day 0 $1.33 \times 10^{-2} \pm 0.07 \times 10^{-2}$, day 8 $1.29 \times 10^{-2} \pm 0.04 \times 10^{-2}$; haloperidol: day 0 $1.31 \times 10^{-2} \pm 0.02 \times 10^{-2}$, day 8 $1.32 \times 10^{-2} \pm 0.03 \times 10^{-2}$).

The glucose infusion rate (GIR) required to maintain euglycemia during hyperinsulinemia was reduced after olanzapine treatment (Figure 1). Although haloperidol did not affect the GIR to a significant extent, the magnitude of its effect did not differ significantly from that of olanzapine. The capacity of insulin to suppress EGP was not affected by either treatment (Figure 1). Glucose disposal during hyperinsulinemia was significantly blunted by olanzapine treatment (Figure 1). Again, although haloperidol did not affect glucose disposal to a significant extent, the magnitude of its effect did not differ significantly from that of olanzapine.

Table 2. Metabolic variables during hyperinsulinemic euglycemic clamp.

	Olanzapine (n=7)		Haloperidol (n=7)	
	Day 0	Day 8	Day 0	Day 8
Glucose (mmol/l)	4.6 ± 0.2	4.5 ± 0.4	5.1 ± 0.1	4.9 ± 0.1
Insulin (mU/l)	71.6 ± 2.3	72.6 ± 2.8	61.6 ± 5.8	61.2 ± 5.7
Background enrichment of 6,6- ² H ₂ glucose (% of total glucose)	1.33 × 10 ⁻² ± 0.07 × 10 ⁻²	1.29 × 10 ⁻² ± 0.04 × 10 ⁻²	1.31 × 10 ⁻² ± 0.02 × 10 ⁻²	1.32 × 10 ⁻² ± 0.03 × 10 ⁻²
GIR (mg·kg ⁻¹ ·min ⁻¹)	6.3 ± 0.9	4.9 ± 0.9 *	8.0 ± 0.5	7.6 ± 0.7
Glucose disposal (mg·kg ⁻¹ ·min ⁻¹)	8.2 ± 0.9	6.9 ± 0.8 *	10.0 ± 0.5	9.6 ± 0.7
EGP basal (mg·kg ⁻¹ ·min ⁻¹)	2.6 ± 0.10	2.6 ± 0.12	2.6 ± 0.08	2.6 ± 0.08
EGP hyperinsulinemic (mg·kg ⁻¹ ·min ⁻¹)	1.9 ± 0.06	2.0 ± 0.15	2.0 ± 0.04	2.0 ± 0.04
EGP %inhibition	25.9 ± 1.8	21.0 ± 4.7	21.6 ± 2.0	20.1 ± 2.3
Ra glycerol basal (μmol·kg ⁻¹ ·min ⁻¹)	2.5 ± 0.27	2.5 ± 0.30	3.0 ± 0.26	3.2 ± 0.24
Ra glycerol hyperinsulinemic (μmol·kg ⁻¹ ·min ⁻¹)	2.1 ± 0.10	2.1 ± 0.14	2.1 ± 0.17	2.0 ± 0.22
Ra glycerol %decline	16.4 ± 5.9	15.4 ± 7.1	28.2 ± 8.1	35.2 ± 6.8
FFA %decline	83.2 ± 2.2	65.3 ± 6.9 *	81.4 ± 2.6	84.7 ± 2.4
TG % decline	17.0 ± 3.6	8.1 ± 3.6 **	19.4 ± 6.2	28.2 ± 3.9

Values are expressed as mean ± S.E.M.

Abbreviations: EGP, Endogenous glucose production; EGP %inhibition, decline of EGP during hyperinsulinemia expressed as percentage of basal value; FFA %decline, decline of circulating FFA during hyperinsulinemia expressed as percentage of basal value; GIR, glucose infusion rate; Ra, rate of appearance; TG %decline, decline of circulating TG during hyperinsulinemia expressed as percentage of basal value.

* $P < 0.05$ vs. day 0

** $P < 0.01$ vs. day 0

Lipid metabolism

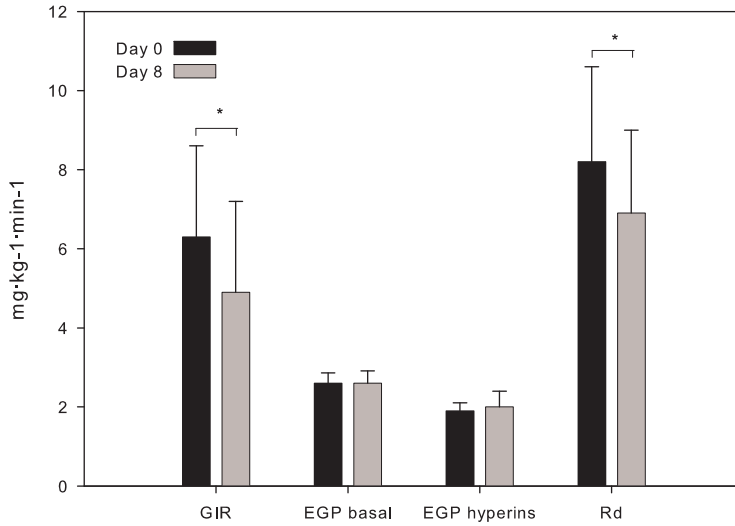
Basal condition

In fasting condition, plasma FFA concentrations significantly decreased during olanzapine treatment, and this effect did not differ from that of haloperidol although haloperidol's impact did not reach statistical significance. Fasting TG concentrations (Table 1) and basal glycerol Ra (Table 2) were not affected by either drug.

Hyperinsulinemic euglycemic clamp

Data on lipid metabolism during insulin infusion are shown in Table 2. Insulin significantly suppressed the glycerol Ra in the haloperidol ($P = 0.028$ on day 0, $P = 0.018$ on day 8) treated group, but not in the olanzapine treated group ($P = 0.071$ on day 0, $P = 0.379$ on day 8). During hyperinsulinemia, the decline of circulating FFA and TG levels, expressed as percentage of basal value, was significantly blunted by olanzapine, whereas the decline of circulating FFA and TG was not affected by treatment with haloperidol. Thus, the propensity of olanzapine to blunt the decline of circulating FFA and TG by hyperinsulinemia differed significantly from the effect of haloperidol.

Olanzapine (n=7)



Haloperidol (n=7)

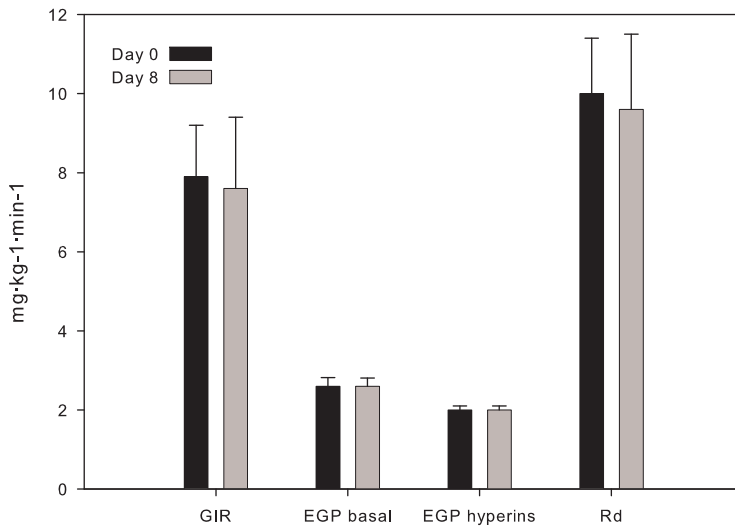


Figure 1. Glucose infusion rate (GIR), endogenous glucose production basal (EGP basal) and hyperinsulinemic (EGP hyperins) and glucose disposal (Rd) before and after 8 days treatment with olanzapine and haloperidol.

Values are expressed as mean $\pm$ S.D.

Abbreviations: EGP, Endogenous glucose production; GIR, glucose infusion rate; Rd, glucose disposal.

* $P < 0.05$

Glucose and lipid oxidation rate

Table 3 provides an overview of the effects of both drugs on substrate oxidation. Resting energy expenditure, RQ, and lipid and glucose oxidation rate were not affected by either drug.

Table 3. Fuel oxidation before and after treatment with olanzapine or haloperidol.

	Olanzapine (n=7)		Haloperidol (n=7)	
	Day 0	Day 8	Day 0	Day 8
RQ				
Basal	0.83 ± 0.015	0.87 ± 0.026	0.82 ± 0.011	0.83 ± 0.012
Hyperinsulinemic	0.86 ± 0.020	0.92 ± 0.034	0.86 ± 0.018	0.86 ± 0.017
Glucose oxidation (mg·kg ⁻¹ ·min ⁻¹)				
Basal	1.92 ± 0.25	2.62 ± 0.52	1.85 ± 0.18	2.07 ± 0.18
Hyperinsulinemic	2.92 ± 0.37	3.60 ± 0.68	2.63 ± 0.28	2.87 ± 0.28
Lipid oxidation (mg·kg ⁻¹ ·min ⁻¹)				
Basal	1.04 ± 0.09	0.76 ± 0.14	1.06 ± 0.07	1.04 ± 0.09
Hyperinsulinemic	0.83 ± 0.11	0.48 ± 0.20	0.94 ± 0.12	0.93 ± 0.14
REE (kcal/day)				
Basal	1344.3 ± 36.4	1351.7 ± 79.9	1303.9 ± 35.3	1341.8 ± 26.6
Hyperinsulinemic	1382.7 ± 38.3	1457.1 ± 64.9	1430.6 ± 54.0	1493.1 ± 56.1

Values are expressed as mean ± S.E.M. There were no significant differences in fuel oxidation after treatment with olanzapine or haloperidol.

Abbreviations: RQ, respiratory quotient; REE, resting energy expenditure.

DISCUSSION

To establish the early effects of AP drugs on glucose and lipid metabolism, we treated healthy young men with 10 mg olanzapine or 3 mg haloperidol once daily for only 8 days. Olanzapine significantly reduced the glucose infusion rate required to maintain euglycemia during insulin infusion, indicating that the drug induces whole body insulin resistance. Specifically, olanzapine reduced insulin mediated glucose disposal, whereas it did not affect insulin's capacity to suppress EGP. These effects did not differ from those of haloperidol to a significant extent, although the glucose infusion rate and disposal during haloperidol treatment were not significantly different from baseline. Olanzapine also curtailed the decline of circulating FFA and TG during hyperinsulinemia, whereas it did not affect the glycerol Ra or the ability of insulin to inhibit this measure of the rate of lipolysis. Notably, these metabolic effects occurred without a measurable effect on body weight or body fat mass, although the waist circumference increased slightly in response to olanzapine treatment. In clear contrast, haloperidol did not affect the insulin-induced decline of FFA and TG concentrations.

Effects on glucose metabolism

These data indicate that olanzapine hampers insulin action on glucose disposal, whereas the effect of haloperidol was less clear. This inference is consistent with data from large

epidemiological studies (19-21), showing that patients treated with atypical AP drugs are more likely to develop diabetes mellitus than patients treated with typical AP drugs. Also in line with our data, Newcomer *et al* (7) reported that schizophrenic patients treated with olanzapine are more insulin resistant than patients treated with typical AP drugs, as estimated by intravenous glucose tolerance test. Relatively few studies have looked at the metabolic effects of AP drugs in healthy subjects. Sowell *et al* (22) assessed meal tolerance and insulin sensitivity, using a 2-step hyperinsulinemic euglycemic clamp and a mixed meal tolerance test, in normal subjects after 3 weeks of olanzapine (10 mg/day; n=22), risperidone (4 mg/day; n=14) or placebo (n=19) treatment. The glucose infusion rate required to maintain euglycemia during hyperinsulinemia was not affected by either treatment, suggesting that the drugs did not impact on insulin action. However, treatment with olanzapine significantly increased fasting insulin and glucose levels, whereas treatment with risperidone or placebo did not. Also, there was a significant increase of the glucose area under the plasma concentration curve (AUC) in response to the mixed meal tolerance test in the group treated with olanzapine. These data are quite difficult to reconcile. Moreover, glucose disposal and EGP were not determined in these studies. In full agreement with our data, 10 days of olanzapine treatment was recently reported to decrease the glucose infusion rate required to maintain euglycemia in healthy men (23). EGP and glucose disposal were not determined in this study.

The (sub)acute nature of the inhibitory impact of olanzapine treatment on glucose disposal is consistent with clinical data indicating that atypical AP drugs can induce hyperglycemia within a couple of weeks, before significant weight gain has occurred (10). Moreover, it corroborates papers reporting that proximate measures of insulin resistance do not correlate with BMI in schizophrenic patients treated with atypical AP drugs (2,9). Also, Dwyer *et al.* (24) reported that atypical AP drugs acutely (<3 h) induce hyperglycemia in mice, whereas typical AP drugs do not. The ability of these medications to induce hyperglycemia *in vivo* was tightly correlated with their effect on glucose transport in pheochromocytoma (PC12) cells *in vitro* (24). However, PC12 cells do not express the GLUT-4 transporter, which is abundant in muscle and responsive to insulin (25), and the concentration of drugs required to block glucose uptake in these cell systems is generally very high (26). Thus, although clozapine and fluphenazine were shown to also block glucose transport in a rat muscle cell line *in vitro* (27), the relevance of these findings for the mechanistic explanation of our data remains uncertain.

Alternatively, our observations may be explained by the distinct receptor affinity profiles of olanzapine and haloperidol. Haloperidol particularly antagonizes dopamine D2 receptors, whereas olanzapine also blocks serotonin 5-HT₂, histamine H₁, α 1 adrenergic, and muscarinic M3 receptors (28). Activation of all of these receptor (sub)types, including the D2 receptor (29), generally inhibits food intake, reduces body weight and/or enhances insulin secretion (30-33). Notably, various receptors blocked by olanzapine appear to be directly (i.e. independent of their effects on body weight) involved in the regulation of glucose metabolism. Indeed, imipramine induces hyperglycemia in mice by blocking 5-HT₂ receptors (14), and a single dose

of ketanserin, a 5-HT₂ receptor antagonist, impairs insulin action on glucose metabolism in healthy humans (12). Blocking H₁ receptors in cardiac muscle tissue impairs glucose uptake (15), whereas, in apparent contradiction, activation of H₁ receptors in the brain acutely elevates plasma glucose levels (34). Thus, the H₁ receptor has multiple, apparently opposite roles in the control of glucose metabolism. Activation of dopamine D₂ receptors ameliorates insulin resistance in obese women through a mechanism that is independent of body weight (13), and D₂ receptor binding sites are reduced in the brain of obese animal models and humans (29). Finally, α ₁ adrenergic receptor knock out mice are glucose intolerant (11), and α ₁ adrenergic receptors stimulate glucose uptake in muscle cells (35). Thus, antagonism of either one of these receptors, alone or in combination, by olanzapine may hamper insulin action and explain our findings.

Effects on lipid metabolism

Neither drug affected insulin's capacity to suppress lipolysis. Olanzapine, but not haloperidol decreased FFA concentrations in fasting condition (although group differences did not reach statistical significance). Moreover, it curtailed the decline of circulating FFA and TG concentrations during hyperinsulinemia, which indeed clearly differed from the effect of haloperidol. In agreement with our findings, olanzapine was shown to reduce FFA concentration in a recent comprehensive evaluation of lipid changes in schizophrenia (36). The cause of these changes in lipid metabolism remains to be established. We speculate that olanzapine inhibits lipoprotein lipase (LPL) activity in muscles and impairs the stimulatory action of insulin on LPL in adipose tissue. LPL hydrolyses the triacylglycerol component of circulating lipoprotein particles, chylomicrons and VLDL, to provide FFA for tissue utilisation. In fasting condition, LPL is active in muscle and inhibited in adipose tissue, whereas (postprandial) hyperinsulinemia stimulates LPL in adipose tissue and inhibits LPL activity in muscle (37,38). Reduced LPL activity in muscles may therefore reduce plasma FFA concentrations and impair fatty acid oxidation in fasting condition. Reduced LPL activity in adipose tissue would explain the blunted decline of plasma FFA and TG during hyperinsulinemia. Inhibition of LPL activity could either result from direct effects of the drug or be secondary to its effect on circulating prolactin levels. Hyperprolactinemia has been reported to inhibit LPL activity in adipose tissue in humans (39) and rodents (40).

In aggregate, these data suggest that olanzapine impairs insulin action on glucose and lipid disposal in muscle and adipose tissue, whereas it does not affect insulin's capacity to inhibit glucose production or lipolysis. Notably, these are early metabolic effects of olanzapine that occur without a measurable change of body fat mass. Our findings may explain the property of olanzapine to induce dyslipidemia and diabetes mellitus in the long term. Short-term haloperidol treatment does not appear to affect lipid metabolism, which corroborates the notion that typical AP drugs are less harmful in a metabolic context.

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