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Chronic treatment with antipsychotics in rats as a model for antipsychotic-induced weight gain in human

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Abstract

Several clinical reports have demonstrated that most antipsychotics of the new generation, but not the typical antipsychotic haloperidol, induce weight gain in schizophrenic patients. Since weight gain induces serious health complications in humans, it is crucial to test upcoming antipsychotic compounds in an animal model of weight gain. With the aim of evaluating whether the rat can be used as a model for antipsychotic-induced weight gain, we have investigated the effect of chronic treatment (3 weeks) with one antipsychotic drug inducing weight gain in clinic (olanzapine) and one antipsychotic not inducing weight gain in clinic (haloperidol), on food and water intake and body weight gain in rats. We included both female and male rats in this study. To reduce spontaneous high food intake in rats, and to be able to evaluate the treatment effect on a potential increase of food intake or metabolic changes, we allowed animal to receive only low-palatability chow. In male rats, none of the two compounds induced weight gain, but in female rats, both compounds induced weight gain. Consequently, the effect observed in rats does not match the clinical situation, and Wistar rats in this set-up cannot be considered a relevant model for antipsychotic-induced weight gain in humans.

Keywords: Antipsychotic; Weight gain; Rats; Olanzapine; Haloperidol

1. Introduction

Several clinical reports have shown that most antipsychotics of the new generation, particularly clozapine and olanzapine, induce weight gain in schizophrenic patients, a side effect with considerable incidence (Allison et al., 1999; Allison and Casey, 2001; Henderson, 2001; Russel and Mackell, 2001; Sussman, 2001; Taylor and McAskill, 2000; Wirshing et al., 1999). Patients under such treatment can gain 4–5 kg after 10 weeks of treatment (Allison et al., 1999). Clozapine and olanzapine can induce Type II diabetes mellitus in 20–30% of patients (Henderson et al., 2000; Henderson, 2001; Hägg et al., 1998; Lindenmayer et al., 2001). Consequently, such compounds have devastating effect on life condition of patients and expose them to health complication related to obesity like cancer, cardiovascular dysfunction, atherosclerosis, heart failure, etc. (Allison et al., 1999; Aronne, 2001). Moreover, these severe side effects reduce compliance and increase the chance for a patient to be rehospitalized (Allison et al., 1999). Some other antipsychotics of the new generation, like risperidone or sertindole, only induce a minor body weight increase (Allison et al., 1999; Allison and Casey, 2001) in comparison with olanzapine (Basson et al., 2001; Sussman, 2001; Taylor and McAskill, 2000). Moreover, the body weight increase induced by treatment with such antipsychotics reach a plateau after 2–3 months of treatment, whereas with olanzapine or clozapine, the body weight of treated patients continues to increase (Wirshing et al., 1999). Contrary to clozapine or olanzapine, the typical antipsychotic haloperidol has been shown not to induce significant weight gain in schizophrenic patients (Allison et al., 1999; Allison and Casey, 2001; Basson et al., 2001; Sussman, 2001). In the worse case, haloperidol has only been described as inducing weight gain at a level similar to the placebo control level (Baptista et al., 2002b; Sussman and Ginsberg, 1999; Wirshing et al., 1999).

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Both genders are affected by major body weight increase after treatment with antipsychotics (Allison and Casey, 2001). Clinical reports related to this gender effect are sometimes controversial and not always related to the body mass index (BMI) of patients at the beginning of these studies, even if this factor appears crucial in the analysis of data (Aronne, 2001; Basson et al., 2001). Using proper control conditions, it appears that men are more vulnerable than women to such side effects, more specifically those men with low BMI (Basson et al., 2001). However, clinical data contradicting this claim has also been published (Allison and Casey, 2001; Russel and Mackell, 2001).

Various authors tried to explain the mechanism of antipsychotic-induced weight gain in patients (Baptista, 1999; Baptista et al., 2002b; Parada et al., 1989), but no general conclusion could be reached. Each drug targets different receptors inducing a similar final consequence on body weight of schizophrenic patients, body weight gain, but via different metabolic and physiologic effects (Casey and Zorn, 2001). However, it has been demonstrated in in vivo studies and clinical reports that compounds with an antagonistic effect on the 5-HT_{2C} (McIntyre et al., 2001), histaminergic H_1 (McIntyre et al., 2001; Morimoto et al., 2001; Taylor and McAskill, 2000; Wirshing et al., 1999), and α_1- or α_2-adrenergic receptors (Hamann et al., 2001; Heinonen et al., 1999; Wellman et al., 1993) or agonistic effect on the muscarinic M_3 (Yamada et al., 2001) receptor would induce weight gain by metabolic effect or increase of appetite (Baptista et al., 2002b; Casey and Zorn, 2001; McIntyre et al., 2001). Thus, prediction of drug-induced weight gain seems possible considering the receptor profile of compounds (McIntyre et al., 2001). However, it can be an easy prediction when considering a specific receptor's antagonistic or agonistic action. On the other hand, antipsychotics have affinity for other receptors than the one previously mentioned and the combinatorial agonistic or antagonistic effects on various receptors makes such predictions difficult or impossible (Casey and Zorn, 2001). Ziprasidone, a new antipsychotic recently launched, has antagonistic effects on both the 5-HT_{2C} and histaminergic H_1 receptors (Tandon et al., 1997). Consequently, the receptor profile of this compound would suggest that it will induce a strong weight gain in clinic, but clinical reports available tend to show that this compound does not induce more weight gain in patients than in placebo controls (Allison et al., 1999; Casey and Zorn, 2001; Russel and Mackell, 2001). The agonist effect of ziprasidone on the 5-HT_{1A} receptor (Tandon et al., 1997) might antagonize the effect of the 5-HT_{2C} and H_1 antagonism on weight gain and explains this lack of body weight increase. Therefore, the full receptor profile of a compound hardly permits prediction about its potency to induce weight gain in patients.

It is crucial to test upcoming antipsychotic compounds in an animal model of weight gain with the receptor profile of new antipsychotics not being fully relevant for prediction of this side effect and with the goal to develop effective antipsychotic treatments not inducing weight gain. This model should have correlation to the clinical situation. Consequently, we have investigated the effect of chronic treatment on body weight gain and food and water intake in rats with one antipsychotic drug that induces weight gain in clinic (olanzapine) and one antipsychotic drug that does not (haloperidol). To study the gender difference being described in the clinic for the effect of antipsychotics on weight gain (Baptista, 1999; Basson et al., 2001; Heimberg et al., 1995; Russel and Mackell, 2001; Wirshing et al., 1999), we included both female and male rats in this study. Male rats would better match the clinical situation, but previous studies demonstrated that female rats gain body weight more easily than males when exposed to antipsychotics (Baptista et al., 1987, 1997a, 2002a; Heiman et al., 2001). It consequently confirms the necessity to investigate the effect of chronic treatment with antipsychotics both in male and female rats. To reduce spontaneous high food intake in rats and to avoid quickly reaching a ceiling effect on measurement of food intake in animals, we allowed our animals to receive only low-palatability chow. This food exposure will consequently permit better evaluation of the treatment effect on a potential increase of food intake or metabolic modification of rats as animals will have a low spontaneous food intake level. Under such conditions, we will highlight the potential metabolic modification induced by chronic treatment with antipsychotics in animals.

2. Materials and methods

2.1. Animals

Eighty Mol:Wistar Hannover rats (M&B, Denmark) were used in this study. The animals, 40 of each gender, weighed in close proximity of 300 g for males and 200 g for females at the beginning of the study. Following arrival, each animal was given a general physical examination to assess the health status. The rats were single-housed in clear plastic cages (42.5 × 26.5 × 18.5 cm Macrolon Type III) in climate-controlled animal facilities (temperature at 21 ± 2 °C and relative humidity at 60 ± 10%). Animals were maintained on a 12-h reversed light–dark cycle (light on between 21:00 and 09:00 h) that started 2 weeks before the first dosing. Animals had access to water ad libitum. All animals were fed the special synthetic (low palatability) rat chow (AIN 93 diet, SDS No. 821002, pellets) ad libitum for approximately 2 weeks before the first dosing. Aiming to avoid stressing the animals and to limit experimental effect on their eating behaviour, the first dosing took place during the late light phase (07:30–08:30 h), when the animals are expecting the dark period (09:00–21:00 h) and still have a low eating behaviour. One week before dosing, the animals were weighed and counterbalanced into the five dosing groups to achieve a similar mean body weight in each of the dosing

groups. All the animal experiments in this study were conducted under the supervision of a veterinarian and in accordance with the Danish legislation of animal use for scientific procedures as described in the "Animal Testing Act" (Consolidation Act No. 726 of 9 September 1993 as amended by Act No. 1081 of 20 December 1995).

2.2. Procedures

2.2.1. Drug treatment

Two dosages of each antipsychotic were used for oral administration (haloperidol: 0.08 and 0.31 mg/kg/day; olanzapine: 5.0 and 20 mg/kg/day). Doses chosen for this experiment were according to those inducing an antipsychotic-like effect in rats models for schizophrenia (Paabøl Andersen and Pouzet, 2001), to the half-life of these compounds in rats ($t_{1/2}$ haloperidol = 1.5 h, Cheng and Paalzow, 1992; $t_{1/2}$ olanzapine = 2.5 h, Aravagiri et al., 1999), with respect to the bioavailability of these drugs as estimated from prior unpublished data, and to reach exposures as close as possible to the therapeutic ones (Eilers, 1995; Perry et al., 1997; Rao et al., 2001).

Rats were treated with one of four drug or vehicle (VEH) conditions for 21 days by oral administration (gavage). Drugs were administered during the same period every day until the last day. The volume administrated to the animals was calculated based on the weekly body weight evaluation. The animals were dosed twice daily. The first dosage was given between 07:30 and 08:30 h. The second dosage was given between 14:30 and 15:30 h. The dosage volume for each administration was 2.5 ml/kg, to reach the full amount of 5.0 ml/kg/day. The VEH animals were treated orally with 0.9% NaCl during the 3 weeks and on the same daily basis as the drug-treated groups.

2.2.2. Body weight measurement

The individual body weights were assessed and recorded once a week, prior to dosing.

2.2.3. Food and water intake measurement

Once a week, at time of dosing, the weekly individual food and water intake were assessed and recorded. Measurement of food intake for each rat was performed by weighing their respective food rack. The weekly water intake was similarly assessed by weighing their respective water bottles.

2.2.4. Drug exposure

Consecutive to the last dosing, seven blood samples were taken from two rats for each dose group and gender, with the aim to assess mean serum exposure of the antipsychotic drugs per dose group. Blood samples were drawn 5, 15, and 30 min and 1, 2, 4, and 7 h after the last drug administration by periorbital puncture. These blood samples were coagulated for 30 min at room temperature and centrifuged for 10 min at 3200 × *g*. Subsequently, the serum (supernatant) was transferred to new vials and frozen at − 20 °C until the time of analysis.

2.2.5. Analysis

The samples were purified by protein precipitation with acetonitrile (1:4) and subsequently filtered through Porvair Microlute protein precipitate plate filters (Porvair, UK). Calibration curves of haloperidol and olanzapine (0–1000 ng/ml) were prepared on each day of analysis from blank rat serum. All samples were spiked with aliquots of sertindole (H. Lundbeck, Denmark) as internal standard (50 ng/ml). The samples were quantified for content of antipsychotics by LC-MS-MS. Ten microliters of each sample was injected on to a Agilent 1100 HPLC system (Agilent Technologies, USA) equipped with a Quatro Ultima MS detector (Micromass, UK). Positive-ion electrospray ionization mode was used for the MS. Sertindole, haloperidol, and olanzapine, respectively, were detected at parent>daughter molecular mass of 441.09>112.96, 376.06>164.91, and 313.01>255.93 Da, using a cone voltage of 48, 54, and 70 V and a collision energy of 30, 25, and 25 eV. Nitrogen was used for the auxiliary and nebulizer gases, and argon was used for the collision gas. The separation was achieved on a reversed-phase column (20 × 2.1 mm I.D.) packed with 2.5 mm particle size (Xterra MS C18, Waters, USA). Samples were eluted at 40 °C with a gradient solvent system of 50 mM ammonium acetate–acetonitrile, running from 10% to 80% organic over 4 min at 0.3 ml/min, reverting back to 10% organic from 4.5 to 4.6 min, and reequilibrating the column until a total run time of 6 min at 0.5 ml/min. Retention times were 3.53, 3.75, and 4.37 min for olanzapine, haloperidol, and sertindole, respectively. Peak areas correlated linearly with serum concentrations of the drugs (r^2>.99) in the range 0.5–2000 ng/ml. Limit of quantification (LOQ) for the drugs was 0.5 ng/ml (*S*/*N*>10).

2.2.6. Statistical analyses

Change from baseline is calculated for all body weight assessments for each of the 3-week periods by subtracting the baseline value, defined as the last assessment in the previous period. To investigate the influence of the different factors (Treatment × Gender × Weeks), an ANOVA has been performed according to the change from the baseline for the assessment of body weight, food and water intake, and "body weight gain/food intake" ratio. Factors of treatment and gender are between-subject factors and weeks is a within-subject factor used as a repeated measurement.

The null hypothesis of no interaction between gender and treatment was tested first. The treatment effect was tested by a post hoc analysis (Fisher's PLSD) within each gender when the test for interaction (Treatment × Gender) reached the significant level (Ps < .05). The effect of treatment within the gender effect has been analyzed for each single week when the three-way interaction (Treatment × Gender × Weeks) reached the significant level (Ps < .05).

2.2.7. Formulations

Olanzapine (H. Lundbeck) was dissolved first in a minimum volume of diluted hydrochloric acid prior to final dilution in 0.9% NaCl. Haloperidol (Sigma-Aldrich, Denmark) was dissolved first in a minimum volume of tartaric acid before final dilution in 0.9% NaCl. VEH was 0.9% NaCl in all cases. All drugs and VEH were given in a final volume of 5 ml/kg. New solutions were prepared weekly.

3. Results

3.1. Effect of antipsychotics on body weight gain

The three-way repeated measurement ANOVA (Treatment × Gender × Weeks) of the cumulative body weight increase of rats over the 3-week treatment with antipsychotics yielded a significant effect for these three main effects (Ps < .001). We also obtained a significant effect for most of the interactions analyzed (Ps < .001): Treatment × Gender, Treatment × Weeks and the full interaction Treatment × Gender × Weeks. This significant full interaction [$F(8,140) = 115.13$, $P < .001$] effect permitted us to reanalyze the effect of treatment within weeks and for each gender via a post hoc analysis. As shown in Fig. 1, there was only a significant difference in males between the VEH- and olanzapine (20 mg/kg/day)-treated group ($P < .001$), demonstrating that this dose of olanzapine induced a decrease of body weight of rats. As shown in Fig. 2, there was a significant difference in females between the VEH- and all other haloperidol- or olanzapine-treated groups (Ps < .01), except for olanzapine 20 mg/kg/day. It demonstrates that irrespective of the antipsychotic, female rats gained body weight as a consequence of this chronic treatment.

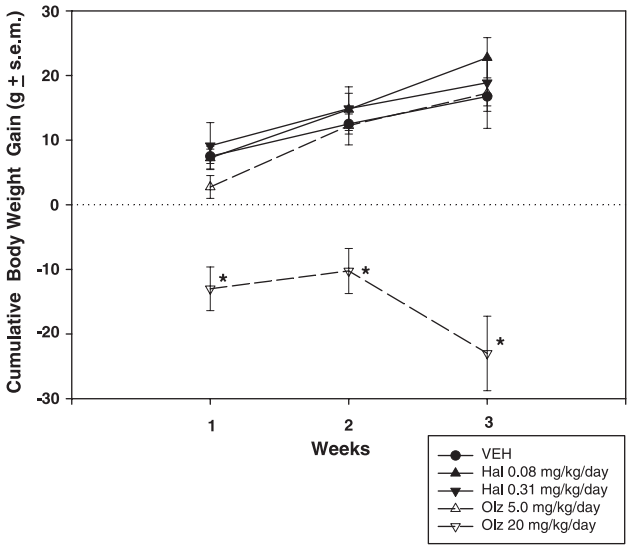

Fig. 1. Effects of chronic treatment (3 weeks) with haloperidol or olanzapine (administered orally twice a day) on cumulative body weight gain in male Wistar rats exposed to low-palatability synthetic chow. * $P < .05$ vs. VEH-treated rats.

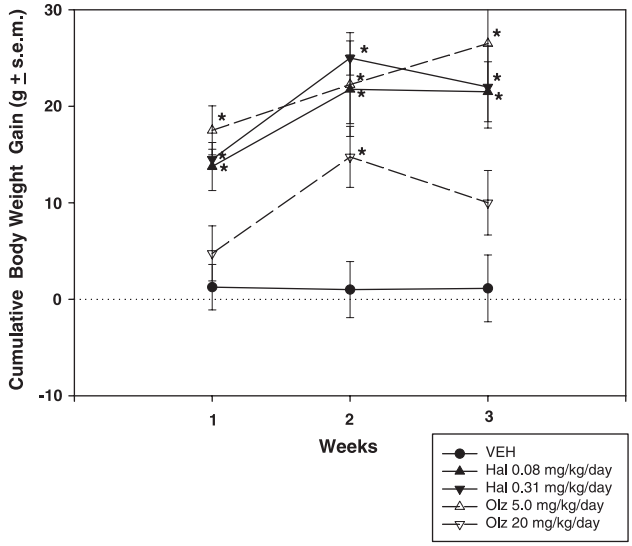

Fig. 2. Effects of chronic treatment (3 weeks) with haloperidol or olanzapine (administered orally twice a day) on cumulative body weight gain in female Wistar rats exposed to low-palatability synthetic chow. * $P < .05$ vs. VEH-treated rats.

3.2. Effect of antipsychotics on food intake

The three-way repeated measurement ANOVA (Treatment × Gender × Weeks) of the cumulative food intake of rats over the 3-week treatment with antipsychotics yielded a significant effect for these three main effects (Ps < .01). We also obtained a significant effect for all the interaction

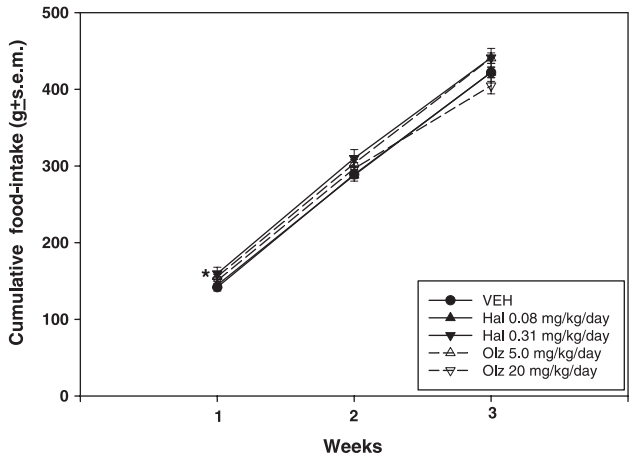

Fig. 3. Effects of chronic treatment (3 weeks) with haloperidol or olanzapine (administered orally twice a day) on cumulative food intake in male Wistar rats exposed to low-palatability synthetic chow. * $P < .05$ vs. VEH-treated rats.

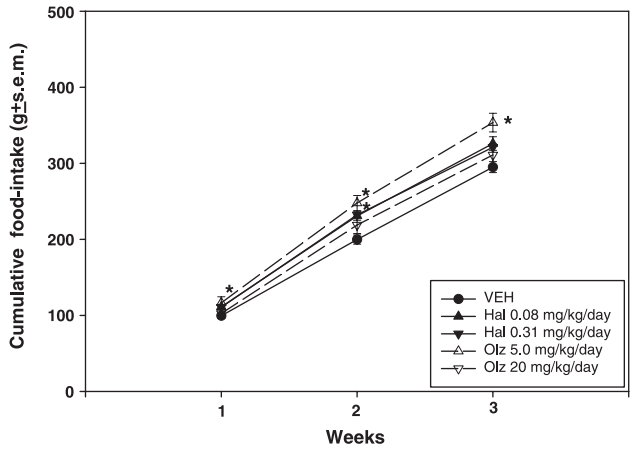

Fig. 4. Effects of chronic treatment (3 weeks) with haloperidol or olanzapine (administered orally twice a day) on cumulative food intake in female Wistar rats exposed to low-palatability synthetic chow. * $P < .05$ vs. VEH-treated rats.

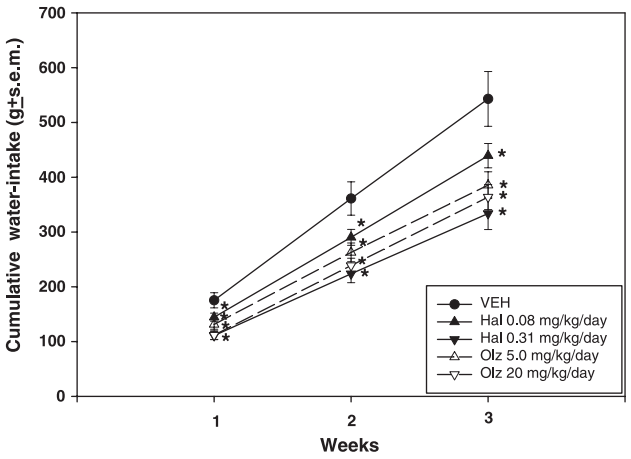

Fig. 6. Effects of chronic treatment (3 weeks) with haloperidol or olanzapine (administered orally twice a day) on cumulative water intake in female Wistar rats exposed to low-palatability synthetic chow. * $P < .05$ vs. VEH-treated rats.

analyzed (Ps < .01), except for the Treatment × Gender interaction (P>.30). The significant full interaction [$F(8,140) = 2.93$, $P < .01$] effect permitted us to analyze the effect of treatment within weeks and for each gender via a post hoc analysis. As shown in Fig. 3, there was a minor effect of treatment in males, as only a significant difference between the VEH- and haloperidol (0.31 mg/kg/day)-treated groups on the first week of treatment ($P < .05$) was reached. As shown in Fig. 4, there was a significant difference in females between the VEH- and olanzapine (5.0 mg/kg/day)-treated groups all over the treatment (Ps < .02). Thus, contrary to 20-mg/kg/day olanzapine, 5.0-mg/kg/day olanzapine induced a constant increase of food intake in female rats. Groups treated with haloperidol (0.08 and 0.31 mg/kg/day) were only significantly different from the VEH-treated groups ($P < .02$ and $P < .01$, respectively) during the second week of treatment.

3.3. Effect of antipsychotics on water intake

The three-way repeated measurement ANOVA (Treatment × Gender × Weeks) of the cumulative water intake of rats over the 3 weeks of treatment with antipsychotics yielded a significant effect for these three main effects (Ps < .005). We obtained a significant effect for the interactions Treatment × Weeks [$F(8,140) = 10.96$, $P < .001$] and Gender × Weeks [$F(2,140) = 6.90$, $P < .005$]. As shown in Fig. 5 vs. Fig. 6, the significant interaction Gender × Weeks demonstrated that over the 3 weeks of treatment males drank more than females (water intake after 3 weeks of treatment: 478.60 ± 20.50 for males and 413.02 ± 17.81 for females). Moreover, the significant interaction Treatment × Weeks demonstrated that over the 3 weeks of treatment and irrespective of sexes, rats treated with antipsychotics drank less than rats treated with VEH.

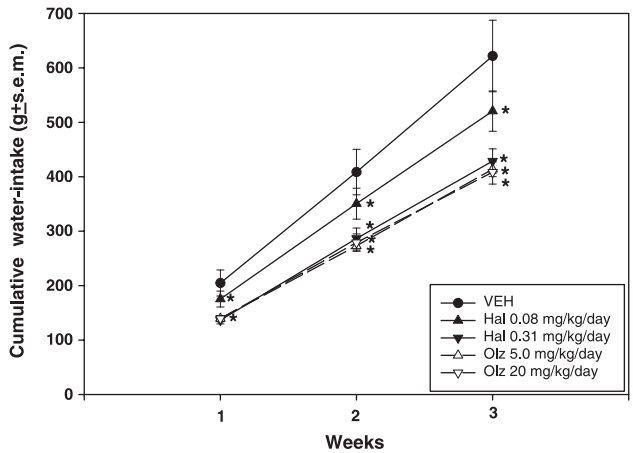

Fig. 5. Effects of chronic treatment (3 weeks) with haloperidol or olanzapine (administered orally twice a day) on cumulative water intake in male Wistar rats exposed to low-palatability synthetic chow. * $P < .05$ vs. VEH-treated rats.

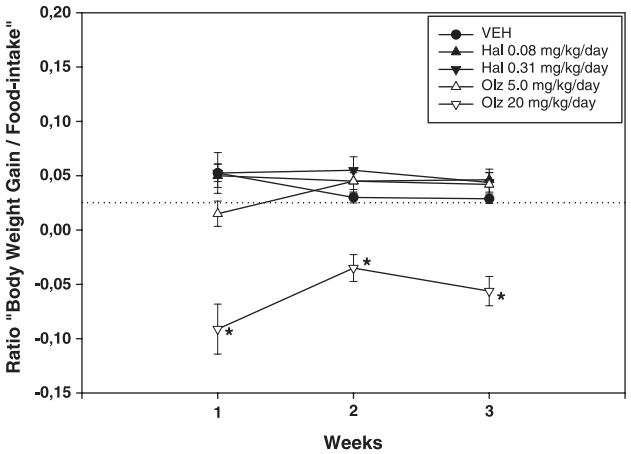

Fig. 7. Effects of chronic treatment (3 weeks) with haloperidol or olanzapine (administered orally twice a day) on the cumulative body weight gain/food intake ratio in male Wistar rats exposed to low-palatability synthetic chow. * $P < .05$ vs. VEH-treated rats.

3.4. Effect of antipsychotics on the ratio body weight increase/food intake

The three-way repeated measurement ANOVA (Treatment × Gender × Weeks) for the ratio of the cumulative body weight increase of rats with their cumulative food intake over the 3 weeks of treatment with antipsychotics yielded a significant effect for the three main effects (Ps < .001). We also obtained a significant effect for all interactions (Ps < .001). The significant full interaction [$F(8,140) = 3.59$, $P < .001$] effect permitted us to reanalyze the effect of treatment within weeks and for each gender via a post hoc analysis. As shown in Fig. 7, for males and over the 3 weeks of treatment, there was only a significant difference between the VEH- and olanzapine (20 mg/kg/day)-treated groups ($P < .001$). The chronic treatment with 20-mg/kg/day olanzapine induced a negative ratio as a consequence of the high reduction of body weight (see Fig. 1). As shown in Fig. 8, for females and over the 3 weeks of treatment, there was a significant difference between the VEH- and the two haloperidol-treated groups (Ps < .005), with treatments with haloperidol increasing this ratio. Only the highest dose of olanzapine (20 mg/kg/day) induced a significant increase of this ratio in comparison with the VEH-treated group during the 3 weeks (Ps < .01) of treatment. This result demonstrated that contrary to the male rats, and irrespective of the antipsychotic given, female rats gained more weight than the VEH as a function of the amount of food eaten.

3.5. Drug exposure

As shown in Fig. 9A, the mean steady-state serum level of haloperidol over the 7-h postadministration was similar between male and female. At the lowest dose of haloperidol (0.08 mg/kg po), the serum levels were very low or close to LOQ for each gender. At the highest dose of haloperidol (0.31 mg/kg po), the serum levels were statistically similar for both genders except that the t_{max} seems to occur a few hours later in females. The mean steady-state serum level of olanzapine (see Fig. 9B) over the 7-h postadministration was identical between male and female.

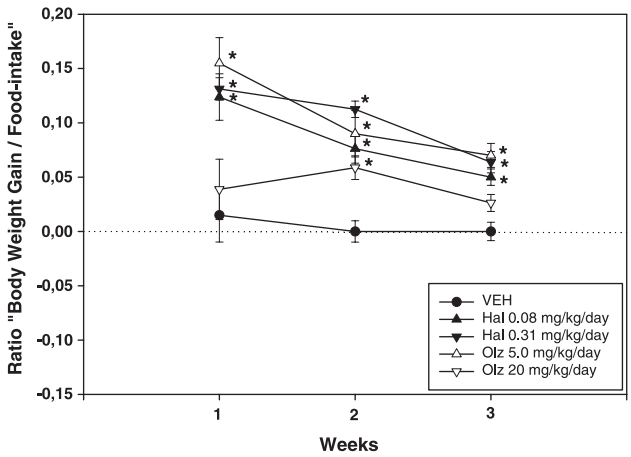

Fig. 8. Effects of chronic treatment (3 weeks) with haloperidol or olanzapine (administered orally twice a day) on the cumulative body weight gain/food intake ratio in female Wistar rats exposed to low-palatability synthetic chow. * $P < .05$ vs. VEH-treated rats.

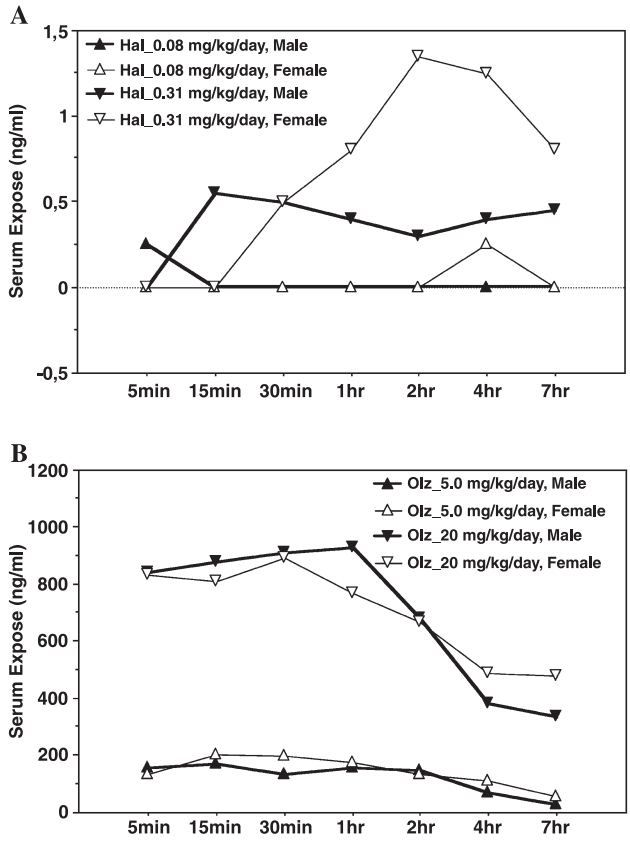

Fig. 9. Mean steady-state serum level of antipsychotics (A) haloperidol and (B) olanzapine after 3 weeks of oral administration twice a day. The values presented are the means of two samples per dose groups for the seven measurements performed 5, 15, and 30 min and 1, 2, 4, and 7 h after the last administrations of this chronic treatment. The minimal level of detection was 0.5 ng/ml for both antipsychotics.

4. Discussion

Our main observation during this study, never described before within a single study, is that after 3 weeks of treatment by gavage, olanzapine induced weight gain in normal female outbred rats, but haloperidol also induced a similar weight gain for this gender. Minor effects of treatment were observed on body weight of male rats. Consequently, the effect observed in this rat set-up does not match the clinical situation and rats cannot be considered as a relevant species for antipsychotic-induced body weight gain, even if extensively used in various other models predictive of antipsychotic action in clinic (Arnt, 2000).

The serum exposure of haloperidol for the lowest dose (0.08 mg/kg po) was quite low, as C_{max} in only one of the

two male and female used for the exposure study was above LOQ (0.5 ng/ml). This exposure is also much lower than the 5–12 ng/ml of haloperidol, which are considered as the relevant therapeutic exposure in schizophrenic patients (Eilers, 1995). This dose could consequently be considered too low, but it appeared to be enough to induce weight gain in female rats. We consequently demonstrate that very low exposure to haloperidol may induce weight gain in rats. The significant positive effect of this dose of haloperidol on the body weight gain/food intake ratio demonstrated that this low dose also permitted to modify the metabolism of female rats. This effect of haloperidol on the metabolism of rats is confirmed by data generated by Heiman et al. (2001) showing that haloperidol (0.1 mg/kg/day sc) shifted the energy balance of female rats. The highest dose of haloperidol chosen in our study (0.31 mg/kg po) permit to obtain a more pronounced effect on weight gain in female rats, but still has no effect in male rats. This dose permitted to reach a serum exposure above the LOQ in both genders, close to 1.5 ng/ml in female rats. We consequently confirm previous claims that females are more sensitive than males to the effect of antipsychotics on body weight gain in rats (Baptista et al., 1987, 1997a, 2002a).

With respect to olanzapine, the lowest dose (5.0 mg/kg/day) induced a very significant body weight increase in female rats over the 3 weeks of treatment, but this dose was without effect in male rats. This weight gain observed in females confirmed previously published data obtained with olanzapine administrated via a sustained released formulation (Goudie et al., 2002; Heiman et al., 2001). Our oral administration permitted to obtain a high and stable serum exposure for both genders up to 4-h posttreatment. Compared to the human situation, the highest dose (20 mg/kg/day) induced a high serum exposure for more than 7-h posttreatment (Perry et al., 1997; Rao et al., 2001). This dose induced body weight gain in female rats, but to a lower extent than the previous lower dose. This high dose reduced weight gain in male rats indicating that this dose probably induced a feeling of sickness. However, the lack of weight gain in male rats receiving a chronic administration of olanzapine confirmed our previous study (Pouzet and Sonne Hansen, 2002) in which we showed that clozapine, an antipsychotic drug inducing also a high weight gain in clinic (Allison et al., 1999; Henderson, 2001; Russel and Mackell, 2001; Sussman, 2001; Taylor and McAskill, 2000; Wirshing et al., 1999), did not induce weight gain in male rats on the doses tested. Our current study also demonstrates that olanzapine given at 5.0 mg/kg/day increased food intake of female rats. This effect on food intake might be due to a reduction of steroid levels (Baptista et al., 2002a; Parada et al., 1989), but it seems surprising that higher exposure to olanzapine did not induce a more severe food intake via this supposed reduction of steroid levels. Olanzapine, irrespective of doses, also had a significant positive effect on the body weight gain/food intake ratio in female rats. It consequently showed that olanzapine, similar to haloperidol, modified the metabolism of female rats, but only the lowest dose of olanzapine can change the appetite of animals. This effect of olanzapine on the metabolism of rats has also been claimed in a study showing the impact of chronic treatment with olanzapine on the energy balance and respiratory quotient of female rats (Heiman et al., 2001).

This sum of results demonstrated that chronic treatment with haloperidol and olanzapine had a similar effect in female rats, i.e., increased body weight. This result is opposite to the clinical situation as only olanzapine induced body weight gain in patients. In male rats, none of the two compounds induced a significant body weight increase. These antipsychotic effects do not match the clinical situation either, as only haloperidol is expected not to induce body weight gain. In accordance with our data, Baptista et al. (1988) demonstrated that sulpiride induced weight gain in rats even if this compound does not induce weight gain in the clinical situation.

The relevance of published studies claiming a beneficial effect of various compounds like sibutramine (Heiman et al., 2001), amantadine (Baptista et al., 1997b), tamoxifen (Baptista et al., 1997a), or others on antipsychotic-induced weight gain can consequently be questioned when these claims are based only on studies performed in rats. Because the effects of antipsychotics on weight gain in rats do not match the clinical situation, we can hardly believe that a compound inhibiting this induction of weight gain in rats could be predictive of a beneficial effect in schizophrenic patients. Moreover, the mechanism for induction of weight gain in patients is not yet elucidated (Allison and Casey, 2001; Kurzthaler and Fleischhacker, 2001; McIntyre et al., 2001; Taylor and McAskill, 2000), and according to our study there is no reason to believe that rats will be the appropriate species to elucidate it. Moreover, when weight gain is observed in rats after administration of antipsychotics like sulpiride, the metabolic process involved seems to be different from the clinical situation as, contrary to humans, lipid levels in the blood of rats are not modified (Baptista et al., 1998). The rats might only permit to describe the effect of antipsychotics on some particular physiological effects like food and water intake and regulation of endocrine activities (Baptista et al., 2002c; Parada et al., 1988).

Finally, this study, supported by our previous published and unpublished data, demonstrated that even if rats are intensively used for screening of drugs with a potential antipsychotic action (Arnt, 2000), this species, at least with regards to healthy rats, has its limitation (Goudie et al., 2002) and is not appropriate for prediction of the side effect of "antipsychotic-induced body weight gain" in schizophrenic patients.

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