Olanzapine-Induced Weight Gain and Increased Visceral Adiposity is Blocked by Melatonin Replacement Therapy in Rats

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The atypical antipsychotic drug olanzapine increases body weight and visceral adiposity in schizophrenia. In rats, aging-associated increased body weight and visceral adiposity are reversed by administration of the pineal hormone melatonin. We asked if melatonin similarly would reverse olanzapine-induced increased weight and visceral adiposity in rats. Four groups ($n = 11/\text{group}$) of female rats (240–250 g) were treated for 8 weeks with olanzapine, melatonin, olanzapine + melatonin, or vehicle alone in drinking water. Body weight and food and water consumption were determined weekly, locomotor activity at weeks 3 and 6, and nocturnal plasma melatonin concentration at week 7. At week 8, the rats were killed and visceral (perirenal, retroperitoneal, omental, and mesenteric) fat pads dissected and weighed. Olanzapine treatment reduced nocturnal plasma melatonin by 55% ($p < 0.001$), which was restored to control levels by olanzapine + melatonin. Body weight increased 18% in rats treated with olanzapine alone, but only 10% with olanzapine + melatonin, 5% with melatonin alone, and 7% with vehicle control. Body weight and visceral fat pad weight increases in rats treated with olanzapine alone were greater than in each of the other three groups (all $p < 0.01$), which were not significantly different. These results suggest that olanzapine-induced increases in body weight and visceral adiposity may be at least in part secondary to olanzapine-induced reduction of plasma melatonin levels, and that melatonin may be useful for the management of olanzapine-induced weight gain in humans.

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INTRODUCTION

The atypical antipsychotic drugs ('atypicals') have become the drugs of choice for treatment of schizophrenia and other chronic psychotic disorders, largely because of their low incidence of extrapyramidal adverse effects (Leucht *et al*, 1999). Unfortunately, some of the most widely used atypical antipsychotics frequently induce substantial weight gain and increased visceral adiposity (American Diabetes Association, 2004; Wirshing *et al*, 1999). These metabolic adverse effects are associated with hyperglycemia and dyslipidemia, and increase long-term risk for diabetes mellitus, ischemic heart disease, and overall mortality (Fontaine *et al*, 2001; Krotkiewski *et al*, 1983; Kissebah *et al*, 1982). They also compromise compliance with long-

term treatment regimens and quality of life (Allison *et al*, 2003).

Among the commonly prescribed atypicals, olanzapine has been reported to have the greatest propensity to produce weight gain (Gothelf *et al*, 2002; Kinon *et al*, 2001; Wirshing *et al*, 1999). In the recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study initiated by the NIMH to compare effectiveness of antipsychotic drugs, olanzapine appeared to be more effective than the other drugs studies, but it was associated with greater weight gain and other metabolic changes implicated in the development of metabolic syndrome (Lieberman *et al*, 2005). Although the negative public health implications of the weight gain and other metabolic adverse effects of olanzapine have become a matter of concern to both the psychiatry and endocrinology communities (American Diabetes Association, 2004), olanzapine continues to be widely prescribed. Approaches to reducing atypical-induced weight gain in schizophrenia using diet, exercise, and appetite suppressant drugs have demonstrated some short-term benefits (Henderson *et al*, 2005; Graham *et al*, 2005a,b). However, long-term efficacy of such

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approaches to maintaining weight reduction is unlikely given disappointing results of such approaches to long-term weight reduction in the general population (Glazer, 2001). Consequently, finding an effective intervention that would prevent or reverse weight gain induced by olanzapine is an important goal.

A potential approach to preventing atypical-induced weight gain is suggested by our previous studies with the hormone melatonin. Melatonin is secreted nocturnally by the pineal gland into blood and, at least in some species, into cerebrospinal fluid (reviewed in Cagnacci, 1996). Although the best understood function of melatonin is photoperiodic entrainment of endogenous circadian rhythms, melatonin also has a role in regulating energy balance and fat distribution in at least some species (Nelson and Demas, 1997). Pinealectomy, which decreases but does not eliminate circulating melatonin, has been demonstrated to increase body weight in rats (Peschke *et al*, 1987). Because normal aging in humans and rats is associated with both increased visceral adiposity and decreased circulating melatonin concentrations (Grad and Rozenzweig, 1993), we previously investigated the effects of daily melatonin supplementation on aging-associated increased body weight and visceral fat in middle-aged rats. Melatonin treatment reduced body weight, and visceral fat was restored to youthful levels within 10 weeks (Rasmussen *et al*, 1999, 2001; Wolden-Hanson *et al*, 2000). Continued melatonin supplementation until old age maintained suppression of this visceral fat accumulation (Rasmussen *et al*, 1999). We have now asked if olanzapine increases body weight and visceral adiposity in rats and, if so, whether melatonin replacement likewise reverses these changes. We also asked if olanzapine suppresses plasma melatonin concentrations.

MATERIALS AND METHODS

Forty-four female Sprague Dawley rats weighing 240–250 g at the start of treatment were individually housed with a 12 h/12 h light/dark cycle. Chow and water were available *ad libitum* throughout the study. All procedures were approved by the University of Washington Institutional Animal Care Committee and the protocol was in accord with the NIH guide for Care and Use of Laboratory Animals.

Four treatment groups of 11 rats each received olanzapine, melatonin, olanzapine + melatonin, or vehicle alone in their drinking water for 8 weeks. Details of olanzapine solution preparation have been described previously (Gao *et al*, 1998). The olanzapine concentration in the drinking water was initially 0.033 mg/ml; this concentration was modified according to measured daily water intake and body weight during the course of the experiment to maintain a dosage of approximately 2 mg/kg/day. This olanzapine dose and method of administration have been demonstrated to maintain rat plasma olanzapine levels in the human therapeutic range (Gao *et al*, 1998). Melatonin was dissolved in 100% ethanol and added to the drinking water at a final concentration of 0.4 µg/ml. All water bottles containing melatonin were covered with aluminum foil to prevent melatonin photodegradation. The final ethanol (vehicle) concentration was 0.01% for all treatment groups. Fresh solutions were prepared twice weekly.

Body weights were determined weekly. Food and water consumption were determined over each weekend. Twelve-hour nocturnal locomotor activity was measured by infrared beam breaks at approximately week 3 of treatment and again at approximately week 6 using an Opto-Varimax Mini Animal Activity Monitoring System (Columbus Instruments, Columbus, OH). Tail blood samples for melatonin assay were collected at the midpoint of the dark period in week 7, briefly exposing each rat to dim red light. After 8 weeks of treatment, rats were killed by decapitation during the last hour of the light period. The retroperitoneal, perirenal, omental, mesenteric, and ovarian fat pads were dissected and immediately weighed.

Plasma melatonin was measured by radioimmunoassay using a Melatonin Rat RIA kit from Labor Diagnostika Nord GmbH & Co., KG (Nordhorn, Germany). All samples were analyzed in a single assay, with 7% intra-assay coefficient of variation.

Data were evaluated by analysis of variance followed by post hoc Student–Newman–Keuls multiple comparison tests. Data are presented as means $\pm$ SEM; $p < 0.05$ was considered significant.

RESULTS

After 8 weeks of treatment, body weight differed significantly among groups ($F = 8.8$, $p < 0.001$), with higher weight in the olanzapine group than in each of the other groups (all $p < 0.001$), which were not significantly different (Figure 1). Body weight of the olanzapine-treated rats increased $17.7 \pm 1.8\%$ over 8 weeks; in contrast, the body weights of rats receiving olanzapine + melatonin, melatonin alone, or vehicle alone increased only 9.8 ± 1.9 , 4.9 ± 1.6 , and $7.3 \pm 1.7\%$, respectively. Percent weight gain in olanzapine-treated rats was significantly greater than in each of the other three groups (all $p < 0.01$), which were not significantly different. Total visceral (perirenal + retroperitoneal + omental + mesenteric) fat pad weights were

Figure 1 Body weight change throughout the course of the study. Each data point represents the mean $\pm$ SE of 11 rats. At week 8 of treatment, body weight was increased ($p < 0.001$) in olanzapine-treated rats relative to each of the other treatment groups.

increased approximately 37% ($p < 0.001$) by olanzapine and restored to control levels by olanzapine + melatonin (Figure 2). This pattern was also apparent for each of the individual visceral fat pads (Table 1). The large intra-abdominal ovarian fat pad exhibited a similar pattern of weight changes, with an increase in response to olanzapine (2.8 ± 0.1 vs 2.0 ± 0.1 g in the vehicle control-treated rats, $p < 0.01$) but no significant change in response to olanzapine + melatonin (2.4 ± 0.2 g) or melatonin treatment alone (1.7 ± 0.1 g).

Nocturnal plasma melatonin levels in week 7 for rats receiving control, melatonin, olanzapine, and olanzapine + melatonin treatments were 197 ± 24 , 519 ± 57 , 88 ± 15 , and 198 ± 31 pg/ml, respectively. Consequently, nocturnal plasma melatonin concentrations in week 7 of treatment were suppressed 55% ($p < 0.001$) in the olanzapine-treated rats, relative to control treatment, and these nocturnal plasma melatonin levels were restored to normal by olanzapine + melatonin treatment.

Nocturnal ambulatory activity was determined as total sequential infrared beam breaks per 12 h night for each rat on each of two nights, after approximately 3 and 6 weeks of treatment. As the activities were not significantly different

between the two determinations, the average of the two values for each rat was used for analysis. The average beam breaks/night for the rats receiving control, melatonin, olanzapine, or olanzapine + melatonin treatment were $11\,740 \pm 430$, $10\,945 \pm 529$, 7946 ± 364 , and 8068 ± 331 , respectively. Consequently, nocturnal locomotor activity was decreased 32% ($p < 0.001$) by olanzapine and addition of melatonin treatment did not alter this decrease.

There was evidence of an initial 2-week increase in food consumption in the olanzapine-treated rats, which was not altered by addition of melatonin treatment (Table 2). Food consumption during the remaining 6 weeks of the study was not significantly different among the treatments (Table 2).

DISCUSSION

Olanzapine treatment for 8 weeks increased body weight and visceral adiposity in adult female rats. These responses to olanzapine in rats are similar to those observed in persons with schizophrenia or other psychiatric disorders treated with olanzapine (Wirshing *et al*, 1999; Stein *et al*, 2002). The olanzapine-induced increases in rat body weight and visceral adiposity were associated with olanzapine-induced decreases in nocturnal plasma melatonin levels. Daily oral melatonin replacement sufficient to return nocturnal plasma melatonin levels to normal also reversed body weight and visceral adiposity to normal. This suggests that olanzapine-induced increases in body weight and visceral adiposity may be at least in part secondary to olanzapine-induced changes in melatonin secretion.

Figure 2 Visceral fat weight determined by dissection at completion of the study. Visceral fat weight for each rat was calculated as the sum of the mesenteric, omental, perirenal, and retroperitoneal fat pad weights. Data represent the mean $\pm$ SE of 11 rats/treatment group. * $p < 0.001$ vs all other groups.

Table 2 Average Daily Food Consumption

	During first 2 weeks of treatment (g/day)	During subsequent 6 weeks of treatment (g/day)
Control	19.8 ± 0.4	19.4 ± 0.3
Melatonin	19.9 ± 0.3	19.4 ± 0.3
Olanzapine	21.8 ± 0.3^a	20.0 ± 0.3
Olanzapine+melatonin	21.6 ± 0.4^a	19.6 ± 0.3

Data represent mean $\pm$ SE of 11 rats/treatment group.

^a $p < 0.01$ vs control and melatonin.

Table 1 Visceral Fat Pad Weights

	Perirenal (g)	Retroperitoneal (g)	Omental (g)	Mesenteric (g)
Control	0.60 ± 0.02	0.66 ± 0.06	0.38 ± 0.02	1.30 ± 0.10
Melatonin	0.43 ± 0.06	0.57 ± 0.07	0.33 ± 0.04	1.09 ± 0.08
Olanzapine	0.93 ± 0.06^a	0.83 ± 0.04^b	0.52 ± 0.04^c	1.72 ± 0.15^d
Olanzapine+melatonin	0.58 ± 0.05	0.65 ± 0.06	0.44 ± 0.04	1.22 ± 0.08

Weights of each individual fat pad were compared between treatments by one-way analysis of variance with Student–Newman–Keuls multiple comparisons without Bonferroni correction, to reveal consistency of patterns among fat pads.

^a $p < 0.001$ vs all other groups.

^b $p < 0.05$ vs melatonin.

^c $p < 0.01$ vs melatonin, $p < 0.05$ vs control.

^d $p < 0.01$ vs all other groups.

There is increased prevalence of obesity in persons with schizophrenia in the absence of treatment with antipsychotic drugs (Mukherjee *et al*, 1996; Ryan *et al*, 2003). Decreased nocturnal plasma melatonin concentrations have also been observed in persons with schizophrenia (Monteleone *et al*, 1992), although the possible role of melatonin in the pathophysiology of schizophrenia-associated weight gain has not, to our knowledge, been investigated. The current results thus suggest that olanzapine treatment may accentuate endocrine and associated metabolic disturbances characteristic of schizophrenia *per se*.

It was recently reported that 3–4 weeks olanzapine administration to eight male schizophrenia patients with predominantly negative symptoms did not significantly alter plasma melatonin levels, although the nocturnal rise appeared earlier (Mann *et al*, 2006). In the present rat study, nocturnal melatonin levels after 7 weeks of treatment were determined in single samples collected at the midpoint of the dark period so it is not possible to determine if the demonstrated olanzapine-induced decrease was due to reduced nocturnal peak amplitude or a similar phase shift in the time of the peak.

The mechanism of the melatonin effect on olanzapine-induced increases in body weight and visceral adiposity in rats is unclear. Locomotor activity was decreased by olanzapine, so decreased caloric expenditure may have contributed to the olanzapine-induced weight gain and increased adiposity. However, as addition of melatonin treatment did not alter this decreased locomotor activity, the melatonin-induced reversal of increased body weight and visceral adiposity during olanzapine treatment does not appear likewise to have been mediated by changes in locomotor activity.

Although olanzapine treatment induced an increase in eating during the first 2 weeks of treatment, food consumption during the subsequent 6 weeks of the trial was not significantly different among the treatment groups. Furthermore, food consumption by olanzapine + melatonin-treated rats was not different from that of rats treated with olanzapine alone, either initially or during the remainder of the study. This suggests that melatonin treatment did not decrease olanzapine-induced weight gain by suppressing eating. Melatonin replacement likewise did not alter food consumption in our previous studies of aging in which eating was rigorously characterized (Wolden-Hanson *et al*, 2000). However, it should be noted that the present study was not designed to thoroughly characterize eating, so the potential role of altered food consumption remains to be resolved.

Another candidate mechanism is suggested by evidence that melatonin may alter adipocyte fatty acid transport (Zurlo *et al*, 1990). This mechanism is consistent with findings in a recent human study of weight gain induced by 12 weeks of olanzapine treatment in unmedicated persons suffering from their first episode of acute schizophrenia (Graham *et al*, 2005a,b). In the human study, the most prominent metabolic effect of olanzapine was to decrease fatty acid oxidation.

Any substance added to drinking water potentially can decrease rat ingestive behaviors by being perceived as a novel taste or as toxic. However, in a previous study, we

demonstrated that addition of melatonin to rats' drinking water at the same concentration as used in the present study did not alter preference relative to water that did not contain melatonin, did not alter volume of water consumed over 24 h, did not alter water consumption in the subsequent 24 h after melatonin removal, and did not induce conditioned taste aversion (Wolden-Hanson *et al*, 2000). Thus, addition of melatonin to the water in this dosage was probably not detectable or perceived as aversive by the rats.

Although these results provide rationale for investigating whether olanzapine-induced endocrine and metabolic deregulation in humans can be blocked or attenuated by melatonin replacement therapy, these preliminary results require replication in longer studies to determine if the observed melatonin reduction of olanzapine-induced weight gain persists in a time course relevant to observations in humans. Olanzapine-induced weight gain has been observed to extend beyond 6 months in persons with schizophrenia (Wirshing *et al*, 1999). Future studies also should accurately measure effects of melatonin on eating and on endocrine parameters relevant to olanzapine-induced weight gain, such as plasma insulin and leptin. In our previous studies, melatonin reduction of rat insulin and leptin concentrations during aging were most clearly demonstrable under specific sampling conditions, that is, at the end of the light period after 9 h fasting for insulin, and during the dark period under non-fasting conditions for leptin (Puchalski *et al*, 2003). Other variability in responses could clearly also be owing to species, gender, and state-related differences.

These results raise several other questions. Would similar results be observed in males, and is there a role for gonadal steroids in mediating metabolic responses to olanzapine? Would bolus administration of an appropriate dosage of melatonin in the evening be as effective as administration throughout the night, consistent with melatonin regulation of reproduction in at least some seasonal breeders (Stetson *et al*, 1986)? If so, evaluation and potential implementation of therapy based on melatonin effects on olanzapine-induced weight gain in humans would be more practical.

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