



Risperidone alters food intake, core body temperature, and locomotor activity in mice

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ABSTRACT

Risperidone induces significant weight gain in female mice; however, the underlying mechanisms related to this effect are unknown. We investigated the effects of risperidone on locomotor activity, core body temperature, and uncoupling protein (UCP) and hypothalamic orexin mRNA expression. Female C57BL/6J mice were acclimated to individual housing and randomly assigned to either risperidone (4 mg/kg BW day) or placebo (PLA). Activity and body temperature were measured over 48-hour periods twice a week for 3 weeks. Food intake and body weights were measured weekly. UCP1 (BAT), UCP3 (gastrocnemius), and orexin (hypothalamus) mRNA expressions were measured using RT-PCR. Risperidone-treated mice consumed more food ($p=0.050$) and gained more weight ($p=0.0001$) than PLA-treated mice after 3 weeks. During the initial 2 days of treatment, there was an acute effect of treatment on activity ($p=0.046$), but not body temperature ($p=0.290$). During 3 weeks of treatment, average core body temperatures were higher in risperidone-treated mice compared to controls during the light phase ($p=0.0001$), and tended to be higher during the dark phase ($p=0.057$). Risperidone-treated mice exhibited lower activity levels than controls during the dark phase ($p=0.006$); there were no differences in activity during the light phase ($p=0.47$). UCP1 ($p<0.01$) and UCP3 ($p<0.05$) mRNA expressions were greater in risperidone-treated mice compared to controls, whereas, orexin mRNA expression was lower in risperidone-treated mice ($p<0.01$). These results suggest that risperidone-induced weight gain in mice is a consequence of increased energy intake and reduced activity, while the elevation in body temperature may be a result of thermogenic effect of food intake and elevated UCP1, UCP3, and a reduced hypothalamic orexin expression.

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1. Introduction

Risperidone, an atypical-antipsychotic drug (AAD) with lower incidence of extrapyramidal side effects compared to typical antipsychotic drugs, is commonly used to treat schizophrenia and bipolar disorder [1]. Unfortunately, AADs, including risperidone, cause weight gain and may exacerbate risk factors for obesity-related metabolic disorders such as type 2 diabetes [2–5]. Although reported less frequently, other side effects related to risperidone treatment include fatigue/tiredness, hyperprolactinemia, akathisia (motor restlessness), and body temperature dysregulation [1,2]. The underlying mechanisms responsible for risperidone-induced weight gain are not clearly defined. A better understanding of the pathways involved in these metabolic related side effects would provide groundwork for clinical application in patients treated with risperidone and other AADs.

Patients with schizophrenia are as overweight and obese as the general population [6] and body mass index increased dramatically

and significantly among young women with schizophrenia between 1987 and 1996 [7]. Due to this underlying risk for obesity among people with mental illness, it is difficult to distinguish between the disease effect and the drug effect on weight gain in patients treated with AADs. To investigate the underlying drug effect without the presence of disease, we developed a mouse model in which normal weight female C57BL/6J mice treated with AADs gain significant body weight relative to PLA-treated mice [4]. Previous reports investigating the effects of AAD-induced weight gain in animals suggest that AAD-induced weight gain is due primarily to an increase in energy intake [3,4,8]; however, few reports have monitored core body temperature and activity during AAD treatment.

Body temperature regulation (thermoregulation) is important for maintaining body mass homeostasis, especially in small rodents [9]. Rodents [10] and humans [11] possess various abilities to engage in adaptive thermogenesis, suggesting a genetic component for defending body weight. In rats given risperidone, body temperature decreased significantly compared to controls and this effect was seen over a 21-day period without weight gain [12]. In humans, risperidone treatment has been associated with both hyperthermia [13] and hypothermia [14] and in a few cases neuroleptic malignant syndrome with extremely high

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fever and muscle rigidity [15]. The effect of risperidone on thermoregulation is possibly related to interactions with dopaminergic and serotonergic receptors or other receptors in the CNS, but the specific mechanisms of how these temperature modifications affect body weight are not known.

Uncoupling proteins (UCPs), including UCP1 and UCP3, have been investigated for their possible roles in body temperature regulation and energy balance. UCP1, found predominately in brown adipose tissue (BAT), dissipates the pH-gradient generated by oxidative phosphorylation, releasing chemical energy as heat [16]. UCP1 expression in BAT is decreased in most genetic and hypothalamic obese animals [16,17] and overexpression of UCP1 in skeletal muscle decreases the percentage of fat in transgenic mice [18]. In contrast, mice lacking UCP1 in BAT are not obese on standard chow or high-fat diets [19,20]. UCP3, mainly expressed in skeletal muscle, is up-regulated during fasting [21] and may be involved with the facilitation of fatty acid oxidation in muscle [22]. UCP3 knockout mice do not become obese on high fat diets [23]. Most reports do not associate UCP3 with thermogenesis and the exact biological function of UCP3 remains unknown. UCPs may be involved with body temperature alterations and energy balance in risperidone-treated mice. However, there are no previous reports investigating UCP mRNA expressions in mice administered risperidone.

Weight gain results from an increase in food intake and/or a decrease in energy expenditure, including resting energy expenditure and activity related energy expenditure [24]. Risperidone's effects on locomotor activity are not well documented. Amphetamine-induced locomotor activity in hippocampal-lesioned Sprague–Dawley rats was prevented with risperidone treatment [25]. Conversely, BALB/c mice treated with amphetamine to produce hyperactivity and self-injurious behavior do not show reduced activity when treated with risperidone, but the treatment does alleviate self-injurious behavior [26]. Risperidone treatment reduced hyperactivity in children with bipolar disorder, autism, and attention-deficit/hyperactivity disorder [27,28]. Risperidone's activity-related effects may be associated with increased risk for weight gain in patients treated with risperidone, particularly if the reduced activity decreases total energy expenditure.

Orexins, neuropeptides located in the hypothalamus, have been associated with regulation of the sleep/wake cycle, feeding behavior, spontaneous physical activity, and thermogenesis [29]. Orexin knockout (KO) mice are unable to reduce their body temperature during inactivity (light phase) and have a phenotype of narcolepsy [30]. This inability of orexin KO mice to reduce body temperature may provide an explanation for fragmented sleep during narcolepsy, because heat loss is an essential aspect of sleep. Body temperatures were not different between orexin KO mice and wild-type (WT) littermates during sustained wakefulness (dark phase); however, locomotor activity was lower in orexin KO mice compared to wildtypes during wakefulness [30]. Rats administered orexin A along with risperidone experienced elevated colonic temperature and heart rate [31]. Risperidone may cause alterations in the gene expression of orexin in the hypothalamus; however, there are no published data showing this relationship.

In this study, we use our mouse model of risperidone-induced weight gain to determine the effect of risperidone on food intake, core body temperature, and locomotor activity. We hypothesized that risperidone-induced weight gain would be associated with increased food intake, decreased body temperature, and decreased activity in mice housed at 22 °C (ambient temperature) during three weeks of treatment.

2. Materials and methods

2.1. Animals and experimental overview

Eight-week-old female C57BL/6J mice (Jackson Laboratory, Bar Harbor, ME, USA) were group housed for one week and then housed individually in a temperature controlled incubator (22.0 ± 1.0 °C) with a 12/12 h light/dark cycle throughout the experiment. Mice were fed a low-fat

condensed milk diet (Research Diets, New Brunswick, NJ, USA; D12489B) and given water *ad libitum*. At ten weeks of age, mice had transmitters surgically implanted to measure activity and body temperature (see below). Following surgery, mice were acclimated to plain peanut butter pill administration (placebo; twice a day; 0900 and 1500 h) for two weeks. After the first week of placebo administration, mice were weighed and randomly assigned to placebo or risperidone-treated groups. All experiments were conducted on a single set of 12 mice (6/group). Risperidone treatment started when mice were 12-weeks-old and ended after three weeks. All procedures were approved by the University of Alabama at Birmingham Institutional Animal Care and Use Committee.

2.2. Surgery, activity and body temperature measurements

In order to measure activity counts and body temperatures, 10-week-old mice had transmitters (Respironics, Bend, Oregon, USA; PDT-4000 E-mitters,) implanted into their abdominal cavity. Mice were anesthetized using isoflurane (2%), the abdomen shaved and wiped with alcohol and betadine and a small incision (1–2 cm) was made, the transmitter was inserted into the abdominal cavity and the abdominal wall and skin were sutured. Following surgery, mice were monitored for two weeks to insure complete recovery before starting the activity experiment [32]: recovery was defined as a return to pre-surgery weight.

Activity and body temperature were measured using Mini-mitter telemetry set-ups (Respironics, Bend, Oregon, USA; ER-4000 telemetry system) at baseline (two days prior to treatment) and during the three weeks of treatment. Mice remained in their home cage and were placed on individual monitoring bases for two 48-hour periods weekly (six measurement periods over the 3 weeks). Each measurement started at 1500 h and ended 48 h later. Data was tabulated using LabVIEW (National Instruments, Austin, TX, LabVIEW Version 5.0) and collected into 60-second bins throughout the 48 h. Software errors were corrected by eliminating activity counts that exceeded 12 counts within a 1-second interval as suggested by the manufacturer. Body temperature was averaged into 1-hour periods for each animal, and then was averaged for the two groups. Activity counts were averaged into counts/minute for each animal, and then were averaged for the two groups.

2.3. Food intake and body weights

Baseline food intake and body weights were measured during a one-week period before treatment initiation. During the three-week experiment, food intake and body weights were measured weekly (weights were measured at 1000 h).

2.4. Drug treatment

Mice were treated twice a day orally with peanut butter pills at 0900 and 1500 h with risperidone-treated mice receiving 4 mg/kg BW day (each pill contained 1/2 the daily dose). This dose was based on a concentration that induced the greatest weight gain in an optimal dosing experiment [4]. As previously described, risperidone (Toronto Research Chemicals; North York, Ontario, Canada) was dissolved in heated (37 °C) peanut butter (Jif, Cincinnati, OH, USA) to achieve the target dosage, mixed for approximately 15 min, placed into plastic molds (Corticosterone pellet molds, Ted Pella, Inc., Redding, CA, USA) to form individual pills (each weighing approximately 100 mg), and stored at –80 °C until used for treatment.

2.5. Real time RT-PCR

Real time RT-PCR was conducted as previously described [33]. Mice were euthanized by decapitation and trunk blood collected. BAT, gastrocnemius muscle, and hypothalamus tissue “blocks” (1.5 mm wide across the midline and 1.5 mm thick bordered anteriorly by the

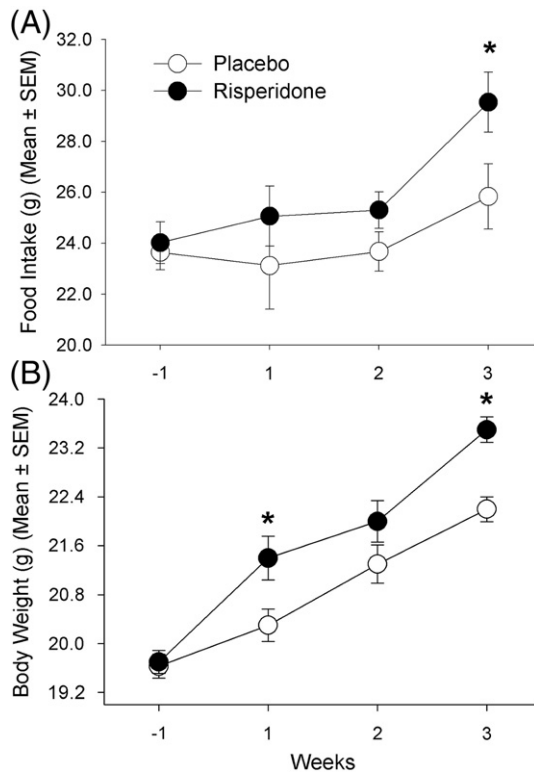


Fig. 1. A) Weekly food intake from one week prior to treatment initiation and during 3 weeks of treatment with placebo or risperidone. Treatment effect ($p=0.050$); time effect ($p=0.003$); time \times treatment interaction ($p=0.49$); B) Body weights at baseline and during 3 weeks of treatment with placebo or risperidone. Treatment effect ($p=0.029$); time effect ($p=0.0001$); time \times treatment interaction ($p=0.004$).

optic chiasm and posteriorly by the mammillary bodies) were rapidly collected, frozen in liquid nitrogen, and stored at -80°C . Total RNA was prepared using TRIzol reagent (Life Technologies, Gathiersburg,

MD) according to the manufacturer's directions after which cDNA was synthesized using SuperScript III kit (Invitrogen). Multiplex Real Time RT-PCR was carried out using LUX-labeled oligonucleotide primers (Invitrogen) analyzed on a Chromo4 Instrument (MJ Research) for each gene of interest with Opticon Monitor™ software version 3.0. Primers for mouse UCP1, UCP3, and orexin were as follows: UCP1 sense 5'-GGT CAG AAT GCA AGC CCA GAG-3'; UCP1 antisense 5'-CGG GTG TAA GCA TTG TAG GTC CCFAMG-3'; UCP3 sense 5'-CGC CAA CTC CAT CAT TAA CTG CGGG FAM G-3'; and UCP3 antisense 5'-GGG ACG TTG TCT GTC ATC AGC-3'; orexin sense primer 5'-GCT CCG TGC AAC AGT TCG TA-3'; orexin antisense primer: 5'-CAG CAA GCC TCT GCC CGA CTG CFAM G-3'. PCR conditions were 50°C for 2 min, 95°C for 2 min and then 45 cycles of 95°C for 15 s, 60°C for 45 s and 72°C for 30 s. Certified housekeeping primer sets were purchased for the housekeeping genes (Invitrogen). The threshold cycle (CT value) corresponding to exponential growth of PCR product during the log-linear phase for both the target gene (FAM labeled) and internal reference gene (b-actin or GAPDH, JOE labeled) were calculated and analyzed for each sample in triplicate using the deltaCT comparative method to determine relative expression levels. Amplification efficiencies and assay validations were determined from control standard curves for both the gene of interest and the reference RNA generated for each 96-well assay. Coefficient of variation was kept at $\leq 3\%$.

2.6. Statistical analyses

All statistical analyses were performed using SAS (Version 8; SAS Institute Cary, NC). Repeated measures analysis of variance (ANOVA) was used to determine if there were significant differences in food intake, body weight, body temperature, and activity levels between PLA- and risperidone-treated mice over time, and post-hoc Bonferoni correction was applied for the multiple comparisons in body temperature and activity. One-way ANOVA was used to determine differences between risperidone- and PLA-treatment on the relative expression of UCP1, UCP3, and orexin in BAT, gastrocnemius muscle, and hypothalamus, respectively. Data are reported as mean \pm standard

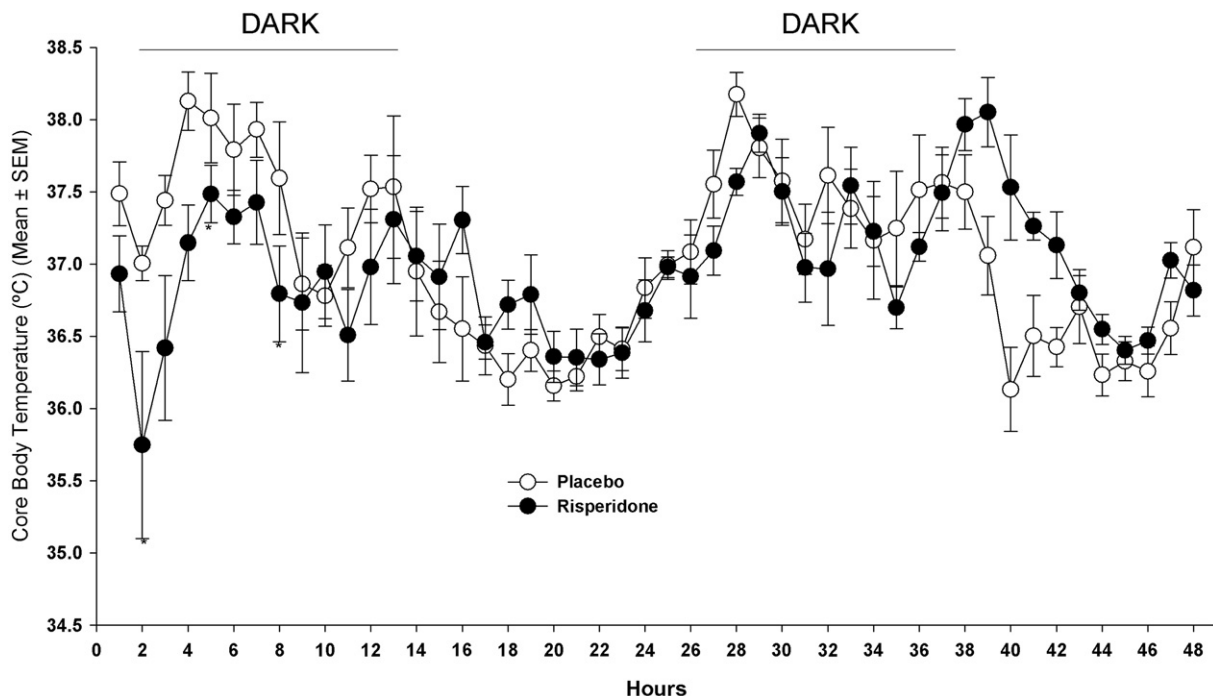


Fig. 2. Core body temperatures for days 1 and 2 of treatment (arrows indicate treatment time; initial treatment given at 0 h; $*p < 0.05$). Treatment effect ($p=0.55$); time effect ($p=0.0001$); time \times treatment interaction ($p=0.0001$).

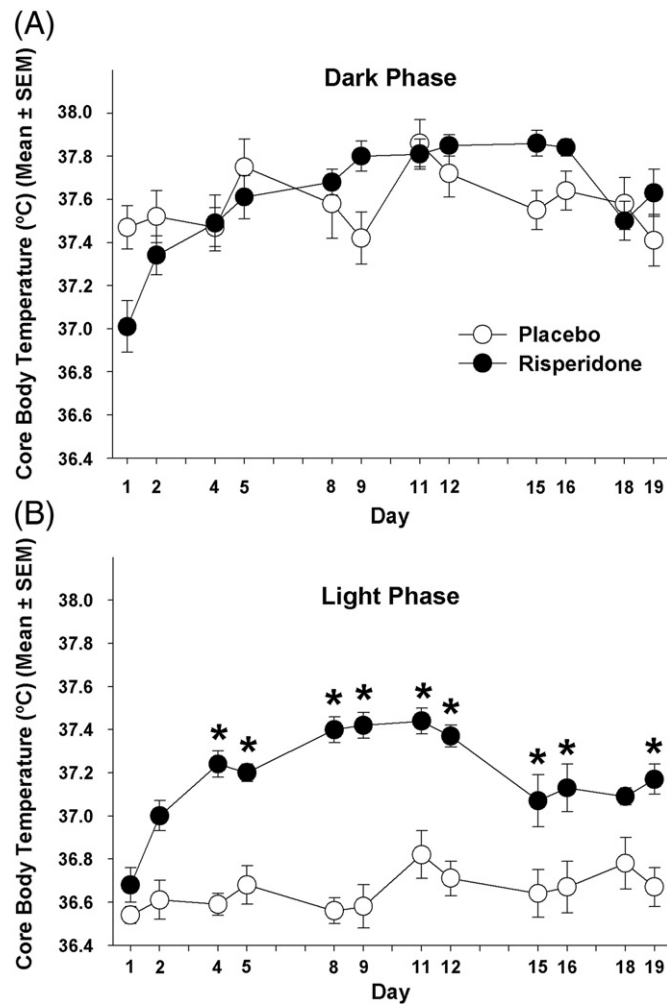


Fig. 3. Core body temperatures of mice treated with placebo or risperidone during the (A) dark phase [Treatment effect ($p=0.057$); time effect ($p=0.0001$); time \times treatment interaction ($p=0.0005$); (B) light phase [Treatment effect ($p=0.0001$); time effect ($p=0.0001$); time \times treatment interaction ($p=0.0001$)] * $p<0.05$ for individual time points after applying the Bonferroni correction.

error of the mean (SEM). The criterion for statistical significance was $p \leq 0.05$ or adjusted by Bonferroni correction if necessary and exact p values are reported.

3. Results

3.1. Food intake and body weight

There was a significant effect of treatment on food intake, and risperidone-treated mice presented significantly higher food intake than placebo-treated mice after 3 weeks (Fig. 1A; $p=0.050$). Both groups increased food intake over time ($p=0.003$), but there was no significant time by treatment interaction ($p=0.49$).

Both placebo and risperidone-treated mice gained significant weight over time ($p=0.0001$). There was a significant effect of treatment on body weight (Fig. 1B; $p=0.029$), and risperidone-treated mice were heavier than PLA-treated mice at the end of the experiment (23.5 ± 0.21 vs. 22.2 ± 0.20 g, respectively; $p=0.001$). A significant time by treatment interaction was also found ($p=0.004$).

3.2. Core body temperature

Baseline body temperatures were not different between placebo and risperidone-treated mice during a 22-hour pre-treatment measurement ($p=0.52$; placebo, 37.1 ± 0.2 °C and risperidone, 36.9 ± 0.2 °C). There was no overall effect of treatment on body temperature during the initial 2 days of treatment ($p=0.55$). Following initial drug administration, risperidone-treated mice had decreased body temperature at 1 h (36.9 ± 0.2 °C at baseline and 35.7 ± 0.6 °C at 1 h) while PLA-treated mice had a slight increase (37.1 ± 0.2 °C at baseline and 37.5 ± 0.1 °C at 1 h). During the initial 47 h following the first treatment there was a significant time effect ($p=0.0001$) and a significant time by treatment interaction ($p=0.0001$). Compared with PLA-treated mice, risperidone-treated mice had significantly lower body temperatures at 4 ($p=0.009$), 18 ($p=0.044$), and 28 h ($p=0.004$) (Fig. 2), but had higher body temperatures at 39 ($p=0.013$), 40 ($p=0.008$), 41 ($p=0.018$), 42 ($p=0.016$) 46 ($p=0.003$) and 47 h ($p=0.04$) after initial treatment (Fig. 2). However, after applying the Bonferroni correction there were no differences in body temperature between PLA- and risperidone-treated mice at any single time point.

Examined over the 3-week experimental period, there was no significant effect of treatment on body temperature during the dark

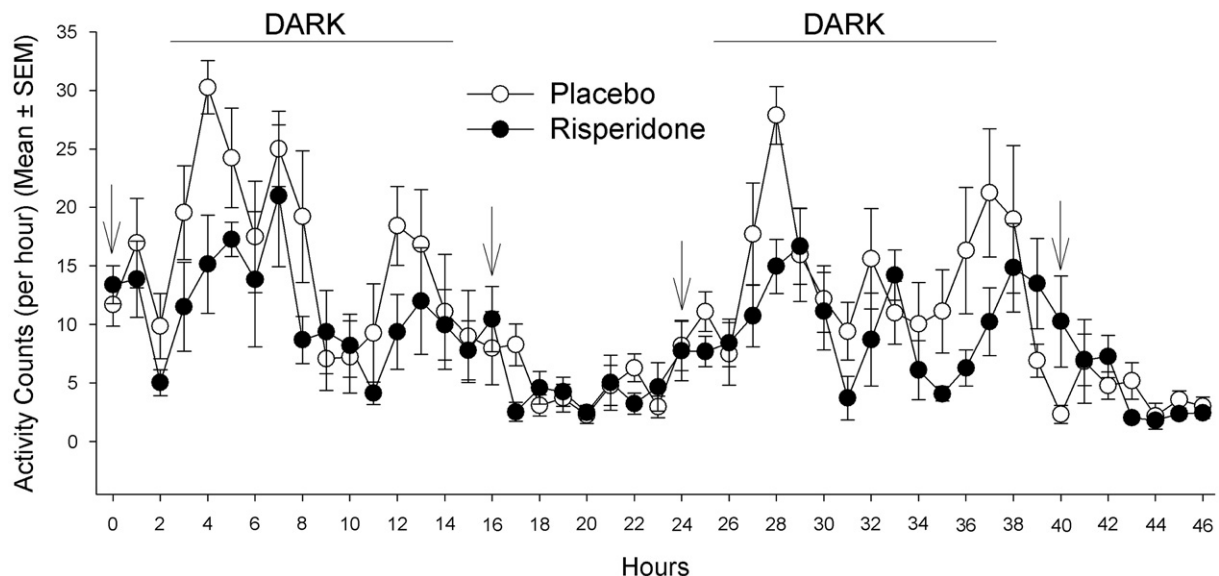


Fig. 4. Activity counts for days 1 and 2 of treatment. Arrows indicate treatment time; initial treatment given at 0 h. Treatment effect ($p=0.049$); time effect ($p=0.0001$); time \times treatment interaction ($p=0.20$).

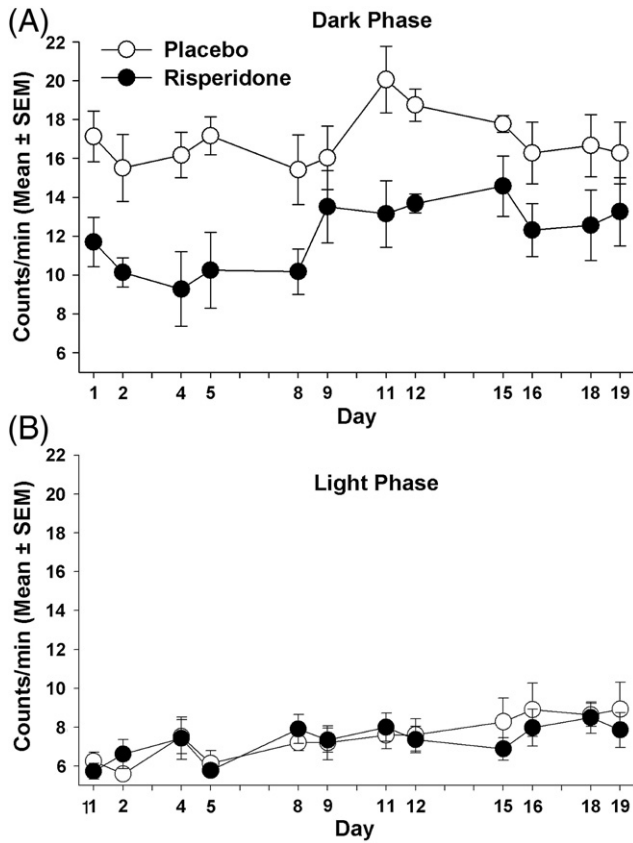


Fig. 5. Activity counts of mice treated with placebo or risperidone during the (A) dark phase [treatment effect ($p=0.006$); time effect ($p=0.0001$); time \times treatment interaction ($p=0.47$)]; (B) light phase [treatment effect ($p=0.472$); time effect ($p=0.011$); time \times treatment interaction ($p=0.51$)].

phase ($p=0.057$). However, a significant time effect ($p=0.0001$) and time by treatment interaction ($p=0.0005$, Fig. 3A) were observed. On day 1 of treatment, risperidone-treated mice had lower body temperatures than PLA-treated mice during the dark phase ($p=0.034$). In contrast, on days 9 ($p=0.011$) and 15 ($p=0.006$), risperidone-treated mice had higher body temperatures than the placebo mice during the dark phase. Following Bonferroni correction there was no difference in body temperature at any single time point during the dark phase on any particular day.

There was a significant effect of treatment ($p=0.0001$), time ($p=0.0001$), and time by treatment interaction ($p=0.0001$) on body temperature during the light phase (Fig. 3B). Risperidone-treated mice had higher body temperatures during the light phase than PLA-treated mice ($p<0.05$) on all treatment days except for days 1 ($p=0.45$) and 18 ($p=0.08$). After Bonferroni correction, risperidone-treated mice had higher body temperatures during the light phase than PLA-treated mice on days 4 ($p=0.0001$), 5 ($p=0.0002$), 8 ($p<0.0001$), 9 ($p<0.0001$), 11 ($p=0.0010$), 12 ($p<0.0001$) and 19 ($p=0.0037$).

3.3. Locomotor activity

At baseline, activity counts were not different between PLA- and risperidone-treated mice during a 22-hour pre-treatment measure ($p=0.51$; 11.7 ± 1.9 and 13.4 ± 1.6 counts/min, respectively). During the initial 2 days of treatment, there was a significant effect of treatment ($p=0.049$) and time ($p=0.0001$) on activity (Fig. 4). On day 1 of treatment, risperidone-treated mice had significantly less activity counts at 4 h post initial treatment (2 h into the dark phase) compared to placebo mice ($p=0.009$; Fig. 4), risperidone-treated mice had significantly less activity counts at 17 ($p=0.016$) and 28 ($p=0.003$) hours after initial treatment and showed a trend to have less activity

counts at 12 ($p=0.08$), 22 ($p=0.07$), 31 ($p=0.09$), 35 ($p=0.08$), and 43 ($p=0.07$) hours after initial treatment. However, there were no differences between groups at any single time point after applying the Bonferroni correction.

There was a significant effect of treatment ($p=0.006$), time ($p=0.0001$), but not a significant time by treatment interaction ($p=0.470$) during the dark phase (Fig. 5A). Risperidone-treated mice had lower activity counts than PLA-treated mice (significantly lower on days 1, 2, 4, 5, 11, 12 and 16; $p=0.006$, 0.025, 0.030, 0.010, 0.018, 0.012 and 0.005, respectively), but no differences were found after Bonferroni correction ($p>0.05$). However, there was no significant effect of treatment ($p=0.47$) nor time by treatment interaction ($p=0.51$) on activity counts during the light phase (Fig. 5B), even though both groups increased activity over time during the light phase ($p=0.011$).

3.4. mRNA expression of UCPs and orexin

After 3 weeks of treatment, mRNA expressions of UCP1 in BAT and UCP3 in gastrocnemius muscles were significantly higher in mice treated with risperidone compared to placebo ($p<0.01$ and $p<0.05$, respectively, Fig. 6). Relative expression of orexin in hypothalamus was significantly lower (0.40% less) in risperidone-treated mice than PLA-treated mice ($p<0.01$, Fig. 6).

4. Discussion

Our previous findings indicate that risperidone-treated mice gain significant body weight compared to controls [4]; however, the mechanism(s) for this weight inducing effect are unknown. In the present experiment, we report for the first time that risperidone-treated mice, compared to PLA-treated mice, experienced the following: 1) consumed more food and gained significantly more weight; 2) had higher body temperatures during the light phase; 3) had lower activity during the dark phase; 4) had higher UCP1 and UCP3 mRNA expressions in BAT and gastrocnemius muscle, respectively; and 5) had lower orexin mRNA expression in hypothalamus.

Weight gain during three weeks of risperidone treatment was associated with increased food intake and a significant reduction in activity levels during the active phase. The reduced activity during the active phase may cause risperidone-treated mice to have reduced total energy expenditure, and combined with significant elevation in food intake, place the mice in greater positive energy balance than the controls. Others have shown that animals treated with risperidone

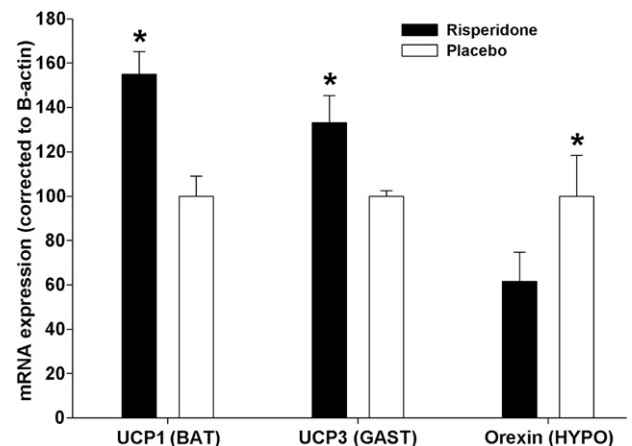


Fig. 6. Relative mRNA expressions of UCP1 in BAT, UCP3 in gastrocnemius muscle (GAST), and Orexin in hypothalamus (HYPO) from mice following three weeks of placebo or risperidone treatment. * $p<0.05$.

have reduced locomotor activity [34]. It has been speculated that AADs reduce activity and energy expenditure, and thus promote excessive energy balance in human [24,35]. However, this contention has not been explored systematically in rodents. Female Wistar rats receiving risperidone (0.5 mg/kg s.c.) for twelve days did not have lower energy expenditure compared to controls [3]. Coccorello et al. [36] found no changes in energy expenditure and locomotor activity in female CD-1 mice after chronic administration of olanzapine, however, a decreased respiratory quotient was observed. A limitation of our current study is that we did not measure energy expenditure during the three weeks of risperidone treatment.

All mice in the current experiment were acclimated for two weeks to individual housing at 22 °C and body temperatures were not different at the beginning of the experiment. During the three weeks of treatment, risperidone-treated mice failed to reduce core body temperature during the light phase as control animals did. There are a number of possible explanations for this failure to reduce body temperature in risperidone-treated mice. Elevated food intake can cause elevated body temperature due to the thermogenic effect of food [37] and elevated UCP1 in BAT can lead to elevated body temperature [38]. Similar to our findings, UCP1 expression in BAT was enhanced following twenty-one days of risperidone treatment (0.5 mg/kg BW day) in rats [39]. In addition, UCP3 expression was higher in the gastrocnemius muscle of risperidone-treated mice. The thermogenic effect of food and the up-regulation of UCPs may be involved with the inability of risperidone-treated mice to reduce body temperature during the light phase.

Body temperature regulation may also involve the hypothalamic neuropeptide orexin, which has been shown to be important in the regulation of food intake and locomotor activity [40]. Similar to risperidone-treated mice, orexin KO mice show a pattern of elevated core body temperature during the light phase and reduced locomotor activity during the dark phase [30]. Furthermore, risperidone can enhance sympathetic firing rate and colonic temperature induced by orexin in rats [41]. These findings suggest that orexin may be involved with risperidone's affect on body temperature and locomotor activity. Further evaluation of risperidone's interactions with specific neuroreceptors and neuropeptides will be needed to determine specific pathways that cause core body temperature to remain elevated during the light phase and locomotor activity to be reduced during the dark phase when mice are treated with risperidone.

In summary, the risperidone-induced weight gain in our mouse model appears to be related to elevated food intake as well as reduced activity. The thermogenic effect of increasing food intake, the increased expression of UCPs, and a reduction in hypothalamic orexin may result in the inability of risperidone-treated mice to lower their body temperature during the light phase of the day. Follow-up experiments investigating the mechanisms in this novel mouse model are needed and could potentially lead to clinical interventions for risperidone-treated patients experiencing weight gain.

Acknowledgements

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