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Different effects of Bifeprunox, Aripiprazole, and Haloperidol on body weight gain, food and water intake, and locomotor activity in rats

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ABSTRACT

Following on the success of Aripiprazole with its high clinical efficacy and minimal side effects, further antipsychotic drugs (such as Bifeprunox) have been developed based on the same dopamine D_2 partial agonist pharmacological profile as Aripiprazole. However clinical trials of Bifeprunox have found differing results to that of its predecessor, without the same significant clinical efficacy. This study has therefore investigated the different effects of 10 week treatment with Aripiprazole (0.75 mg/kg, 3 times per day), Bifeprunox (0.8 mg/kg, 3 times per day) and Haloperidol (0.1 mg/kg, 3 times per day) on body weight gain, food and water intake, white fat mass, and 8 week treatment on locomotor activity. Treatment with Bifeprunox was found to significantly reduce all of the measured parameters except white fat mass compared to the control group. However, Aripiprazole and Haloperidol treatment reduced water intake compared to the control, without any significant effects on the other measured parameters. These findings further demonstrate the potential pharmacological differences between Aripiprazole and Bifeprunox, and identify potential weight loss side effects and increased anxiety behaviour with Bifeprunox treatment.

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1. Introduction

First and second generation antipsychotic drugs (APD) are well-documented for inducing severe detrimental side effects with varying treatment success rates for the symptoms of schizophrenia. First generation APDs (e.g. Haloperidol) induce severe extra-pyramidal side effects (EPS) (DeLeon et al., 2004; Conley and Kelly, 2005; Seeman et al., 1976; Creese et al., 1996; Agid et al., 2008; Tarsy and Baldessarini, 2006) via a potent dopamine (DA) D_2 receptor antagonist mechanism. Second generation APDs (e.g. Olanzapine) potentially induce weight gain and other metabolic disorders (e.g. hyperlipidemia and type II diabetes) (Ujike et al., 2008; Weston-Green et al., 2008; Lieberman et al., 2005; Zipursky et al., 2005; Patel et al., 2009) via their action on multiple neurotransmitter receptors including histamine H_1, 5-HT_{2C} and muscarinic M3 receptors (DeLeon et al., 2004; Feenstra et al., 2001; Scatton and Sanger, 2000; Correll, 2010; Nasrallah, 2008; Deng, 2013).

Aripiprazole is regarded as a third generation APD with excellent therapeutic efficacy in controlling schizophrenia symptoms and a low incidence of EPS and weight gain side effects (Mailman and Murthy, 2010; Wood and Reavill, 2007; Stip and Tourjman, 2010; Bhattacharjee and El-Sayeh, 2008). Although there are mixed reports on whether Aripiprazole has a DA D_2 partial agonist (DeLeon et al., 2004; Wood and Reavill, 2007; Burris et al., 2002; Mamo et al., 2007; Etievant et al., 2009; Natesan et al., 2011) or functionally selective mechanism of action (Mailman and Murthy, 2010; Shapiro et al., 2003; Han et al., 2009a), it has been found to exhibit a very high affinity (Ki value: 0.45 nM) (DeLeon et al., 2004; Correll, 2010) and high occupancy rate (more than 90%) for D_2 receptors at the regular clinical dosage of 15–30 mg (DeLeon et al., 2004; Hamamura and Harada, 2007; Yokoi et al., 2002). Although Aripiprazole has partial agonist and partial antagonist properties at 5-HT_{1A} and 5-HT_{2A} receptors respectively (DeLeon et al., 2004; Correll, 2010; Mailman and Murthy, 2010; Mamo et al., 2007; Shapiro et al., 2003; Newman-Tancredi et al., 2005), studies have found it to have low occupancy and activity levels at 5-$HT_{1A,\ 2A}$ receptors at therapeutic doses (Wood and Reavill, 2007; Mamo et al., 2007; Han et al., 2009b). Following the success of Aripiprazole, a potential APD Bifeprunox (1-(2-Oxo-benzoxazolin-7-yl)-4-(3-biphenyl)methylpiperazinemesylate) was developed on the basis of the DA D_2 receptor partial agonist pharmacological model of Aripiprazole. Despite a similar partial agonist affinity for DA D_2 (Ki value: 8.5 nM) and 5-HT_{1A} receptors (Ki value: 5.2 nM) (Newman-Tancredi et al., 2007; Wadenberg, 2007), Bifeprunox was found to lack the therapeutic effects of Aripiprazole clinically, throwing up questions as to the potential pharmacological differences between the two drugs (Nasrallah, 2008; Bardin et al., 2007; Bishara and Taylor, 2008; Casey et al., 2008; Dahan et al., 2009).

Aripiprazole has also been found to induce very limited to no weight gain side effects (DeLeon et al., 2004; Stip and Tourjman, 2010; Han et al., 2009a). While there is no current evidence on Aripiprazole

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treatment alone decreasing body weight in both clinical and animal models, clinical studies have found it capable of reducing Olanzapine and Clozapine induced weight gain (Henderson et al., 2006, 2009; Deng et al., 2010). These studies report that after the weight gain seen with Olanzapine and Clozapine treatment, co-treatment with Aripiprazole over a period of 6 or 10 weeks is correlated with significant decreases in both body weight and body mass index. It is interesting that short-term (6 weeks) Bifeprunox treatment significantly reduced body weight when compared to the control in two clinical trials (Casey et al., 2008; Barbato et al., 2006). The pharmacological differences between Bifeprunox and Aripiprazole are currently unclear, with further knowledge into the differences between the two drugs potentially providing critical information towards the development of new APDs with a higher therapeutic efficacy and lower side effects. We have therefore investigated the effects of chronic treatment of Bifeprunox, Aripiprazole and Haloperidol (as a reference APD) on body weight gain, food and water intake, and locomotor activity in rats.

2. Materials and methods

2.1. Animals and housing

Male Sprague-Dawley rats (8 weeks old) were obtained from the Animal Resources Centre (Perth, WA, Australia). After arrival, the rats were housed in pairs for 1 week to adapt to the new environment before the study commenced. They were allowed ad libitum access to water and standard laboratory chow diet (3.9 kcal/g: 10% fat, 74% carbohydrate, 16% protein) throughout the experiment. During the experiment, they were housed in individual cages under environmentally controlled conditions (22 °C, light cycle from 07:00 to 19:00 and dark cycle from 19:00 to 07:00). All experimental procedures were approved by the Animal Ethics Committee, University of Wollongong, NSW, Australia (AE 11/02).

2.2. Drug treatment

Before the drug treatment commenced, the rats were trained for self-administration drug treatment by feeding them cookie dough (0.3 g) without drugs 2 times per day for 1 week. Rats were randomly assigned into one of the following treatments ($n = 12$/group) for 10 weeks: (1) Aripiprazole (0.75 mg/kg, 3 times per day; Otsuka, Japan), (2) Haloperidol (0.1 mg/kg, 3 times per day; Sigma, Australia), (3) Bifeprunox (0.8 mg/kg, 3 times per day; Otava, Ukraine), or (4) control (vehicle, 3 times per day). Drugs were administered orally to the respective treatment groups by mixing cookie dough powder (containing sucrose 30.9%, cornstarch 30.9%, casein 15.5%, minerals 8.4%, fibre 6.4%, gelatine 6.3% and vitamins 1.6%), the drug, and a small amount of distilled water until even in consistency (Han et al., 2009a; Weston-Green et al., 2011). The rats in the control group received an equivalent pellet without the drug. The dosages of Bifeprunox, Aripiprazole and Haloperidol in the current study used the dosage translation between species based on body surface area (Reagan-Shaw et al., 2008). A 0.8 mg/kg Bifeprunox dosage in rats is equivalent to ~8 mg in humans (60 kg body weight), while 0.75 mg/kg Aripiprazole and 0.1 mg/kg Haloperidol is equivalent to ~7.5 mg and ~1 mg respectively; all of which are within the used/recommended clinical dosages (Emsley, 2009). It has been previously reported that, at these used dosages, Aripiprazole and Bifeprunox drug treatments reach about 90% DA D_2 receptor occupancy rates in the rat brains (Wadenberg, 2007), while Haloperidol reaches approximately 70–80% DA D_2 receptor occupancy (Kapur et al., 2003; Naiker et al., 2006; Natesan et al., 2006). The drug dosages used in this study have been previously proven to be physiologically and behaviourally effective in rats and mice (Han et al., 2009a; Wadenberg, 2007; Assié et al., 2006), while not causing any signs of extra-pyramidal side effects (Wadenberg, 2007; Natesan et al., 2006). The 0.3 g dry cookie dough pellets with or without drugs were fed to the rats 3 times per day (07:00 h, 14:00 h in the light phase and 22:00 h in the dark phase; with 8 ± 1 h intervals) over the 10 week treatment period. Rats were observed throughout the experiment to ensure that they completely consumed the cookie dough pellet and that there was no missing water or laboratory chow. Body weight and food and water intake were measured weekly.

2.3. Open field test

An open field test was performed on day 56 of the drug treatment to determine whether Aripiprazole, Haloperidol or Bifeprunox influenced the locomotor activity of rats, according to procedures used by our laboratory (Weston-Green et al., 2011; du Bois et al., 2008; Deng et al., 2012a). Briefly, a rat was placed in the centre of a black rectangular arena (60 × 60 cm^2, 40 cm high) exposed to an average lighting of 25 lx. A video camera recorded the behaviour of the rats for 30 min from the top of the arena. The locomotor activity of the rats was analysed by using EthoVision Color-Pro software (Noldus Information Technology, Wageningen, The Netherlands). The total distance moved (cm), mean velocity (cm/s), rearing frequency, duration of time and frequency of entries into both the central and peripheral zones were measured.

2.4. Adiposity measures

Following the 10 week treatment, all rats were sacrificed by carbon dioxide asphyxiation 2 h after the last drug treatment. Post-mortem white adipose tissue (WAT), including perirenal, epididymal and inguinal fat, were dissected and individually weighed (g) (Olds and Olds, 1979; Deng et al., 2012b).

2.5. Statistical analysis

All collected data were analysed by using the SPSS (Windows version 19.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to examine the distribution of data from all experiments. Two-way repeated analysis of variance (ANOVA) (TREATMENT x DURATION as repeated measures) were applied to analyse body weight gain and food and water intake data. One-way ANOVA was used to examine behavioural and fat mass data. Multiple comparisons were performed using post-hoc Dunnett t-tests. Pearson's correlation test was used to examine the relationships among the measurements. All data were expressed as mean ± standard error of the mean (SEM), and statistical significance was accepted when $p < 0.05$.

3. Results

3.1. Body weight gain

Two-way repeated ANOVAs (TREATMENT × DURATION as repeated measures) showed significant main effects of TREATMENT ($F_{3,48} = 5.423$, $p < 0.01$) and DURATION ($F_{9,48} = 1241.065$, $p < 0.001$) on accumulated body weight gain, as well as a significant interaction between TREATMENT and DURATION factors ($F_{27,48} = 5.471$, $p < 0.01$; Fig. 1A). A post-hoc Dunnett *t*-test indicated a significant decrease in the overall body weight gain of the Bifeprunox drug treatment group compared to the control over the 10 week duration of the study (−16.76%; $p < 0.05$). Further analysis on the weekly data revealed that Bifeprunox treatment significantly decreased body weight gain compared to the control, occurring in weeks 7, 9 and 10 ($p < 0.05$), with a trend to significance in week 8 of the treatment ($p = 0.059$). On the other hand, no significant differences in body weight gain were found in the Haloperidol ($p > 0.05$) and Aripiprazole ($p > 0.05$) groups compared to the control. Therefore, the 10 week drug treatment with Bifeprunox decreased body weight gain compared with the control group over the same time period.

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