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Rapid communication

Ziprasidone suppresses olanzapine-induced increases in ingestive behaviour in the rat

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Abstract

Many atypical antipsychotic drugs, such as olanzapine, induce significant weight gain. However, ziprasidone produces minimal weight gain, the mechanism of which remains unclear. The aim of the present study was to investigate whether ziprasidone would reduce the acute effect of olanzapine on feeding behaviour. The results suggest that ziprasidone suppresses the significant increases in food intake produced by olanzapine, indicating that it has an intrinsic protective mechanism against drug-induced increases in food intake.

Keywords: Antipsychotic; Weight gain; (Rat)

Many atypical antipsychotic drugs, in particular olanzapine and clozapine, induce significant weight gain, which can have serious implications for patient compliance and morbidity. Previous studies have shown that olanzapine enhances feeding behaviour in the runway to food-goal paradigm, suggestive of an inhibition of the natural progression of satiety (Thornton-Jones et al., 2002). The underlying mechanisms for antipsychotic-induced weight gain are likely to be multifactorial, although drug action at several receptor subtypes, including 5-hydroxytryptamine $(5\text{-HT})_{2C}$ and histamine H_1 receptors, has been proposed to be important. Ziprasidone is an atypical antipsychotic that does not appear to share this propensity to produce weight gain (Allison et al., 1999), although it is not free of 5-HT_{2C} or histamine H_1 receptor antagonism (Schotte et al., 1996). However, it does have some pharmacological properties unique to an atypical antipsychotic drug including high (nM) affinity and partial agonist action at 5-HT_{1A} receptors and some 5-HT and noradrenaline reuptake inhibition (Schmidt et al., 2001). It remains unclear whether the lack of substantial weight gain with ziprasidone is due to a weaker action in vivo at receptors implicated in weight gain or whether the pharmacology of ziprasidone provides an intrinsic protective mechanism.

The present study aimed to investigate this by assessing whether ziprasidone could prevent the acute effect of olanzapine on feeding behaviour.

Adult male hooded-Lister rats weighing 350±35 g (S.D.) (Harlan, UK) were maintained at 85–90% free-feeding weight and trained to run for 45 mg Noyes pellets (Sandown Chemicals, Hampton, Middlesex, UK) in a runway to food goal paradigm. Animals (n=8 per group) were tested as described previously (Neill et al., 1990; Thornton-Jones et al., 2002) with food intake being measured in five trial blocks each consisting of three trials of 3-min duration. Locomotor activity following the same treatment regime was recorded for 1 h in Plexiglas cages (20×45×25 cm) fitted with photocells placed 5 cm apart. All statistical

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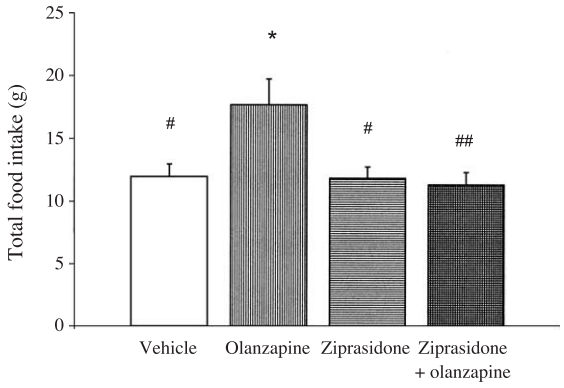

Fig. 1. Effect of a combination of olanzapine and ziprasidone on total food intake in the runway to food goal paradigm. Drugs were injected i.p. 30 min prior to testing. Data are expressed as mean±S.E.M. *P<0.05 vs. vehicle treated group and #P<0.05, ##P<0.01 vs. olanzapine treated group (n=8 per group).

comparisons were made by analysis of variance with post hoc Dunnett's t-test. Data are expressed as mean±S.E.M.

Ziprasidone was dispersed in distilled water by sonication and olanzapine was dissolved in a minimum volume of acetic acid before the addition of distilled water and brought to pH 6.0 by addition of 1 M NaOH. The drugs were injected intraperitoneally in a volume of 1 ml/kg, 30 min prior to testing. The effect of olanzapine (0.5 mg/kg) co-administered with ziprasidone's vehicle, ziprasidone (1 mg/kg) plus olanzapine's vehicle or ziprasidone co-administered with olanzapine, on food intake in the runway paradigm and on locomotor activity was recorded.

Olanzapine induced a significant increase in food intake compared to the vehicle control group in trial block 1 (2.54±0.56 g vs. 1.48±0.26 g, P<0.05) and the increase observed in trial block 2 closely approached significance (1.96±0.32 vs. 1.21±0.26 g, P=0.052). As animals in this experiment demonstrated elevated initial food intake rather than a delay in satiety with olanzapine, the results are presented as total food intake (Fig. 1). This was also significantly increased following olanzapine treatment (P<0.05). In contrast, ziprasidone did not affect total food intake or food intake in any trial block. Ziprasidone co-administered with olanzapine significantly reduced the increase in total food intake induced by olanzapine alone (P<0.05), reducing food intake to the levels observed with vehicle and ziprasidone alone. Assessment of locomotor activity following drug administration showed no significant differences between the groups (olanzapine 985±213, ziprasidone 1237±254, ziprasidone with olanzapine 949±119 vs. vehicle 1271±156 beam breaks per hour).

The results demonstrate that ziprasidone not only does not enhance ingestive behaviour but also prevents the hyperphagic effect of olanzapine in this test. Sedative or other effects on locomotor activity did not appear to be a confounding influence on these results. The mechanism involved in the effect of ziprasidone in preventing olanzapine-induced hyperphagia remains to be determined, although the receptor pharmacology of ziprasidone suggests at least one possible mechanism. This could be the partial agonist/antagonist action of ziprasidone at 5-HT_{1A} receptors; here ziprasidone has low intrinsic agonist activity (Newman-Tancredi et al., 1998); full agonists at this site can have hyperphagic effects (Dourish et al., 1985). Whatever the mechanism, an understanding of the pharmacological basis for the protection from drug-induced hyperphagia and weight gain will provide potential for novel therapeutic measures to avoid this major side effect of antipsychotic drug treatment.

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