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Brief Report

Increased Food Consumption by Clozapine, But Not by Olanzapine, in Satiated Rats

Mark J. Benvenga* and J. David Leander

Neuroscience Division, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Indiana

Strategy, Management and Health Policy				
Venture Capital Enabling Technology	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT Various drugs used to treat schizophrenia have been repeatedly shown to increase body weight in both animals and humans. There are different theories as to why this occurs, but the most recently studied theory is that these drugs which cause weight gain do so because of an antagonist effect at the $5HT2_C$ receptor. In this work, we studied the effects of olanzapine, clozapine, and risperidone on feeding behavior. Over a 4-hour test period in satiated rats, clozapine, over a broad dose range, significantly increased food consumption. Similarly, risperidone increased food consumption relative to control. In contrast, olanzapine did not significantly increase food consumption in rats at any dose tested over the 4-hour test period. This suggests that olanzapine may be different from clozapine and risperidone with respect to potential weight gain in schizophrenic patients. Moreover, we believe that the effect produced by clozapine and risperidone is due to the alpha-adrenergic activity of these compounds, since olanzapine has a much lower affinity for alpha adrenergic receptors than does clozapine or risperidone, and not due to the $5HT2_C$ activity, which all three compounds have in common. Drug Dev. Res. 41:48–50, 1997.

Key words: hyperphagia; $5HT2_C$; atypical antipsychotics; alpha adrenergic

Phenothiazine neuroleptics have been known to increase feeding in schizophrenic patients since the early 1960s [Caffrey, 1961; Gordon and Croth, 1964]. The dibenzodiazepine clozapine was first reported to increase feeding in rats by Antelman et al. [1977], and then later in humans [Leadbetter et al., 1992; Jalenques et al., 1996]. This effect of clozapine has been attributed to its antagonistic effect at the $5HT2_C$ receptor [Curzon, 1992]. Moreover, it is now widely reported that compounds which block 5HT2 receptors, and more specifically, block $5HT2_C$ receptors, are hyperphagic in animals [Fletcher, 1988; Dourish et al., 1989; Curzon et al., 1997]. This would suggest that those atypical antipsychotics which block $5HT2_C$ receptors, similar to clozapine, would also produce hyperphagia in humans. In this study, we compared the effects of olanzapine [Moore et al., 1992] to the effects of clozapine and risperidone on feeding in satiated rats.

We used male Sprague-Dawley rats (300–400 g; Harlan Sprague-Dawley, Indianapolis, IN; n = 8/test group) that were housed individually in a temperature- and humidity-controlled room with a 12 h light-dark cycle (lights on: 0600–1800). Standard laboratory chow and water were available ad libitum. All testing took place in the animal colony between 0900–1500 h and all studies were approved by the Eli Lilly and Company Animal Care and Use Committee. Rats were randomly assigned to either drug- or vehicle-treated groups, weighed, administered drug or vehicle subcutaneously, and placed back in the home cage. All feeders with food were weighed before rats were injected, 4 h post-injection, and 24 h post-injection. Food consumed (plus spillage) by drug-treated groups was compared to the vehicle-treated

*Correspondence to: Mark J. Benvenga, Neuroscience Division, Lilly Research Laboratories, mail code 0510, Eli Lilly and Co., Indianapolis, IN 46285; E-mail: M.Benvenga@Lilly.Com.

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group using a one-way ANOVA. Individual differences were subsequently analyzed using a Dunnetts test. Olanzapine and risperidone were synthesized at Lilly Research Laboratories. Clozapine HCl was purchased from Research Biochemical, Inc. (Natick, MA).

The effects of clozapine, olanzapine, and risperidone are shown in Figure 1. Clozapine significantly increased food consumption over the first 4 hours at all doses tested. In fact, at a dose of 3 mg/kg, the rats consumed tenfold more food than control animals did over the same time period. An increased feeding effect was not evident over the 24-hour time period after injection. Additionally, there were no overt behavioral effects produced by clozapine in these animals.

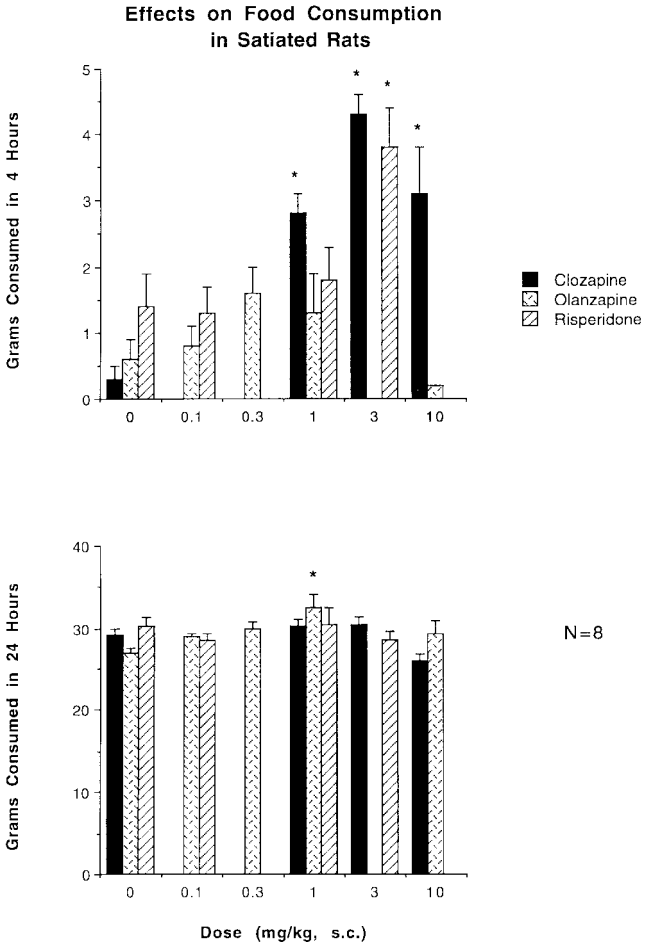

Fig. 1. Effects of clozapine (filled bars), olanzapine (hatched bars), and risperidone (lined bars) on feeding behavior over 4 hours (upper panel) and 24 hours (lower panel) in satiated rats. Each bar represents the mean (S.E.) grams of food consumed for eight rats. Clozapine was tested at 1, 3, and 10 mg/kg (3.0, 9.0, and 31.0 μmoles/kg, respectively). Olanzapine was tested at 0.1, 0.3, 1, and 10 mg/kg (0.3, 0.9, 3.0, and 32.0 μmoles/kg, respectively). Risperidone was tested at 0.1, 1, and 10 mg/kg (0.2, 2.0, and 24.0 μmoles/kg, respectively). * represents those effects that are significantly different from 0 ($P < 0.05$). Missing bars represent no drug treatment at that dose.

Similar to clozapine, risperidone, at 3 mg/kg, significantly increased feeding over the 4-hour time period in satiated rats. There was no significant increase at lower doses. This increased feeding at 3 mg/kg was accompanied by light sedation, which was apparent in the animals. Over the 24-hour time period, there was no significant increase in feeding produced by risperidone.

Olanzapine did not significantly increase feeding compared to control over the 4-hour time period at any dose tested. A dose of 0.3 mg/kg of olanzapine produced the peak effect to slightly increase feeding, but it was less than threefold what the control animals consumed over the same time period. A dose of 10 mg/kg of olanzapine produced profound sedation and a decrease in feeding. Over the 24-hour time period, a dose of 1 mg/kg of olanzapine, which produced an insignificant increase over the first 4 hours, had a small significant increase in feeding.

It is also important to note that control feeding, reported as 0 mg/kg for each compound in Figure 1, varies by compound. This occurred since each drug was run on separate days using separate rats so that drug effects would not be confounded by environmental or physiological differences in the animals.

Olanzapine did not significantly increase feeding over the 4-hour time period at any dose tested. In contrast, clozapine and risperidone both produced significant increases in feeding—risperidone at one dose, and clozapine at all doses tested. This would indicate a differential effect of olanzapine from both clozapine and risperidone on feeding behavior in rats. If, indeed, the increased feeding caused by compounds like clozapine and risperidone is related to their affinity for the $5HT2_C$ receptor, one might expect that olanzapine, which has a higher affinity for the $5HT2_C$ receptor than does risperidone [Bymaster et al., 1996], would have a much greater effect on feeding. However, in this study it did not. Also, olanzapine has a high affinity at D_2 receptors, which can explain the sedation which is produced by higher doses of olanzapine. This could explain why animals treated with olanzapine don't consume as much food as those treated with clozapine or risperidone. However, since risperidone binds with much higher affinity to D_2 receptors than does olanzapine, and Clifton et al. [1991] reported that D_2 receptor antagonism cannot explain an enhancement of feeding in rodents, this difference on feeding is not likely due to an action on the D_2 receptor. We believe that the difference in feeding between olanzapine, clozapine, and risperidone cannot be explained alone by the effects of these compounds at the $5HT2_C$ receptor. Clozapine and risperidone both bind to alpha-1 receptors with much higher affinity than does olanzapine [Bymaster et al., 1996]. It has long been known that compounds which block alpha adrenergic activity

increases feeding in rodents [Ritter et al., 1975]. We believe that both the adrenergic and serotonergic effects of these atypical antipsychotics is intimately involved in producing hyperphagia in rats. However, more studies are necessary to confirm the adrenergic effects of these compounds on feeding.

We have shown that olanzapine does not have the propensity to cause hyperphagia in satiated rats. These results suggest that olanzapine may have less liability for causing weight gain in humans than does clozapine or risperidone. This hypothesis will only be confirmed as comparative clinical studies between olanzapine, clozapine, and risperidone are completed.

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