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Preferential inhibition of dizocilpine-induced hyperlocomotion by olanzapine

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Abstract

This study examined the putative inhibitory effect of the atypical antipsychotic, olanzapine, on dizocilpine (MK-801)-induced stereotypy and hyperlocomotion. Dizocilpine (0.1, 0.25 and 0.5 mg/kg) produced a dose-dependent increase in both stereotypy and hyperlocomotion. Pretreatment with olanzapine (0.25 and 0.5 mg/kg) inhibited the dizocilpine (0.5 mg/kg)-induced hyperlocomotion but not the stereotypy. At the higher doses (1, 2 and 4 mg/kg), olanzapine blocked both the stereotypy and hyperlocomotion induced by dizocilpine. Similarly, olanzapine, 0.25 and 0.5 mg/kg, did not inhibit apomorphine (3 mg/kg)-induced stereotypy, whereas the higher dose (1 mg/kg) blocked it. We also studied the effect of olanzapine on spontaneous locomotor activity and catalepsy. Olanzapine (0.25 and 0.5 mg/kg) did not induce a decrease in spontaneous locomotor activity but did so at the higher doses (1, 2 and 4 mg/kg). The lower doses (0.25, 0.5 and 1 mg/kg) did not induce catalepsy but higher doses (2 and 4 mg/kg) induced a significant catalepsy which lasted for more than 4 h. The results thus showed that, at lower doses, olanzapine selectively inhibited behaviours mediated by the mesolimbic/mesocortical system while at higher doses it inhibited behaviours mediated by both mesolimbic/mesocortical and nigrostriatal systems. Therefore, the minimal extrapyramidal side-effects produced by olanzapine at effective doses might be due to its preferential action at the mesolimbic/mesocortical area.

Keywords: Olanzapine; Dizocilpine; Apomorphine; Mesolimbic/mesocortical area; Locomotion; Stereotypy; Catalepsy

1. Introduction

Since the discovery of the clinical antipsychotic activity of chlorpromazine in the 1950s, the pharmacological antagonism of central dopamine receptors, specifically dopamine D_2 receptors, remains the only proven method for treating schizophrenia, as demonstrated by extensive number of agents with varied chemical structures that have been found to share this property and to have clinical benefit. There is convincing evidence that the efficacy of these agents in treating psychotic symptoms results from dopamine D_2 receptor antagonism in the mesolimbic/mesocortical dopamine systems (Losonczy et al., 1987; Davis et al., 1991). Unfortunately, chronic treatment with dopamine antagonists, while effectively treating some of the symptoms of schizophrenia, can also result in the onset of Parkinson-like extrapyramidal side-effects and a progressively increasing risk of tardive dyskinesia. These phenomena are thought to be a consequence of the blockade of dopamine receptors in the corpus striatum, the terminal region of the nigrostriatal dopamine track (Baldessarini, 1990). An increasing body of evidence suggests that agents that antagonize 5-HT_{2A} receptors in the brain along with dopamine D_2 receptors may have an improved ratio of therapeutic effect to extrapyramidal side-effects.

Clozapine, which has affinity for a variety of receptors, including the dopamine D_2 and 5-HT_{2A} receptors, has efficacy against both positive and negative symptoms and has minimal liability for extrapyramidal side-effects (Matz et al., 1974; Kane et al., 1988). Clozapine's dual profile of efficacy against negative symptoms and low extrapyramidal side-effects has resulted in its designation as an 'atypical' antipsychotic. Olanzapine is a novel thienobenzodiazepine that closely resembles clozapine in terms of its pharmacological and behavioural profiles. Like clozapine, olanzapine has been found to antagonize dopamine (D_1,

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D_2, D_4), 5-HT (5-HT_{2A}, 5-HT_{2C}, 5-HT_3 and 5-HT_6), acetylcholine (M_1–M_5) and histamine H_1 receptors (Moore et al., 1993), and α_1-adrenoceptors. Recently, we have reported that olanzapine behaves similarly to clozapine as a partial agonist at dopamine D_2 receptors in dopamine-depleted animals but as a stronger antagonist than clozapine at dopamine D_1 receptors (Ninan and Kulkarni, 1998a,b,c).

A role of the glutamatergic system has been speculated about for a number of neurological disorders. Overactivity of excitatory aminoacid transmission in the brain as the pathophysiological basis of Parkinson's disease and a possible role of NMDA receptor antagonists in its treatment have been suggested (Carlsson and Carlsson, 1990; Porter et al., 1994). Also, a malfunctioning corticostriatal glutamatergic pathway has been envisaged as a possible cause of schizophrenia (Grace, 1991). Dizocilpine (MK-801), a non-competitive NMDA receptor antagonist induces in the rodents a complex behavioural syndrome which includes hyperlocomotion, stereotypy and ataxia (Iverson et al., 1988; Koek et al., 1988). Multiple receptor systems such as dopamine D_1 and D_2 receptors, 5-HT_{1A} and 5-HT_{2A} receptors and α_1-adrenoceptors may be involved dizocilpine-induced stereotypy and hyperlocomotion in animals (Verma and Kulkarni, 1991; Löscher and Honack, 1993; Carlsson, 1995; Mathe et al., 1996; Martin et al., 1997a; Ninan and Kulkarni, 1998d). Clozapine, in comparison to haloperidol, appears to be a selective antagonist of the dizocilpine-induced impairment of learning tasks (Hauber, 1993). This atypical action of clozapine may be due to its selectivity at certain limbic areas at the lower doses used (Kinon and Lieberman, 1996). Recently, Farber et al. (1996) reported on the prevention of dizocilpine-induced neurotoxicity in rats by olanzapine. Olanzapine is reported to inhibit phencyclidine-induced deficits in prepulse inhibition and dizocilpine-induced social withdrawal in animals (Bakshi and Geyer, 1995; Corbett et al., 1995). It was thus of interest to determine the effect of olanzapine on dizocilpine-induced hyperlocomotion and stereotypy, apomorphine-induced stereotypy, spontaneous locomotion and catalepsy.

2. Materials and methods

2.1. Animals

Male Balb/C mice (Central Animal House, Panjab University, Chandigarh) weighing 20–30 g were maintained on a 12-h light and dark cycle. The animals were maintained on standard pellet food and water and were habituated to laboratory conditions before the test. All experiments were undertaken between 0900 and 1300 h. Each animal was used only once.

2.2. Measurement of stereotypy

Stereotypy was measured by placing mice individually in glass containers. Sniffing, rearing, licking, biting, gnawing and grooming were observed as stereotypic behaviors at 0, 15, 30, 45, 60, 90 and 120 min, respectively, after drug administration. The intensity of stereotypy was recorded using a modified ranked-intensity scale where 0 = absent, 1 = equivocal, 2 = present, 3 = intense and 4 = intense and continuous (Costall and Naylor, 1973). The cumulative stereotypy score was calculated by adding all the scores for the purpose of comparison (Verma and Kulkarni, 1993). The median value was calculated. There were eight mice in each group.

2.3. Measurement of locomotor activity

Locomotor activity (ambulation) was measured using a computerized animal activity meter (Opto Varimex Mini, Columbus Instruments, OH, USA). Briefly, 30 min after drug treatment mice were individually placed in a transparent plastic cage ($30 \times 23 \times 22$ cm) and activity was recorded for 5 min after they had adapted to the new environment for 2 min. An array of 11 infrared emitter/detector pairs (spaced at 2.65 cm intervals; beam wave-length = 875 nm; distance between the emitter and detector mounted on an external frame = 50 cm) measured activity along a single axis of motion, the digital data being displayed on the front panel meter as ambulatory activity. Locomotion was expressed in terms of total photobeam counts per 5 min per animal. There were eight mice per group and the data were expressed as means ± S.E.M.

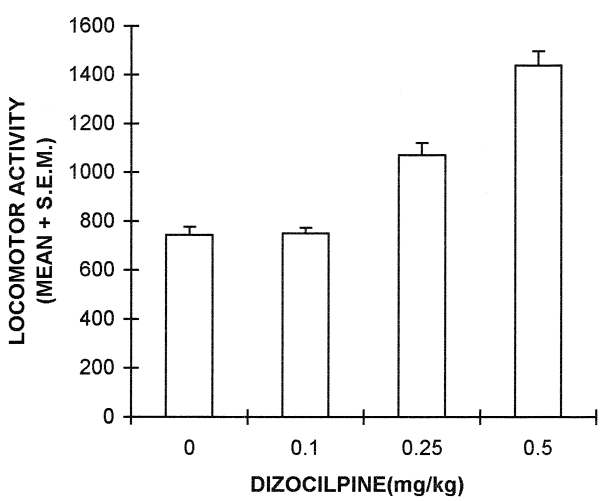

Fig. 1. The effect of various doses of the non-competitive NMDA receptor antagonist, dizocilpine (0.1, 0.25 and 0.5 mg/kg) on locomotor activity in mice. Dizocilpine was given 30 min prior to the start of the locomotor activity recording. The means ± S.E.M. for eight animals are shown. Dizocilpine (0.1, 0.25 and 0.5 mg/kg) showed a dose-dependent effect.

Table 1
The effect of various doses of the non-competitive NMDA receptor antagonist, dizocilpine (0.1, 0.25 and 0.5 mg/kg), on stereotypy in mice

No.	Treatment (mg/kg)	Stereotypy score Median [range]
1	Dizocilpine (0.1)	3 [0–4]
2	Dizocilpine (0.25)	5.5 [2–7]
3	Dizocilpine (0.5)	15.5 [9–19]

Sniffing, rearing, licking, biting, gnawing and grooming were observed as stereotypic behaviors at 0, 15, 30, 45, 60, 90 and 120 min, respectively, after drug administration. The cumulative stereotypy score was calculated by adding all the scores for the purpose of comparison. The median value was calculated. There were eight animals in each group.

2.4. Measurement of catalepsy

Catalepsy was determined by placing the animal's front paws over a rod (diameter 1 cm) raised 6 cm above the bench. The time the animal remained in this position was recorded every hour for 4 h. The time the animals remained on the rod at each observation was added for comparison.

2.5. Drugs

Dizocilpine maleate (Merck, Sharp and Dohme, Rahway, NJ, USA), apomorphine hydrochloride (Sigma, St. Louis, MO, USA) and olanzapine (Eli Lilly, Indianapolis, USA) were used in the study. Dizocilpine and apomorphine were dissolved in saline. Olanzapine was dissolved in few drops of diluted HCl and made up to volume with saline and the pH was adjusted. All drugs were administered intraperitoneally in a constant volume of 1 ml per 100 g body weight. The selection of doses was based on previous results from our laboratory. Olanzapine was administered 30 min prior to dizocilpine and apomorphine treatment.

2.6. Statistical analysis

The locomotor and catalepsy data are expressed as means ± S.E.M. The stereotypy score is expressed as median value with interquartile ranges. The locomotor activity data and catalepsy score were subjected to one-way ANOVA (analysis of variance) followed by Student's *t*-test, whereas the stereotypy score was subjected to a non-parametric Kruskal–Wallis ANOVA followed by the Mann–Whitney *U*-test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Effect of dizocilpine on locomotor activity and stereotypy

Dizocilpine (0.1, 0.25 and 0.5 mg/kg) induced a dose-dependent increase in locomotor activity [($F(3,28) = 5.45$, $P < 0.05$)]. (Fig. 1). Similarly, dizocilpine (0.1, 0.25 and 0.5 mg/kg) induced a dose-dependent increase in stereotypic behaviours, severe rearing, circling behaviour, sniffing and grooming [$H(2) = 17.21$, $P < 0.05$] (Table 1). The peak effect was observed at 30–35 min after the administration of dizocilpine.

3.2. Effect of olanzapine on dizocilpine (0.5 mg/kg)-induced hyperlocomotion

To examine the effect of different doses of olanzapine on dizocilpine (0.5 mg/kg)-induced hyperlocomotion, we

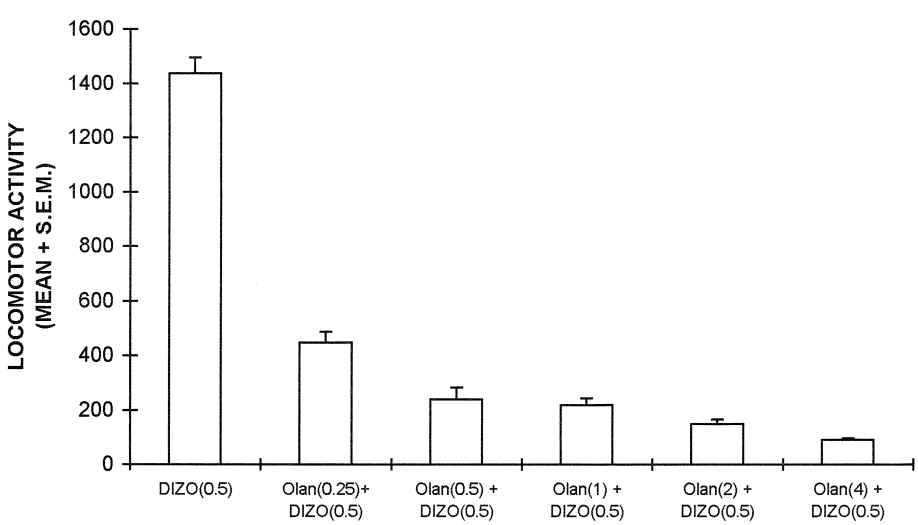

Fig. 2. Effect of olanzapine (0.25, 0.5, 1, 2 and 4 mg/kg) on dizocilpine (0.5 mg/kg)-induced hyperlocomotion in mice. Olanzapine was administered 30 min prior to dizocilpine treatment. The means ± S.E.M. for eight animals are shown. At all the doses, olanzapine inhibited dizocilpine-induced hyperlocomotion.

Table 2
Effect of olanzapine (0.25, 0.5, 1, 2 and 4 mg/kg) on dizocilpine (0.5 mg/kg)-induced stereotypy in mice

No.	Treatment (mg/kg)	Stereotypy score Median [range]
1	Dizocilpine (0.5)	15.5 [9–19]
2	Olanzapine (0.25) + Dizocilpine (0.5)	15.5 [8–18]
3	Olanzapine (0.5) + Dizocilpine (0.5)	15.5 [8–17]
4	Olanzapine (1) + Dizocilpine (0.5)	9 [6–11][a]
5	Olanzapine (2) + Dizocilpine (0.5)	7.5 [5–9][a]
6	Olanzapine (4) + Dizocilpine (0.5)	2 [0–4][a]

Olanzapine was administered 30 min prior to dizocilpine treatment. Sniffing, rearing, licking, biting, gnawing and grooming were observed as stereotypic behaviors at 0, 15, 30, 45, 60, 90 and 120 min, respectively, after dizocilpine administration. The cumulative stereotypy score was calculated by adding all the scores for the purpose of comparison. The median value was calculated. There were eight animals in each group.
[a] $P < 0.05$ as compared to saline-pretreated group (Kruskal–Wallis ANOVA followed by Mann–Whitney *U*-test).

administered 0.25, 0.5, 1, 2 and 4 mg/kg of olanzapine 30 min prior to dizocilpine treatment. As shown in Fig. 2, olanzapine dose dependently inhibited the dizocilpine-induced hyperlocomotion [$F(5,42) = 8.78$, $P < 0.05$]. All the doses, decreased locomotor activity to well below that of saline-treated (control) animals.

3.3. Effect of olanzapine on dizocilpine (0.5 mg/kg)-induced stereotypy

Pretreatment with olanzapine (0.25 and 0.5 mg/kg) did not modify the dizocilpine (0.5 mg/kg)-induced stereotypy. The higher doses (1, 2 and 4 mg/kg) of olanzapine dose dependently blocked the dizocilpine-induced stereotypic behaviours [$H(5) = 560.32$, $P < 0.05$] (Table 2).

3.4. Effect of olanzapine on apomorphine (3 mg/kg)-induced stereotypy

Apomorphine (3 mg/kg) produced a marked stereotyped behaviour characterized by intense sniffing, licking, gnawing and rearing. The peak effect was observed at 15 min after the administration of apomorphine. Olanzapine at lower doses (0.25 and 0.5 mg/kg) failed to block, while at the higher dose (1 mg/kg), it significantly blocked apomorphine stereotypy [$H(3) = 19.17$, $P < 0.5$] (Table 3). Olanzapine at still higher doses (2 and 4 mg/kg) completely blocked apomorphine-induced stereotypy.

Table 3
Effect of olanzapine (0.25, 0.5 and 1 mg/kg) on apomorphine (3 mg/kg)-induced stereotypy in mice

No.	Treatment (mg/kg)	Stereotypy score Median [range]
1	Apomorphine (3)	6 [4–8]
2	Olanzapine (0.25) + Apomorphine (3)	6 [3–7]
3	Olanzapine (0.5) + Apomorphine (3)	5.5 [3–7]
4	Olanzapine (1) + Apomorphine (3)	1 [1–3][a]

Olanzapine was administered 30 min prior to apomorphine treatment. Sniffing, rearing, licking, biting, gnawing and grooming were observed as stereotypic behaviors at 0, 15, 30, 45, 60, 90 and 120 min, respectively, after apomorphine administration. The cumulative stereotypy score was calculated by adding all the scores for the purpose of comparison. The median value was calculated. There were eight animals in each group.
[a] $P < 0.05$ as compared to saline-pretreated group (Kruskal–Wallis ANOVA followed by Mann–Whitney *U*-test).

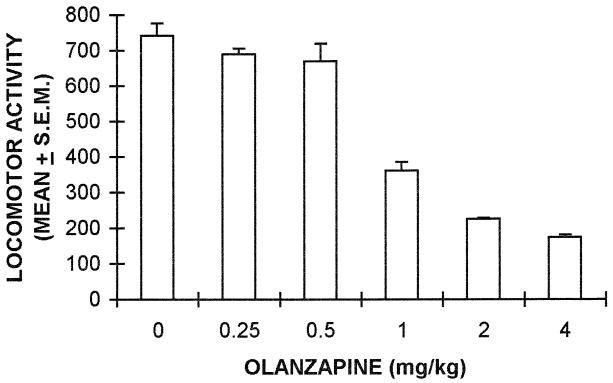

Fig. 3. Effect of olanzapine (0.25, 0.5, 1, 2 and 4 mg/kg) on spontaneous locomotor activity in mice. Olanzapine was administered 30 min prior to dizocilpine treatment. Olanzapine was given 1 h prior to the start of the locomotor activity recording. At doses 0.25 and 0.5 mg/kg, olanzapine did not reduce spontaneous locomotor activity significantly while at higher doses (1, 2 and 4 mg/kg), it reduced spontaneous locomotor activity significantly. The means ± S.E.M. for eight animals are shown.

3.5. Effect of olanzapine on spontaneous locomotor activity

To assess the effect of olanzapine (0.25, 0.5, 1, 2 and 4 mg/kg) on spontaneous locomotor activity, we measured locomotor activity 1 h after its administration. Olanzapine, 0.25 and 0.5 mg/kg, did not decrease spontaneous locomotor activity but did so dose dependently at higher doses (1, 2 and 4 mg/kg) (compared to saline-treated group, $F(5,42) = 7.78$, $P < 0.05$) (Fig. 3).

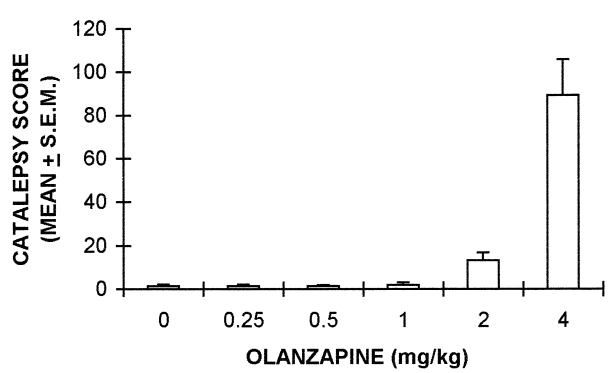

Fig. 4. Effect of olanzapine (0.25, 0.5, 1, 2 and 4 mg/kg) on catalepsy in mice. At lower doses (0.25, 0.5 and 1 mg/kg), olanzapine did not produce marked catalepsy but at higher doses (2 and 4 mg/kg), it produced catalepsy which lasted for more than 4 h. The means ± S.E.M. for eight animals are shown.

3.6. Olanzapine-induced catalepsy in mice

Olanzapine (0.25, 0.5 and 1 mg/kg) did not change the time the animals remained on the rod compared to the saline-treated group. At higher doses (2 and 4 mg/kg) olanzapine dose dependently increased the time the animals remained on the rod to more than 4 h [$F(5,42) = 21.53$, $P < 0.05$] (Fig. 4).

4. Discussion

The results showed that olanzapine at lower doses selectively blocked dizocilpine-induced hyperlocomotion but not the stereotypy. At the higher doses, olanzapine blocked both the hyperlocomotion and stereotypy induced by dizocilpine. Clozapine selectively blocks dizocilpine-induced hyperlocomotion (Hoffman, 1992; Gattaz et al., 1994; Ninan and Kulkarni, 1998e). There at least two mechanisms by which antipsychotic drugs could exert glutamatergic effects. The first involves effects on neurotransmitter systems such as dopamine, serotonin and noradrenaline which could be affected by manipulation of glutamate receptors (Verma and Kulkarni, 1991; Löscher and Honack, 1993; Carlsson, 1995; Mathe et al., 1996; Martin et al., 1997a; Ninan and Kulkarni, 1998d). The second mechanism involves direct effects of antipsychotic drugs on glutamate receptors. Clozapine may antagonize glutamate receptors directly at the NMDA receptor as suggested by results of displacement of [^{3}H]MK-801 binding experiments (Lidsky et al., 1993; Giardino et al., 1997). There are, however, no reports available on a direct effect of olanzapine on glutamate receptors. It was suggested that the selective action of clozapine on dizocilpine-induced hyperlocomotion might be due to its preferential action in the mesolimbic/mesocortical area. Olanzapine, a congener of clozapine appears to be the only antipsychotic agent with this degree of selectivity. The observation that olanzapine reduced the dizocilpine-induced hyperlocomotion to well below that of control animals could be due to the fact that hyperlocomotion is more readily inhibited than normal, spontaneous locomotion. The effect of lower doses of olanzapine on apomorphine-induced stereotypy was similar to its effect on dizocilpine-induced stereotypy. At higher doses, however, olanzapine completely blocked apomorphine-induced stereotypy while dizocilpine-treated animals showed mild stereotypy. This could have been due to the intense stereotypy elicited by dizocilpine as compared to that with apomorphine. We had observed that clozapine potentiated apomorphine-induced stereotypy but not locomotion in dopamine-depleted mice (Ninan and Kulkarni, 1998a). On the other hand, olanzapine preferentially blocked apomorphine-induced hyperlocomotion but not stereotypy in dopamine-depleted mice (Ninan and Kulkarni, 1998c). In rodents, exploratory locomotion has been used as a functional index of mesolimbic dopaminergic activity, and stereotypy as a measure of nigrostriatal dopaminergic activity (Costall and Naylor, 1977; Radhakishun and Van Ree, 1987). Therefore, olanzapine's ability to block dizocilpine-induced hyperlocomotion and its inability to block apomorphine-induced stereotypy at lower doses could be due to its preferential action in the mesolimbic area and this might be one of the reasons for the lack of motor side-effects. The present findings thus provide further evidence that olanzapine and clozapine may be functionally similar compounds.

Olanzapine was found to be selective for dizocilpine-induced hyperlocomotion as compared to spontaneous locomotion. The 5-HT_{2A} receptor antagonists such as ketanserin, ritanserin, seganserin and M100907 [*R*-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol] were found to be selective for dizocilpine-induced hyperlocomotion as compared to spontaneous locomotion (Martin et al., 1997b; Ninan and Kulkarni, 1998d). The 5-HT_{2A} receptor antagonistic effect of olanzapine might contribute to its preferential action on dizocilpine-induced hyperlocomotion as compared to spontaneous locomotion. The lack of effect on spontaneous locomotion suggests that olanzapine, compared to classical antipsychotics should be less prone to induce psychomotor side-effects. Similarly, low doses of olanzapine, which block dizocilpine-induced hyperlocomotion, did not induce catalepsy while the higher doses produced catalepsy and decreased spontaneous locomotion.

The pharmacological basis of atypical antipsychotic drug action has been the target of intensive study since the clinical efficacy of clozapine was first appreciated. One of the various hypotheses proposed involves the anatomic specificity characteristics of atypical antipsychotic drugs. Different brain regions mediate catalepsy and locomotor hyperactivity and stereotypy. The potency of atypical antipsychotic drugs as compared to the potencies of the typical antipsychotics to influence these behaviours may indicate an anatomic specificity of action that confers a favourable spectrum of activity on the typical drugs. The expression of neuroleptic-induced catalepsy requires the antagonism of striatal postsynaptic dopamine receptors, whereas locomotor hyperactivity and stereotypy are mediated through the nucleus accumbens and striatum, respectively (Costall and Naylor, 1977; Radhakishun and Van Ree, 1987). Atypical antipsychotics such as clozapine, thioridazine and sulpiride are reported to selectively affect mesolimbic-mediated animal behaviour, dopamine turnover, electrophysiological activity, gene expression and cognitive functions whereas classical antipsychotics are non-selective at mesolimbic and nigrostriatal areas (Kinon and Lieberman, 1996).

The findings of the present study further support the hypothesis that atypical antipsychotics show selectivity for mesolimbic area-mediated behaviours. Interestingly, the use of clozapine in the treatment of schizophrenia, and its classification as an atypical antipsychotic, are based on its

unique ability to improve both positive and negative symptoms in patients resistant to traditional neuroleptics such as haloperidol and on its lack of extrapyramidal side-effects. Clinical study indicated that olanzapine also reduces both positive and negative symptoms of schizophrenia (Beasely et al., 1995). An animal model such as dizocilpine-induced hyperlocomotion and stereotypy in which the former is highly sensitive to blockade by atypical antipsychotics such as clozapine and olanzapine but not by the classical antipsychotics, should have good predictive validity for screening atypical antipsychotics.

In conclusion, the present results showed that, at lower doses, olanzapine selectively inhibits behaviour mediated by mesolimbic/mesocortical system, while at higher doses, it inhibits behaviours mediated by both the mesolimbic/mesocortical and the nigrostriatal system. Therefore, the minimal extrapyramidal side-effects of olanzapine at effective doses might be due to its preferential action at the mesolimbic/mesocortical area.

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