Differential effects of olanzapine at dopamine D1 and D2 receptors in dopamine depleted animals

Abstract The aim of the present study was to investigate the locomotor stimulant effects of the atypical antipsychotic agent, olanzapine, in mice depleted of their dopamine by reserpine and a-methyl-DL-p-tyrosine pretreatment. Olanzapine (0.5, 1 and 2 mg/kg) dose-dependently increased locomotor activity, which was completely blocked by the selective dopamine D2 receptor antagonist, pimozide (0.5 mg/kg) but not by selective dopamine D1 receptor antagonist, SCH 23390 (0.5 and 1 mg/kg). Unlike olanzapine, the selective dopamine D2 receptor antagonists such as haloperidol (0.25 and 0.5 mg/kg) and pimozide (0.5 and 1 mg/kg), the selective 5-HT2A receptor antagonist, ritanserin (0.5 and 1 mg/kg) or the antimuscarinic agent scopolamine (0.5 and 1 mg/kg) failed to produce any locomotor stimulant effect. Olanzapine (1 and 2 mg/kg) and SCH 23390 (0.5 and 1 mg/kg) blocked hyperlocomotion and stereotypy induced by the selective dopamine D1 receptor agonist, SKF 38393 (10 and 25 mg/kg). Olanzapine (1 and 2 mg/kg) blocked hyperlocomotion and stereotypy induced by B-HT 920 (1 and 2 mg/kg), a selective dopamine D2 receptor agonist, whereas it blocked the hyperlocomotion but not stereotypy induced by the non-selective dopamine receptor agonist, apomorphine (0.5 and 1 mg/kg). The higher dose (4 mg/kg) of olanzapine blocked both stereotypy and hyperlocomotion induced by apomorphine. Olanzapine, in mice depleted of their dopamine stores, exhibited properties consistent with those of a D2 partial agonist having strong D1 antagonist property. The atypical nature of its clinical effect may be explained by a dual effect, partial agonistic-like action at D2 receptors and antagonist-like activity at D1 receptors, respectively.

Key words Olanzapine · Dopamine D1 receptor · Dopamine D2 receptor · SKF 38393 · Partial agonist

Introduction Olanzapine (LY 170053, 2-methyl-4-(4-methyl-1-piperazinyl)-1OH-thieno [2, 3-b] [1, 5] benzodiazepine) is the most recent example of an “atypical” neuroleptic. Olanzapine not only possesses few extrapyramidal side effects, but also has clinical efficacy against negative symptoms in schizophrenia and treatment-resistant schizophrenia (Beasley et al. 1996). Olanzapine was also active in behavioral paradigms in animals that may be indicative of atypical antipsychotic activity. For example, olanzapine inhibited conditioned avoidance responses and was active at doses lower than those required to produce catalepsy, indicating reduced potential for EPS (Moore et al. 1992). Olanzapine increased punished responding in both rats and pigeons, an effect not seen with typical antipsychotics (Moore et al. 1994; Benvenga and Leander 1996). The electrophysiological effects of olanzapine are similar to those of the atypical antipsychotic clozapine (Chiado and Bunney 1983; Stockton and Rasmussen 1996).

Olanzapine is similar to clozapine in molecular structure, but it has not been associated with agranulocytosis or lowering seizure threshold (Meltzer and Flibiger 1996). Radioligand binding studies have shown olanzapine to have high affinity for a number of neuronal receptors, including dopamine (DA) D1, D2, D4, serotonin 5-HT2A, 5-HT2C, α1-adrenergic, histaminic H1 and muscarinic receptors (Moore et al. 1993; Bymaster et al. 1996). Blockade of DA receptors in vivo has been demonstrated by inhibition of apomorphine-induced climbing behavior in mice and antagonism of pergolide-induced elevation of serum corticosterone concentrations in rats (Fuller and Snoddy 1992; Moore et al. 1992). Olanzapine antagonized 5-hydroxytryptophan-
induced head twitches in mice and quipazine-induced elevation of serum corticosterone concentration in rats, indicating blockade of 5-HT receptors. Furthermore, olanzapine antagonized tremors induced by the muscarinic agonist oxotremorine (Moore et al. 1992). Recently, we have reported partial agonistic action of clozapine at DA D2 receptors in DA depleted animals (Ninan and Kulkarni 1998a,b). In the present study, we examined whether it was possible to demonstrate behavioral properties of olanzapine in vivo which would be compatible with a direct or indirect stimulation of DA receptors. We chose a model that is documented to involve both DA D1 and D2 receptors, i.e., receptor agonist-induced locomotor stimulation in rats depleted of their stores of DA (Jackson et al. 1995). The granule-depleting agent, reserpine, and the inhibitor of tyrosine hydroxylase, the rate-limiting step in the synthesis of DA, p-methyl-DL-p-tyrosine (AMPT), were used to deplete brain DA stores.

Materials and methods

Male Balb/C mice (Central Animal House, Punjab University) weighing 20–30 g were maintained on a 12-h light and dark cycle at 25 ± 2°C. The animals were maintained on standard pellet food and water and were habituated to laboratory conditions before the test. In the DA depletion studies, mice were pretreated with reserpine (5 mg/kg) and 20 h later with AMPT (200 mg/kg). Drugs were injected 1 h after AMPT treatment. Drugs used in these studies were olanzapine (Eli Lilly, Indianapolis, Ind., USA), SKF 38393 hydrochloride (Research Biochemicals Inc. Natick, Mass., USA), B-HT 920 hydrochloride (Boehringer Ingelheim, Ingelheim am Rhein, Germany), SCH 23390 maleate (Schering Plough Co., Bloomfield, N.J., USA), pimozide (Endo Laboratories, N.Y., USA), scopalamine hydrobromide (Merck & Co. Inc., N.J., USA), ritanserin (Janssen Research Foundation, Belgium), apomorphine (Sigma, St Louis, Mo., USA), haloperidol (Searle, Skokie, Ill., USA), AMPT methylester hydrochloride (Sigma, St Louis, Mo., USA) and reserpine (Loba, Bombay, India). Olanzapine, pimozide and ritanserin were dissolved in a few drops of dilute HCl and the volume was made up with distilled water. Reserpine and haloperidol were dissolved in a minimum of glacial acetic acid and diluted with distilled water. All other drugs were dissolved in distilled water. Drugs were injected intraperitoneally in a volume of 1 ml/100 g body weight.

Measurement of cumulative stereotypy was done 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 and 90 min, respectively, after drug administration. The intensity of stereotypy was recorded as described by Costall and Naylor (1973). The cumulative stereotypy score was calculated by adding all the scores for the purpose of comparison (Verma and Kulkarni 1993).

Measurement of locomotor activity (ambulation) was done using computerized animal activity meter (Opto Varimex Mini, Columbus Instruments, Ohio, USA). Briefly, after 1 h of drug treatment mice were individually placed in a transparent plastic cage (30 × 23 × 22 cm) and the activity was recorded for 5 min after allowing the mice to adapt 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 = 50 cm) measured the animal activity along single axis of motion, the digital data being displayed on the front panel meter as ambulatory activity. The locomotion was expressed in terms of total photobeam counts per 5 min per animal. The data were analysed using analysis of variance (ANOVA) followed by Student’s t-test and Mann-Whitney U-test for locomotor studies and stereotypy studies, respectively. P < 0.05 was considered statistically significant.

Results

The mice pretreated with reserpine and AMPT were completely akinetic and displayed characteristic sign(s) of DA depletion, which included ptosis, hunched back and severe diarrhea. The normal control animal showed a locomotor activity of 453.82 ± 47.3. Olanzapine (0.5, 1 and 2 mg/kg) dose-dependently increased locomotor activity, whereas olanzapine at 4 mg/kg did not show marginal increase in locomotor activity (Fig. 1). Pimozide (0.5 mg/kg) completely blocked olanzapine (2 mg/kg)-induced locomotor activity stimulation but not by SCH 23390 (0.5 and 1 mg/kg) (Fig. 2). However, olanzapine did not show any stereotypic behavior. Unlike olanzapine, haloperidol (0.25 and 0.5 mg/kg), pimozide (0.5 and 1 mg/kg), ritanserin (0.5 and 1 mg/kg) or scopalamine (0.5 and 1 mg/kg) failed to produce any locomotor stimulating effect.

![Fig. 1 Effect of olanzapine (0.5–4 mg/kg) on spontaneous locomotor activity in mice depleted of their DA by reserpine (5 mg/kg) and AMPT (200 mg/kg)](image)

![Fig. 2 Effect of SCH 23390 (0.5 and 1 mg/kg) on olanzapine (2 mg/kg)-induced hyperactivity in mice depleted of their DA by reserpine (5 mg/kg) and AMPT (200 mg/kg)](image)