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# 5-$HT_{2A}$ receptor antagonists block MK-801-induced stereotypy and hyperlocomotion

Ipe Ninan, Shrinivas K. Kulkarni *

*Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh 160014, India*

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**Abstract**

The present study was undertaken to examine the effect of 5-$HT_{2A}$ receptor antagonists on MK-801 (5-methyl-10,11-dihydro-5*H*-dibenzo (*a*,*d*) cyclohepten-5,10-imine)-induced stereotypy and hyperlocomotion. MK-801 (0.1, 0.25 and 0.5 mg/kg) dose-dependently increased stereotypy and locomotion in mice. The 5-$HT_{2A}$ receptor antagonists, ketanserin (2.5, 5 and 10 mg/kg) and ritanserin (0.5, 1 and 2 mg/kg), dose-dependently blocked MK-801 (0.5 mg/kg)-induced hyperlocomotion. Only the higher dose (2 mg/kg) of seganserin could block locomotor activity. Similarly, ketanserin (2.5, 5 and 10 mg/kg), ritanserin (1 and 2 mg/kg) and seganserin (0.5, 1 and 2 mg/kg) dose-dependently blocked MK-801 (0.5 mg/kg)-induced stereotypy. The results suggest the involvement of 5-$HT_{2A}$ receptors in MK-801-induced stereotypy and hyperlocomotion. The lack of effect on spontaneous locomotion further suggests that 5-$HT_{2A}$ receptor antagonists will be less prone to induce psychomotor side-effects. 

*Keywords:* MK-801; 5-$HT_{2A}$ receptor antagonist; Stereotypy; Hyperlocomotion

## 1. Introduction

A role of the glutamatergic system has been speculated about for a number of neurological disorders. An overactive excitatory aminoacid transmission in the brain as the pathophysiology 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). Further, a malfunctioning corticostriatal glutamatergic pathway has been envisaged as a possible cause of schizophrenia (Grace, 1991). MK-801 (5-methyl-10,11-dihydro-5*H*-dibenzo (*a*,*d*) cyclohepten-5,10-imine), a non-competitive NMDA receptor antagonist induces a complex behavioural syndrome in rodents which includes hyperlocomotion, stereotypy and ataxia (Iverson et al., 1988; Koek et al., 1988). It is widely assumed that these behavioural alterations are mediated at least in part by activation of the mesolimbic dopaminergic system as a result of an interaction between glutamatergic and dopaminergic transmission (Carlsson and Carlsson, 1990). There is also a report that MK-801 can stimulate locomotion by dopamine-independent mechanisms (Carlsson and Carlsson, 1989a,b). Some studies have indicated that activation of the 5-HT system is involved in the behavioural actions of non-competitive NMDA receptor antagonists (Balster, 1987; Nabeshima et al., 1984; Johnson, 1987). Recently, Loscher and Honack (1993) have shown that 5-$HT_{1A}$ receptors are involved in the stereotypic behaviour induced by the NMDA receptor antagonist, MK-801, in rats.

Recent advances in the treatment of schizophrenia have led to the clinical introduction of drugs with a 5-$HT_{2A}$ receptor blocking property, such as clozapine, setoperone, risperidone, olanzapine, sertindole and iloperidone. Such compounds are predicted to be efficacious in the treatment of negative symptoms of schizophrenia and treatment-resistant schizophrenia.They exhibit a low incidence of extrapyramidal side-effects (Ceulemans et al., 1985; Castelao et al., 1989; Gelders, 1989). Atypical antipsychotics such as clozapine and risperidone, have a high affinity for 5-$HT_{2A}$ receptors, and an association between good response to clozapine and allele 1 of the T102C polymorphism of the 5-$HT_{2A}$ receptor gene has been reported (Arranaz et al., 1995). Williams et al. (1996) have recently suggested that allelic variation at the 5-$HT_{2A}$ receptor gene is involved in the pathogenesis of schizophrenia. Ritanserin, the selective 5-$HT_{2A}$ receptor antagonist, has been shown to ameliorate the negative symptoms of schizophrenia and reduce the incidence of extrapyramidal

* Corresponding author. Fax: +91-172-541142.

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symptoms resulting from the maintenance therapy (Bersani et al., 1986). Earlier, Maj et al. (1991) suggested that dopamine receptors rather than 5-$HT_{2A}$ receptors or adrenoceptors are mainly involved in MK-801-induced locomotor hyperactivity. Recent evidence however indicates that 5-$HT_{2A}$ receptors have a critical role in MK-801-induced behaviours (Carlsson, 1995; Martin et al., 1997b). More and more experimental evidence points to the fact that dopamine may be playing a less critical role than had been supposed in the regulation of psychomotor functions. This view is supported by the finding that, even in the complete absence of brain dopamine, pronounced behavioural activation is produced in mice following suppression of glutamatergic neurotransmission. Therefore, the present study was initiated to examine the effect of three 5-$HT_{2A}$ receptor antagonists namely, ketanserin, ritanserin and seganserin, on MK-801-induced hyperlocomotion and stereotypy in mice.

## 2. Materials and methods

### 2.1. Animals

Male Balb/C mice (Central Animal House, Panjab University, Chandigarh, India) 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 1700 h, using a randomized design. Each animal was used only once.

### 2.2. Measurement of stereotypy

Stereotypy was measured by placing mice individually in glass containers. Behaviours counted as stereotypy included: sniffing, circling behaviour, rearing, licking, biting, gnawing and grooming. Mice were rated for a 5-min period after 30 min of 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 maximum possible score was four. The median value was calculated. There were eight mice per 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, after 30 min of drug treatment mice were placed individually in a transparent plastic cage (30 × 23 × 22 cm) and 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

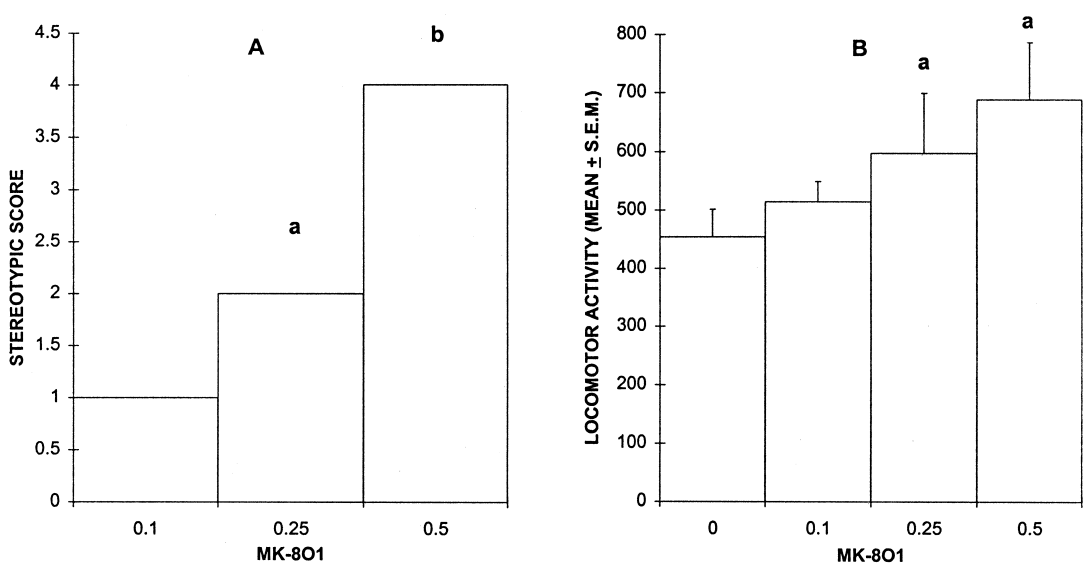


Fig. 1. (A) The effect of various doses of the non-competitive NMDA receptor antagonist, MK-801 (0.1, 0.25 and 0.5 mg/kg), on stereotypy in mice. Stereotypic behaviours were observed for 5 min after 30 min of drug administration, and the median value was calculated. There were eight animals per group. [a,b]Significantly different from MK-801 (0.1 mg/kg)-and MK-801 (0.25 mg/kg)-treated groups, respectively ($P < 0.05$, Mann–Whitney *U*-test). (B) The effect of various doses of the non-competitive NMDA receptor antagonist, MK-801 (0.1, 0.25 and 0.5 mg/kg), on locomotor activity in mice. MK-801 was given 30 min prior to the start of the locomotor activity recording. The means ± S.E.M. for eight animals are shown. MK-801 (0.1, 0.25 and 0.5 mg/kg) had a dose-dependent effect ($F(3, 28) = 3.63$, $P < 0.05$). [a]Significantly different from saline-treated group ($P < 0.05$, ANOVA followed by Student's *t*-test).

detector mounted on an external frame = 50 cm) measured the animal's 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.

### 2.4. Drugs

MK-801 (5-methyl-10,11-dihydro-5*H*-dibenzo (*a*,*d*) cyclohepten-5,10-imine) (dizocilpine; Merck, Sharp & Dohme, Rahway, NJ, USA), ketanserin tartrate, ritanserin and seganserin hydrochloride (all gifts from Janssen Research Foundation, Belgium) were used in the study. The

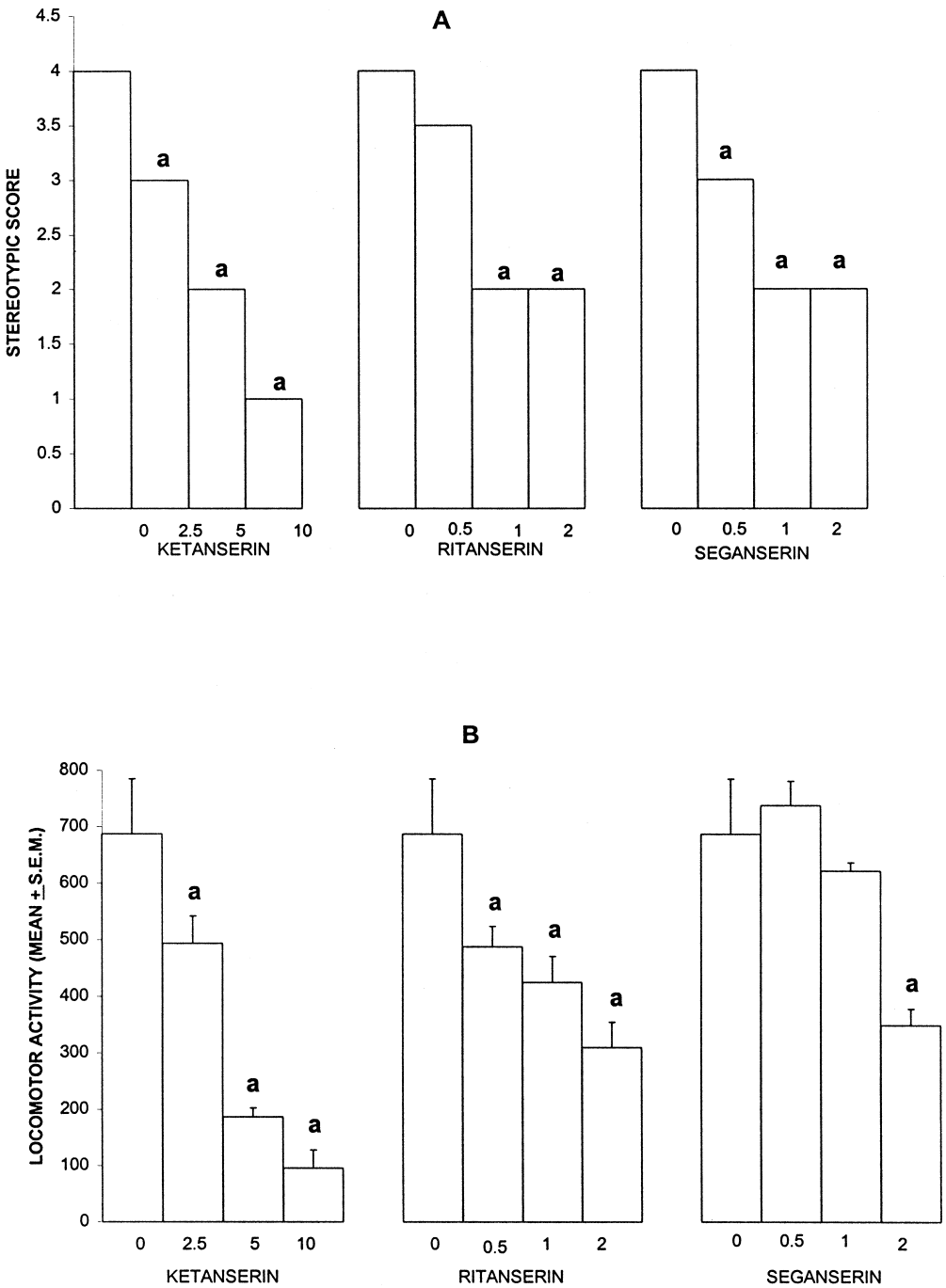


Fig. 2. (A) Effect of ketanserin (2.5, 5 and 10 mg/kg), ritanserin (0.5, 1 and 2 mg/kg) and seganserin (0.5, 1 and 2 mg/kg) on MK-801 (0.5 mg/kg)-induced stereotypy in mice. There were eight animals per group. [a]Significantly different from saline pretreated group (Mann–Whitney *U*-test). (B) Effect of ketanserin (2.5, 5 and 10 mg/kg) ($F(3, 28) = 5.4$, $P < 0.05$), ritanserin (0.5, 1 and 2 mg/kg)) ($F(3, 28) = 9.31$, $P < 0.05$) and seganserin (0.5, 1 and 2 mg/kg) ($F(3, 28) = 9.86$, $P < 0.05$) on MK-801 (0.5 mg/kg)-induced hyperlocomotor activity in mice. The means ± S.E.M. for eight animals are shown. [a]Significantly different from saline-pretreated group (One-way ANOVA followed by Student's *t*-test).

drug solutions were made in distilled water except that for ritanserin. Ritanserin was dissolved in a few drops of hydrochloric acid, the volume was made up with distilled water and the pH was adequately adjusted. All drugs were administered intraperitoneally in a constant volume of 1 ml per 100 g of body weight of mice. The selection of doses was based on previous reports from our laboratory. In combination studies, 5-$HT_{2A}$ receptor antagonists were administered 30 min prior to MK-801 treatment.

### 2.5. Statistical analysis

The data were subjected to analysis of variance (ANOVA) followed by Student's *t*-test in locomotor activity studies and the Mann–Whitney *U*-test in stereotypy studies. $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Effect of 5-$HT_{2A}$ receptor antagonists on MK-801-induced stereotypy

MK-801 (0.1, 0.25 and 0.5 mg/kg) produced a dose-dependent increase in stereotypic behaviours, with severe rearing, circling behaviour, sniffing, and grooming (Fig. 1A). The peak effect was observed 30–35 min after the administration of MK-801. Ketanserin (2.5, 5 and 10 mg/kg) dose-dependently blocked MK-801 (0.5 mg/kg)-induced stereotypic behaviour. Animals receiving a higher dose (10 mg/kg) of ketanserin showed only slight circling behaviour. Similarly, ritanserin (1 and 2 mg/kg) and seganserin (0.5, 1 and 2 mg/kg) blocked the MK-801 (0.5 mg/kg)-induced stereotypy in a dose-dependent fashion (Fig. 2A). None of the 5-$HT_{2A}$ receptor antagonists, ketanserin, ritanserin or seganserin had any effect per se.

Table 1
Effect of ketanserin (2.5, 5 and 7.5 mg/kg), ritanserin (0.5, 1 and 2 mg/kg) and seganserin (0.5, 1 and 2 mg/kg) on spontaneous locomotor activity

| No. | Treatment (mg/kg) | Ambulatory activity |
|---|---|---|
| 1 | Saline | $450 \pm 50$ |
| 2 | Ketanserin (2.5) | $370 \pm 55$ |
| 3 | Ketanserin (5) | $120 \pm 25$[a] |
| 4 | Ketanserin (10) | $115 \pm 20$[a] |
| 5 | Ritanserin (0.5) | $460 \pm 20$ |
| 6 | Ritanserin (1) | $400 \pm 35$ |
| 7 | Ritanserin (2) | $220 \pm 30$[a] |
| 8 | Seganserin (0.5) | $410 \pm 30$ |
| 9 | Seganserin (1) | $360 \pm 35$ |
| 10 | Seganserin (2) | $350 \pm 20$ |

Data is expressed as mean ± S.E.M. Each group consists of eight mice.
[a]Significantly different from saline treated group ($P < 0.05$).

### 3.2. Effect of 5-$HT_{2A}$ receptor antagonists on MK-801-induced hyperlocomotion

MK-801 (0.1, 0.25 and 0.5 mg/kg) produced a dose-dependent increase in locomotion (Fig. 1B). Ketanserin (2.5, 5 and 10 mg/kg) and ritanserin (0.5, 1 and 2 mg/kg) dose-dependently blocked the hyperlocomotion induced by MK-801 (0.5 mg/kg). Only the higher dose (2 mg/kg) of seganserin could block locomotor activity (Fig. 2B). Ketanserin (5 and 10 mg/kg) and ritanserin (2 mg/kg) produced a decrease in spontaneous locomotor activity per se at the doses indicated (Table 1). But seganserin per se (0.5, 1 and 2 mg/kg) did not significantly decrease spontaneous locomotor activity.

## 4. Discussion

It is a widely accepted hypothesis that most of the classical antipsychotic drugs act by blocking dopamine $D_2$ receptors, whereas the newer atypical antipsychotics modify the activity of dopamine-5-HT receptors in schizophrenia. On the other hand, the glutamate hypothesis of schizophrenia supposed a relative deficiency of glutamate transmission that may result in a dysregulated dopamine system (Deutsch et al., 1989; Carlsson and Carlsson, 1990; Sherman et al., 1991). However, involvement of the serotonergic system in MK-801-induced stereotypy and hyperlocomotion, and evidence of serotonergic dysfunction in schizophrenia, e.g., an abnormal concentration of 5-hydroxyindoleacetic acid in the cerebrospinal fluid and of 5-HT in the blood of some groups of schizophrenic patients supported the dopamine–serotonin hypothesis of schizophrenia (Van Kammen and Gelernter, 1987; Csernansky et al., 1990). It has been proposed that antagonism of 5-$HT_{2A}$ receptors is a critical element in the action of clozapine (Meltzer, 1989). The hypothesis that 5-$HT_{2A}$ receptor antagonism may be fundamentally important in schizophrenia has been further strengthened by the recent finding of Nordstrom et al. (1993) who reported that clinical treatment with clozapine induces a very high cortical 5-$HT_{2A}$ receptor occupancy in psychotic patients.

In the present experiments, the 5-$HT_{2A}$ receptor antagonists, ketanserin, ritanserin and seganserin, blocked the MK-801-induced hyperlocomotion and stereotypy in a dose-dependent manner. This observation supports the conclusion from previous studies that activation of the 5-HT system is involved in the stereotyped behaviour and hyperlocomotion produced by non-competitive NMDA receptor antagonists (Balster, 1987; Johnson, 1987). Martin et al. (1997a) reported that ritanserin markedly counteracted the antipsychotic action of the selective 5-$HT_{2A}$ receptor antagonist, M100907 [*R*-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol], in MK-801-treated mice. Ritanserin is known to alter

both dopamine and serotonin neurotransmission in the nucleus accumbens (Devaud and Hollingsworth, 1991; Shi et al., 1995). Therefore, it is reasonable to assume an interaction between ritanserin and M100907 in the nucleus accumbens, the brain region which is directly related to antipsychotic activity as well as locomotor activity in humans and animals, respectively. However, in the present experiments when ritanserin was used alone it produced a dose-dependent inhibition of MK-801-induced hyperlocomotion. Activation of 5-$HT_{2A}$ receptors can enhance NMDA receptor-mediated electrical activity in the neocortex and this effect can be blocked by systemic administration of 5-$HT_{2A}$ receptor antagonists (Neuman and Zebrowska, 1992). Results of a recent study of current–voltage relationships indicated that clozapine preferentially potentiated NMDA-receptor mediated transmission (Arvanov et al., 1997). Recent neurochemical data have demonstrated that MK-801 increases 5-HT turnover in several brain regions, including cortex, hippocampus, nucleus accumbens, amygdala and striatum (Loscher et al., 1991; Ping et al., 1992). Activation of the 5-HT system is not restricted to non-competitive NMDA receptor antagonists, such as MK-801, but seems also to be involved in the stereotypic behaviour induced by high doses of competitive NMDA receptor antagonists (Annies and Loscher, 1991; Loscher and Honack, 1991). In addition to direct glutamatergic–serotonergic interactions, dopaminergic–serotonergic interactions might be involved in alterations of serotonin turnover produced by NMDA receptor antagonists (Annies and Loscher, 1991; Loscher et al., 1991). The serotonergic system, via the 5-$HT_{2A}$ receptor may be playing a permissive role in the regulation of forebrain dopaminergic systems via glutamate (Carlsson, 1995; Schmidt and Fadayel, 1996). The doses of 5-$HT_{2A}$ receptor antagonists required for blocking MK-801-induced stereotypy and hyperlocomotion are much higher than the doses required for the 5-$HT_{2A}$ receptor antagonistic effects of these compounds. This could be due to the involvement of other receptor systems such as 5-$HT_{1A}$ receptors, dopamine $D_1$ and $D_2$ receptors and $\alpha_1$-adrenoceptors in MK-801-induced stereotypy and hyperlocomotion (Verma and Kulkarni, 1991; Loscher and Honack, 1993; Mathe et al., 1996).

Ketanserin (2.5 mg/kg), ritanserin (0.5 and 1 mg/kg) and seganserin (0.5, 1 and 2 mg/kg) per se did not affect spontaneous locomotion. Another 5-$HT_{2A}$ receptor antagonist, MIOO907, was reported to be selective for MK-801-induced locomotion as compared to spontaneous locomotion (Martin et al., 1997b). The lack of effect on spontaneous locomotion suggests that 5-$HT_{2A}$ receptor antagonists will be less prone than dopamine receptor antagonists to induce psychomotor side-effects. Recently, we have reported the preferential action of clozapine on MK-801-induced hyperlocomotion (Ninan and Kulkarni, 1998). On the basis of the present results, it is suggested that 5-$HT_{2A}$ receptors are involved in MK-801-induced stereotypy and hyperlocomotion. Should the stereotypy and hyperlocomotion elicited by acutely administered MK-801 be a valid model of at least some aspects of schizophrenia, these results indicate that the 5-$HT_{2A}$ receptor antagonists will have a place in treating the condition.

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