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EFFECT OF THE 5-HT_3 RECEPTOR ANTAGONIST ONDANSETRON ON AMPHETAMINE-INDUCED HYPERACTIVITY AND STEREOTYPY IN RATS

RAVI P. SHANKAR, RAJESH S. KARAN, SHAILENDRA S. HANDU AND VINOD K. BHARGAVA*

Department of Pharmacology,
Postgraduate Institute of Medical Education and Research,
Chandigarh – 160 012

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Abstract : The effects of different doses of ondansetron (0.1, 0.5, 1, 2 mg/kg) administered intra-peritoneally were studied on amphetamine-induced hyperactivity and stereotypy in wistar rats. Ondansetron was administered 30 minutes prior to d-amphetamine (3 mg/kg, i.p.). Ondansetron in doses of 0.5 and 1 mg/kg significantly decreased the mean number of head dippings and crossings in the hole board test and in doses of 0.1 and 0.5 mg/kg significantly decreased the average stereotypic score. Since the hyperactivity and stereotypy are dopamine mediated, the effect of ondansetron to reduce these states suggests a potential role for ondansetron in conditions with dopamine excess.

Key words : 5–HT_3 antagonist ondansetron amphetamine hyperactivity stereotypy

INTRODUCTION

5–HT_3 receptors are present in both the central and peripheral nervous systems and are associated with several serotonin-mediated physiological and pathological processes (1).

Ondansetron, a selective serotonin 5–HT_3 receptor antagonist has been shown in animal studies to inhibit or reduce raised mesolimbic dopamine activity and to antagonise increased locomotor activity caused by mesolimbic dopamine excess (1, 2).

In experiments on locomotor activity, an inverted U-shaped dose-response curve was obtained (1). Animal studies over a range of doses on amphetamine-induced stereotypy are lacking. So the present study was carried out to investigate the effect of ondansetron on amphetamine-induced hyperactivity and stereotypy.

A previous study has highlighted the importance of serotonergic mechanisms for the induction of hyperactivity by d-amphetamine and this has been used as an animal model for psychotic disorders in man (3).

*Corresponding Author

METHODS

Male wistar rats weighing between 250–300 gm kept on standard diet and tap water *'ad libitum'* and maintained under natural light/dark conditions were used. All observations were made between 10 am–12 noon in a diffusely illuminated room maintained at 25 ± 3°C. The Postgraduate Institute of Medical Education and Research guidelines for the care and use of laboratory animals were followed.

Drugs : Ondansetron (purchased from Natco, Hyderabad) was administered intraperitoneally in doses of 0.1, 0.5, 1 and 2 mg/kg, 30 minutes before d-amphetamine. In the holeboard test and the test for stereotypy, d-amphetamine (Sigma-Aldrich, St Louis, USA) was administered in the dose of 3 mg/kg for induction of stereotypy and hyperactivity. Both the drugs were dissolved in normal saline.

Control experiments : The dose of amphetamine (3 mg/kg) was arrived at by carrying out control experiments comparing behaviours (stereotypy and locomotor activity) induced by saline (1 ml/kg) and amphetamine in the doses of 1, 2, 3 and 5 mg/kg. 3 mg/kg of amphetamine was the lowest dose, consistently and significantly different from the saline group. There was no difference between the behaviour induced by ondansetron alone and saline alone. Results of these control experiments have however not been mentioned.

Holeboard test : Locomotor activity and exploratory behaviour were measured using the holeboard test (4). The holeboard was 48×48 cm and it was divided into 9 equal squares. The observations were made for a period of 5 minutes. A crossing was taken as positive when both the front paws of the animal crossed from one square to another. A dip was taken as positive when the animal dipped its head upto the level of the eyes. 10 animals wer taken for each group and the dippings and mean number of crossings were calculated for each dose level.

Stereotypy : Amphetamine-induced stereotypy was induced by administering d-amphetamine (3 mg/kg i.p.). Stereotyped behavior (SB) was assessed over a 30 sec. observation period at 10 min. intervals for a duration of 30 min (half an hour after amphetamine injection). The scoring system of Costall and Naylor (5) was used, where periodic sniffing = 1; continuous sniffing = 2; periodic biting, gnawing, infrequent rearing = 3; continuous rearing = 4; trying to climb the wall of the perspex cage = 5 and the final score was obtained by averaging the scores obtained at 10 min. intervals. 10 animals were taken in each group.

RESULTS

Holeboard test : In the control group (d-amphetamine 3 mg/kg) the mean number of dippings was 37.4 ± 3.14. In the groups pretreated with ondansetron in the doses of 0.1, 0.5, 1 and 2 mg/kg the mean number of dippings were 37.9 ± 9.16, 19.3 ± 9.97, 23.4 ± 8.37 and 21.4 ± 14.5 respectively. The values were significantly lower compared to the control group at the doses of 0.5, 1 and 2 mg/kg ($P<0.05$), (Fig. 1).

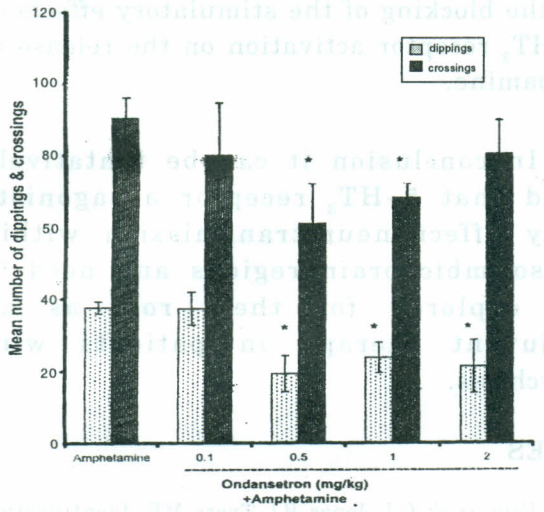

Fig. 1: Effect of ondansetron on amphetamine-induced hyperactivity (Values represent mean ± SD of the observations from 10 animals).

*P<0.05 compared to control values.

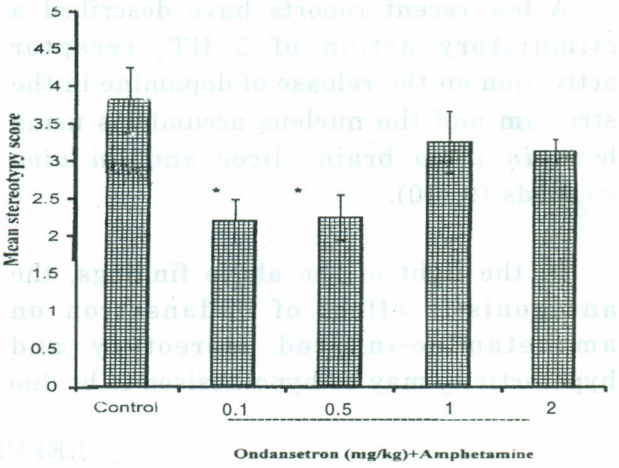

Fig. 2: Effect of ondansetron on amphetamine-induced stereotypy (Values represent mean±SD of the observations from 6 animals).

*P<0.05 compared to control values.

In the control group, the mean number of crossings were 90.5 ± 11.61. In the groups pretreated with ondansetron in the doses of 0.1, 0.5, and 2 mg/kg the corresponding values were 79.7 ± 29.7, 60.9 ± 22.07, 70.7 ± 7.75 and 80.4 ± 19.24 respectively. The values were significantly lower at the doses of 0.5 and 1 mg/kg when compared to the control group (P<0.05), (Fig. 1).

Amphetamine-induced stereotypy: In the control group (d-amphetamine; 3 mg/kg) the average stereotypy score was 3.83 ± 0.92. In the groups pretreated with ondansetron in the doses of 0.1, 0.5, 1 and 2 mg/kg the average stereotypy scores were 2.208 ± 0.39, 2.25 ± 0.82 and 3.125 ± 0.64 respectively. The values were significantly lower when compared to the control group at the doses of 0.1 and 0.5 mg/kg (P<0.05), (Fig. 2).

DISCUSSION

The results of this study show that ondansetron in doses of 0.5 and 1 mg/kg significantly decreased the mean number of crossings and dippings in the holeboard test for spontaneous motor activity. In the test for d-amphetamine-induced stereotyped behavior, ondansetron in doses of 0.1 and 0.5 mg/kg significantly decreased the average stereotypic score.

Amphetamine causes hyperactivity and stereotypy due to stimulation of dopamine release. The cell bodies of the dopaminergic neurons in the mesolimbic pathway lie in various groups in the midbrain (mainly the A10 cell group). High to moderate densities of 5–HT_3 receptors have been demonstrated in limbic dopamine-innervated brain areas (6, 7). Further, behavioral as well as biochemical studies have indicated that 5–HT_3 receptors exert a modulatory action on dopamine function in the mesolimbic part of the rat brain (8).

A few recent reports have described a stimulatory action of 5–HT_3 receptor activation on the release of dopamine in the striatum and the nucleus accumbens using both *in vitro* brain slices and *in vivo* methods (9, 10).

In the light of the above findings, the antagonistic effect of ondansetron on amphetamine-induced stereotypy and hyperactivity may be hypothesised to be due to the blocking of the stimulatory effects of 5–HT_3 receptor activation on the release of dopamine.

In conclusion it can be tentatively said that 5–HT_3 receptor antagonists may affect neurotransmission within mesolimbic brain regions and need to be explored for their role as an adjuvant therapy in patients with psychosis.

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