Ondansetron amelioration of scopolamine induced cognitive deficits in three-panel runway apparatus in rats

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Effect of ondansetron (5-HT3-receptor antagonist) was studied on the working memory deficits induced by scopolamine, a muscarinic receptor antagonist in rats using a three-panel runway apparatus. Varying doses of scopolamine (0.1-0.56 mg/kg, ip) were administered alone or in combination with ondansetron (0.01-1.0 mg/kg, ip) and memory errors and latency period of the session were recorded on a three-panel runway apparatus. Treatment with scopolamine (0.56 mg/kg) produced working memory deficits in rats. Treatment with ondansetron (1.0 mg/kg) significantly reduced the scopolamine-induced working memory deficits.

Keywords: Three-panel runway apparatus; Working memory; Ondansetron, Scopolamine

Disruption of central cholinergic system results in cognitive deficits. Serotonergic neurotransmission plays a modulatory role on the central cholinergic activity. Studies on rodents have demonstrated ondansetron (specific 5-HT3-receptor antagonist) to reverse scopolamine (a muscarinic receptor antagonist) induced memory deficits in passive avoidance task and spatial memory task. However, more recent animal studies on short-term and spatial memory tasks have shown conflicting results.

The present study investigates the acute effect of ondansetron on the scopolamine induced working memory deficits in rats by using the three-panel runway apparatus.

Materials and Methods

Animals—Male albino rats of wistar strain were used. Initially their free feeding weights were 230-290 g. Their body weights were maintained at approximately 80% of the free feeding level during the experimental period. The rats were provided commercial food pellet and water ad libitum. Animals were housed in groups of 3-4 per cage and kept under controlled room temperature (24±2°C) in a 12:12 hr L:D cycle. All experiments were conducted between 0900 and 1700 hrs in a noise free environment. The institutional ethical committee had approved the study protocol.

Apparatus—Working memory was assessed with a three-panel runway apparatus. Briefly, this apparatus has a start box, a goal box and 4 consecutive intervening choice points. Each choice point consisted of 3 panels or gates. The rats were prevented from passing through two of the three panels or gates, by front stoppers and also prevented from returning to the start box or to the previous choice point, by the one-way opening hinged panel gate. When the rats reached the goal box, they received two food pallets, of about 50 mg each.

Acquisition training—Initially all the front stoppers were removed so that a rat could pass through any of the 3 panel gates at each choice point. The rats were made to run the task repeatedly until the time that elapsed from leaving the start box to reaching the goal box (latency period) was consistently below 30 sec. Once this time was reached, the rats were given 1 session of 6 consecutive trials per day, with inter-trial period of 2 min. Each day, the sequence of correct panel gate position (open gate) for each rat, was changed according to the sequence chart. The number of times an animal pushed an incorrect panel gate (errors) and the time required for the animal to reach the goal box (latency period) were recorded in every trial of the session. Errors and latency periods of each of the 6 trials were added to obtain the total number of errors and total latency period of the
session. A rat was selected for the experiment if it achieved the criterion of ≤ 12 mean errors per session in 3 consecutive sessions.

**Drugs**—Scopolamine [Sigma Laboratories, USA] was administered in three doses: 0.1, 0.32 and 0.56 mg/kg, 20 min before the runway session. Ondansetron (gifted by Dr. Reddy’s Laboratories, Hyderabad, India) was administered 20 min before the runway task, in the doses of 0.01, 0.1 and 1 mg/kg. All the drugs and saline were administered intraperitoneally (ip), at a volume of 0.1ml/100g-body weight.

**Data analysis**—Working memory errors and latency period per trials and session were presented separately and expressed as mean ± SE. The comparison of difference in errors and latency periods between different groups was determined with a one-way analysis of variance (ANOVA), followed by Dunnett’s multiple comparisons test when F-ratios reached significance (P<0.05).

**Results and Discussion**

During the acquisition training on the three-panel runway task, the random performance level was four errors per trial and 24 errors per session. Rats were trained in around 15 training sessions.

Scopolamine treatment (0.1-0.56 mg/kg) dose dependently increased the total working memory errors and the total latency period of a session but resulted in no significant increase in the number of errors in the first trial, when compared to the saline treated group. (Table 1), a finding similar to other studies on the three-panel runway apparatus. Further, physostigmine (cholinesterase inhibitor) administration in rats has been demonstrated to dose dependently reduce the increase in errors induced by scopolamine on the three-panel runway apparatus.

In the present study co-administration of ondansetron, dose-dependently reduced the scopolamine (0.56 mg/kg) induced increase in the total working memory errors and total latency period, an effect that reached significance at a dose of 1 mg/kg of ondansetron. (Table 1). Several animal studies have reported similar findings. Ondansetron at a dose of 1 mg/kg in mice attenuated the performance deficits induced by scopolamine in a passive avoidance task and reversed atropine induced spatial task deficits in rats on the morris water maze. Ondansetron attenuated the cognitive deficits induced by scopolamine in a T-maze reinforced alteration task in rats and improved acquisition and performance of object discrimination and reversal task in scopolamine treated marmosets. Further electrophysiological studies have revealed that blockade of 5-HT₃ receptors induces LTP, a form of synaptic plasticity that underlies the memory formation.

Taken together, these preclinical reports and the present study findings, suggest that 5-HT₃ receptor antagonisms can ameliorate the cognitive deficits produced by a muscarinic antagonist.

To summarize, the present study revealed that treatment with ondansetron (a specific 5-HT₃-receptor antagonist) at a dose of 1 mg/kg reversed the working memory deficits produced by scopolamine.

**Table 1**—Effect of scopolamine and ondansetron on first trial and total number of working memory errors in rats in a session and the total latency period of a session

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of errors in the first trial</th>
<th>Total no. of errors in a session</th>
<th>Total latency of a session (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>4.17 ± 0.31</td>
<td>8.00 ± 0.90</td>
<td>42.37 ± 5.99</td>
</tr>
<tr>
<td>Scop (0.1mg/kg)</td>
<td>4.00 ± 0.26</td>
<td>11.00 ± 0.73</td>
<td>57.25 ± 1.31</td>
</tr>
<tr>
<td>Scop (0.32mg/kg)</td>
<td>4.17 ± 0.31</td>
<td>12.68 ± 1.41</td>
<td>112.45 ± 14.24b</td>
</tr>
<tr>
<td>Scop (0.56mg/kg)</td>
<td>4.33 ± 0.21</td>
<td>19.00 ± 0.82c</td>
<td>151.96 ± 10.73c</td>
</tr>
<tr>
<td>Ondan (0.01mg/kg)+</td>
<td>5.00 ± 0.37</td>
<td>17.84 ± 1.59</td>
<td>141.84 ± 8.07c</td>
</tr>
<tr>
<td>Scop (0.56mg/kg)</td>
<td>4.50 ± 0.34</td>
<td>15.83 ± 1.52b</td>
<td>109.00 ± 11.44b</td>
</tr>
<tr>
<td>Ondan (0.1mg/kg)+</td>
<td>4.67 ± 0.33</td>
<td>11.34 ± 0.96c</td>
<td>68.89 ± 4.26d</td>
</tr>
<tr>
<td>Scop (0.56mg/kg)</td>
<td>3.33 ± 0.33</td>
<td>97.66 ± 0.62</td>
<td>44.15 ± 2.82</td>
</tr>
</tbody>
</table>

Scop: scopolamine; Ondan: ondansetron

P values: *< 0.05, **< 0.01, ***< 0.001 versus saline group

< 0.01; *< 0.05 compared to scopolamine (0.56 mg/kg) group

One-way ANOVA: F₁,₄₂ = 9.39, P < 0.0001 [Errors]; F₁,₄₂ = 12.049; P < 0.0001[Latency period]
References


