ANTAGONISM BY YOHIMBINE ON THE LOCOMOTOR STIMULANT EFFECT OF METHAMPHETAMINE

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Abstract

Yohimbine (0.25 – 4 mg/kg) reduced the spontaneous locomotor activity of mice in a dose-dependent manner. Similarly, clonidine (0.5–10 mg/kg) depressed the activity of mice. Yohimbine (1 mg/kg) did not antagonize the locomotor depressant effect of clonidine (2.5 mg/kg). However, it antagonized methamphetamine-induced locomotor activity and potentiated the locomotor depressant activity of bromocriptine (1 mg/kg). These results suggest that the effects of yohimbine on locomotor activity may be mediated via the dopaminergic systems but are probably not due to antagonism by yohimbine or alpha adrenoceptors.

Introduction

Recreational use of amphetamine and its analogs has increased considerably during the last decade (Barberg, Nelson et al., 1996). The amphetamines are reported to produce neurotoxic effects in a number of animal models including the mouse (O’Callaghan and Miller, 1994). The adverse effects of the amphetamines are numerous; some of these are life threatening e.g. acute myocardial infarction has been reported as a result of intravenous amphetamine abuse in man (Packe, Garton et al., 1990).

Dopamine receptor antagonists are drugs currently used in the treatment of some of the adverse effects of the amphetamines. They occasionally produce Parkinsonian-like movement disorders as side effects. Therefore, a search for better and selective amphetamine antagonists is needed for the treatment of individuals intoxicated by amphetamines.

In this study, yohimbine seemed to be a potential antagonist to the locomotor stimulant effect of methamphetamine. The mechanism of this antagonism has been investigated.

Materials and Methods

Female albino mice (25-30 g, Animal Care Centre, College of Pharmacy, King Saud University, KSA) were used and the experiments were performed at a room temperature of 23 ± 1 °C. Drugs used were yohimbine HCl (E. Merck. AG Darmstadt), D-N-methylamphetamine HCl (E. Merck. AG Darmstadt), clonidine HCl (Boehringer Ingelheim) and bromocriptine mesylate (Sandoz). Except for clonidine, the doses of the drugs represent the free base. Solutions of these drugs were freshly prepared in normal saline and administered ip in a volume of 0.01 mL/g body weight.

The test animals were treated with yohimbine and the controls received saline. After 15 mm, animals were administered the second injection (drugs and doses given in Table I). Immediately after
the second injection, each group of animals was placed in the

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transparent plastic cage of an activity meter (Varimex, Columbus Instruments, OH, USA). They were allowed 10 mm for familiarization and, their activities were then recorded on a printing counter at 10-mm interval for a period of 120 mm. The initial 60-mm readings were used for calculations.

Experiments were run at the same time (9:30 A.M) each day. Four groups of 5 mice each were used at each dose level. One-way ANOVA was used for statistical analysis of results. Results of the test groups were compared with their respective control groups, using Tukey-Kramer multiple comparisons test.

**Results**

Yohimbine (4 mg/kg) significantly reduced spontaneous locomotor activity in mice (Table I). Reduction of locomotor activity by yohimbine was dose-dependent since the effect of 1.0 mg/kg dose was significantly lower than that of 0.25 mg/kg dose (p < 0.05), and the locomotor depressant effect of the former dose was also significantly different form that of 4.0 mg/kg yohimbine (p < 0.01). The onset of action of yohimbine was observed at 10-20 mm after its administration to mice. The normal activity of mice was regained at about 90 mm after yohimbine injection.

**TABLE I**

Effects of Yohimbine and Clonidine on Spontaneous Locomotor Activity of Mice and Activity Resulting from their Interactions with Methamphetamine and Bromocriptine. (In all experiments, n = 4 groups of 5 mice each.)

<table>
<thead>
<tr>
<th>Treatment (mg/kg)</th>
<th>Activity at 60 mm (mean ± SE)</th>
<th>Change %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + saline</td>
<td>5424 ± 432</td>
<td></td>
</tr>
<tr>
<td>Yohimbine + saline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.25)</td>
<td>5321 ± 83</td>
<td>1.9</td>
</tr>
<tr>
<td>(1.0)</td>
<td>3843 ± 245</td>
<td>29.2</td>
</tr>
<tr>
<td>(4.0)</td>
<td>1997±lsl***</td>
<td>63.2</td>
</tr>
<tr>
<td>Saline + clonidine:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.5)</td>
<td>5247 ± 108</td>
<td>3.3</td>
</tr>
<tr>
<td>(2.5)</td>
<td>3829 ± 358</td>
<td>29.4</td>
</tr>
<tr>
<td>(10.0)</td>
<td>2105±168***</td>
<td>61.2</td>
</tr>
<tr>
<td>Yohimbine (1.0)+clonidine (2.5)</td>
<td>4351 ±326</td>
<td>19.8</td>
</tr>
<tr>
<td>Saline + methamphetamine (1.0)</td>
<td>11215 ± 328</td>
<td>+106.8</td>
</tr>
<tr>
<td>Yohimbine (1.0) +Methamphetamine (1.0)</td>
<td>5807 ± 542***</td>
<td>7.0</td>
</tr>
<tr>
<td>Saline + bromocriptine (1.0)</td>
<td>3394 ± 321</td>
<td>37.4</td>
</tr>
<tr>
<td>Yohimbine (1.0) + bromocriptine (1.0)</td>
<td>1459 ± 165**</td>
<td>73.1</td>
</tr>
<tr>
<td>Clonidine (2.5)±bromocriptine (1.0)</td>
<td>4351 ±326</td>
<td>19.8</td>
</tr>
</tbody>
</table>

(Tukey Kramer Multiple Comparisons Test
* *p < 0.01, ***p < 0.001, When compared with respective control).

Clonidine showed a similar profile to yohimbine on locomotor activity. Only the higher dose of clonidine produced a significant reduction in locomotor activity of mice. The reduction of spontaneous
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Pretreatment of mice with yohimbine (1 mg/kg) abolished the locomotor stimulant effect of 1 mg/kg methamphetamine (Table I). On the other hand, yohimbine pretreatment significantly potentiated the slight locomotor depressant effect of bromocriptine (1 mg/kg). It did not, however, reverse the depressant activity of clonidine (2.5 mg/kg). When clonidine (2.5 mg/kg) was given before bromocriptine (1 mg/kg) no significant change of locomotor activity of mice was observed, as compared with mice treated with saline + bromocriptine (1 mg/kg).

**Discussion**

The locomotor stimulant effect of methamphetamine in normal mice was completely blocked by a low dose of yohimbine. This dose of yohimbine (1 mg/kg) did not significantly reduce locomotor activity when administered alone to mice. The amphetamines are known to produce their actions via catecholamines release (Moore, 1977 for review). Yohimbine also affects catecholaminergic systems; thus, being an $\alpha_2$-antagonist at low doses, it stimulates noradrenaline release and at high doses, yohimbine blocks $\alpha_2$-postsynaptic receptors and reduces noradrenergic function. Also, it increases central dopamine turnover by its action on dopamine receptors (Anden, Pauksens et al., 1982).

Antagonists at $\alpha_2$-receptors are reported to decrease the activity of rodents (e.g. Scatton, Dedek et al., 1983). The locomotor depressant effect of a high dose of yohimbine (e.g. 4 mg/kg) could be explained as due to this mechanism. Blockade of $\alpha_2$ receptor by yohimbine, however, is unlikely to be responsible for its antagonism of methamphetamine-induced locomotor activity since the dose of yohimbine used in studying the yohimbine-methamphetamine interaction was relatively small and it did not suppress activity when it was used alone.

The relatively smaller dose of yohimbine (i.e. 1 mg/kg) may selectively block $\alpha_2$ presynaptic adrenoceptors. Potentiation rather than the observed suppression of methamphetamine locomotor stimulant effect would have been expected in view of the noradrenaline releasing effect of yohimbine to result from yohimbine-methamphetamine interaction. On the other hand, the $\alpha_2$-agonist clonidine, did not produce hyperactivity but it behaved like yohimbine and caused dose-dependent locomotor depressant effect. Moreover, yohimbine pretreatment did not significantly modify the locomotor depressant effect of clonidine. Therefore, a role for $\alpha_2$ receptors in the locomotor activity of mice is not clearly established from this study.

Regarding the dopaminergic system, yohimbine (1 mg/kg) potentiated the locomotor depressant effect of the known dopamine $D_2$ receptor agonist bromocriptine. Dopamine agonists have been shown to cause depressed activity in the mouse when administered at low doses (e.g. Bradbury, Costall et al., 1983) possibly via activation of presynaptic dopamine $D_2$ receptors.

The findings of this study clearly support the involvement of dopaminergic systems in yohimbine’s action on locomotion. The complete antagonism of methamphetamine-induced locomotor activity by yohimbine could be viewed as due to enhancement by yohimbine of the release of dopamine by methamphetamine. Thus, an imbalance between the released quantities of dopamine and noradrenaline induced by methamphetamine is created resulting in more inhibition of the dopaminergic activity by clonidine was also dose dependent.
function. Involvement of $\alpha_2$-adrenoceptors in the regulation of dopaminergic transmission, however, should be considered unlikely as previously indicated by Scatton, Dedek et al. (1983).

The present study indicates the possible importance of low doses of yohimbine in the management of amphetamine abuse. Yohimbine appears to be advantageous to the antipsychotics in regard to safety.

References