LETTER TO THE EDITOR

EFFECT OF BETA-ADRENOCEPTOR BLOCKING AGENTS ON ISOLATION AND APOMORPHINE-INDUCED AGGRESSION IN RODENTS

Sir,

(Received on March 27, 1987)

Neurotransmitters like noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) play an important role in isolation and apomorphine-induced aggression (7,8,13,15). Fighting attacks induced by isolation result from an increased 5-HT release and action of 5-HT on postsynaptic receptors (6,9,14,17,19). Weinstock et al. (16) have reported that propranolol, pindolol and metoprolol are potent 5-HT antagonists (3).

Apomorphine has been reported to produce "bizarre" social behaviour consisting of "wrestling" postures and vigorous fighting in rats (7,13). It acts directly upon DA receptors to induce fighting (13). Combination of clonidine and apomorphine induces intense fighting and appears to involve the central NA, DA and 5-HT neurones (5,18). We made an attempt to elicit the effect of propranolol, sotalol and practolol on aggression induced by isolation and apomorphine.

Albino mice (20-30 g) and albino rats (100-280 g) of Haffkine strain and of either sex were used. The method of Dunham and Miya (4) was employed to determine the relatively nontoxic dose and the peak activity time for propranolol, sotalol and practolol. The median effective dose (ED50) in mice was determined by the method Miller and Tainter (10). For isolation-induced aggression the method of Yen et al. (20) was used. Male albino mice were isolated for a period of 3 weeks. The animals were not allowed to see each other or to have any physical contact. Fighting occurred when a non-isolated mouse was placed in the home cage of the isolated mouse. The fighting response was recorded for 5 min. Fighting was also induced by administration of apomorphine (5 mg/kg, ip) in pairs of rats covered by a glass bell jar (13). Fighting started within 5 minutes of apomorphine administration, and lasted up to 45 min.

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Statistical analysis
means.

Propranolol HCl, Pharmaceuticals, Bombay. The beta-blockers were administered intraperitoneally. The control groups received the same volume of saline. In rotarod test, propranolol, sotalol and practolol were in further tests dependent.

Propranolol (14 mg, ip) it inhibited fighting little effect on apomorphine-induced inhibited significantly (T).

Sotalol (94 and 18) increased fighting attacks, but fighting was insignificant in rota rod test. p

Higher doses of propranolol inhibited fighting attacks. Practolol (3.5,9,16,19). Propranolol and sotalol possess central nervous activity. It is suggested that propranolol possibly acts by stimulating aggression (11,14). Propranolol, sotalol and practolol inhibit 5-HT action of beta-b
Statistical analysis of data was done by the Student's t-test for independent means.

Propranolol HCl, sotalol HCl, practolol HCl and apomorphine HCl (all fromICI Pharmaceuticals, Bombay) were dissolved in normal saline (0.9% NaCl) and injected ip. The beta-blockers were administered in accord with their pre-treatment time (see below). The control groups received normal saline (1.0 ml/kg, ip).

In rotarod test, propranolol, sotalol and practolol had an ED50 ± SEM of 28.30±3 39, 374.0±61.09 and 370.9±102.3 mg/kg, ip respectively. The peak activity time for propranolol, sotalol and practolol was 10, 20 and 10 min, respectively. Use of beta-blockers in further tests depended on this information.

Propranolol (14 mg/kg, ip) had no major effect, but in higher doses (21.28 mg/kg, ip) it inhibited fighting attacks significantly (Table I). Propranolol (14 mg/kg, ip) had little effect on apomorphine-induced fighting, but with 21 mg/kg, ip fighting attacks were inhibited significantly (Table I).

Sotalol (94 and 187 mg/kg, ip) significantly reduced the number of isolation-induced fighting attacks, but in higher of the two doses the effect on apomorphine-induced fighting was insignificant (Table I). Practolol (278 mg/kg, ip) had little effect on isolation-induced or on apomorphine-induced fighting attacks (Table I).

Higher doses of propranolol and sotalol caused reduction in isolation-induced fighting attacks. Practolol even in a high dose was ineffective. Isolation-induced aggression results from an increased 5-HT release acting on postsynaptic 5-HT receptors (3,5,9,16,19). Propranolol perhaps antagonizes this action at the postsynaptic receptor sites, whereas practolol has an insignificant effect.

Propranolol alone reduced apomorphine-induced fighting attacks. Apomorphine possibly acts by stimulation of both pre- and postsynaptic DA receptors leading to aggression (11,14). Propranolol in high doses has known antidopamine effect. In addition, propranolol and some other beta-adrenoceptor blockers have been reported to possess central nervous system depressant (1,12), and peripheral neuromyoplectic (2) activity. It is suggestible that these activities may in part account towards the antiaggression action of beta-blockers.
TABLE 1: Effects of propranolol, sotalol and practolol on isolation and apomorphine-induced aggression in rodents.

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Pretreat time (min)</th>
<th>Drug Dose (mg/kg, ip)</th>
<th>Fighting attacks observed in 45 min in mice (Mean±S.E.M.)</th>
<th>Fighting attacks observed in 5 min in rats (Mean±S.E.M.)</th>
<th>Fighting attacks observed in 45 min in rats (Mean±S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>(Saline)</td>
<td>6</td>
<td>1</td>
<td>18±1.04</td>
<td>17±0.86</td>
<td>16±0.86</td>
</tr>
<tr>
<td>II</td>
<td>Propranolol</td>
<td>6</td>
<td>10</td>
<td>21±0.58</td>
<td>12±0.58</td>
<td>6±0.58</td>
</tr>
<tr>
<td>III</td>
<td>Sotalol</td>
<td>6</td>
<td>20</td>
<td>84±0.68</td>
<td>8±0.68</td>
<td>6±0.68</td>
</tr>
<tr>
<td>IV</td>
<td>Practolol</td>
<td>6</td>
<td>10</td>
<td>278±8.04</td>
<td>156±8.04</td>
<td>15±6.04</td>
</tr>
</tbody>
</table>

**1/2 EDso** = Not significant.

NS = Not significant.
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A. SHARMA AND F.S.K. BARAR
Department of Pharmacology
S.M.S. Medical College, Jaipur - 302 004

REFERENCES


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**LETTER TO THE EDITOR**

GABAERGIC MEDICATIONS

Sir,

There are conflicting reports on whether muscimol and GABA transport inhibitors have reported antagonistic effects and since the apparent similarity with that of morphine analgesia, the effect of diazepam, a drug which enhances GABAA receptor antagonism, by inhibiting its degradation or by inhibiting its synthesis (1-3).

Male albino mice, from a colony maintained in this laboratory, were used in the study. Antinociceptive activity was measured by the hot plate apparatus. Mice were subjected to a first hindpaw lick. Mice required more than three attempts to escape within 45 secs was arbitrated to exhibit antinociceptive activity.

Mice divided into groups of 10. Morphine sulphate (Benegic) and sodium valproate (Toreine base; Sigma) solutions of concentrations 0.01, 0.05 and 0.1 mg/ml were given in a volume of 0.2 ml.