The effect of selective 5-hydroxytryptamine uptake inhibitors on 5-methoxy-N,N-dimethyltryptamine-induced ejaculation in the rat

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1 The ejaculatory response and the 5-hydroxytryptamine (5-HT) behavioural syndrome induced by 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) (3 mg kg\(^{-1}\) i.p.) were studied following acute and repeated treatment of rats with the selective uptake inhibitors of 5-HT, fluoxetine, zimeldine, alaproclate, and citalopram. The oral doses used were based on the respective ED\(_{50}\) values for uptake inhibition.

2 Acute doses of fluoxetine and zimeldine significantly reduced the ejaculatory response when given 48 h before 5-MeODMT. This blockade was prevented by treatment of the rats with the postsynaptic 5-HT receptor antagonist methergoline.

3 An acute dose of fluoxetine given 7 and 14 days before 5-MeODMT significantly enhanced the ejaculatory response. On day 24, the response returned to the control level. Repeated treatment every second day (5 times over 9 days and 10 times over 19 days) with fluoxetine caused a longer blockade of the ejaculatory response and the sensitization of the response came later than after an acute dose. Parallel with the ejaculatory response three other components of the 5-HT behavioural syndrome also decreased significantly.

4 Acute doses of alaproclate and citalopram significantly blocked the ejaculatory response at 1 h, but they failed to affect the response at any other time point after either acute or repeated treatment. Neither did these drugs attenuate the 5-HT syndrome.

5 It is concluded that acute and repeated treatment of rats with different selective 5-HT uptake inhibitors does not produce a common alteration in 5-HT\(_2\)-receptor functions.

Introduction

During recent years there has been an increasing interest in studies on the development of secondary effects due to drugs which affect the transmitter amines 5-hydroxytryptamine (5-HT), dopamine, and noradrenaline in the brain (for review see Curzon, 1982; Sugrue, 1983). Such secondary effects, e.g. up- and down-regulation of receptors, can be studied after acute and repeated administration of drugs using various methods. Receptor binding, kinetics of enzyme activated by receptor responses, turnover and utilization of the transmitter amines and behavioural changes represent some of the methodological bases involved in the measurement of these effects. Of particular interest is the examination of the profile of secondary effects induced by antidepressant and neuroleptic drugs, since such studies may give information about the therapeutic actions of these drugs.

Recently, it was observed that drugs which stimulate postsynaptic 5-HT receptors in the brain, e.g. the 5-HT releasing compound \(p\)-chloroamphetamine and the 5-HT receptor agonist 5-methoxy-N,N-dimethyltryptamine (5-MeODMT; Fuxe et al., 1972) induce ejaculations in the rat (Rényi, 1985). In addition to the 5-HT receptors, \(\alpha_1\)-adrenoceptors, probably peripherally localized, are involved in the drug-induced ejaculatory response. Since this response can be quantified by weighing the seminal material produced, the 5-HT receptor-mediated ejaculatory response may become a valuable model for studying acute and long-term drug effects on 5-HT neurotransmission in the rat brain.

In the present study the acute and long-term effects of four selective inhibitors of 5-HT uptake, alaproclate (Lindberg et al., 1978), citalopram (Hyttel, 1982), fluoxetine (Wong & Bymaster, 1981) and zimeldine (Ross et al., 1976), on the ejaculatory response induced by 5-MeODMT are described. Three other components of the 5-HT syndrome were also investigated:
abduction of the hind limbs, forepaw treading and Straub tail, responses evidently mediated by 5-HT₂ receptors (reviewed by Green, 1984; Green & Heal, 1985). Observations from the thorough investigation of these aspects of rodent behaviour served as a control for the ejaculatory response model. The present results show the usefulness of this model for detecting changes in functions mediated by 5-HT receptors.

Part of this work was presented at the 9th Annual Meeting of the European Neuroscience Association (Oxford, 1985).

Methods

Sprague-Dawley rats, about 4 months old, weighing 400–450 g, were used. The tests were performed between 08 h 00 min and 12 h 00 min in a soft-lighted, quiet room at 20–22°C. All the drugs used in this study were administered in a volume of 1 ml kg⁻¹ body weight. The 5-hydroxytryptamine (5-HT) uptake inhibitors were dissolved in distilled water, 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) and methergoline in 0.5% ascorbic acid. The animals were starved for 16 h before the first oral administration of the 5-HT uptake inhibitors, but water was supplied ad libitum. One hour after the administration of the 5-HT uptake inhibitors the rats were again supplied with food.

Ejaculatory response

The method described by Rényi (1985) was somewhat modified. The rats were tested individually in plastic cages (55 × 35 × 19 cm) without sawdust flooring and placed on black plastic covers. Rats were injected with 5-MeODMT (3 mg kg⁻¹ i.p.) during the move from their home cages to the plastic cages. The dose of 5-MeODMT (3 mg kg⁻¹ i.p.) used in all experiments in the study was chosen as he smallest dose which gave a full effect (Rényi, 1985). Five control rats were scored alternately with 5 treated rats in each experiment. The seminal material was removed from the sheath by drawing back the foreskin, exposing the penis and removing the compact seminal material with a pair of forceps 5 and 10 min after the injection of 5-MeODMT. The ejaculation did not occur in connection with penile erection. The seminal material was either hidden within the sheath, coagulated around the sheath or found, occasionally, on the bottom of the cage. The plug material was placed on filter paper, dried on each side and after about 5 min weighed on an electromillibalance (Cahn, Model 7550).

Behavioural response

The method used was a modified version of that described by Andrews et al. (1982). Behavioural responses (hind limb abduction, forepaw treading, and Straub tail) were scored individually. Rats housed singly were observed for three 0.5 min periods, once every 3 min over a total period of 9 min after the injection of 5-MeODMT (3 mg kg⁻¹ i.p.). In each experiment control and treated animals were scored in parallel. The rats were removed from their home cages to two plastic cages (55 × 35 × 19 cm) without sawdust flooring and placed close to each other on black plastic covers. 5-MeODMT was administered to the control and treated rats during the move exactly 3 min before the first observation period. The behavioural responses were assessed on a scale of 0–4.

1) Hind limb abduction 0 – absent, 1 – rigid posture, occasional and slow forward movements, 2 – rigid posture, some expanded body, no forward movements, 3 – like 2 – plus one of the hind limbs being quite visible and abducted to the side or backwards, 4 – both of the hind limbs are quite visible and abducted to the side or backwards (‘seal-posture’).

2) Forepaw treading 0 – absent, 1 – treading ‘piano-playing’ with one paw now and then, 2 – treading alternately with both of the paws, 3 – treading simultaneously with the two paws (‘chord-playing’) but the treading is inaudible, 4 – the ‘chord-playing’ is audible.

3) Straub tail 0 – absent, 1 – the tail is somewhat rigid and held just above the bottom of the cage, 2 – the tail forms an angle of about 30–40 degree to the bottom of the cage, 3 – the angle is now about 90 degrees, 4 – the tail is quite recurved and almost touches the head. At the end of the observation period, the scores were summed up. The maximum total score obtainable was 3 × 4 = 12.

Drugs

The following drugs were used: alaproclate HCl and zimeldine 2 HCl (Astra Läkemedel AB), citalopram HBr (Lundbeck A/S), fluoxetine HCl (Eli Lilly & Co.), methergoline base (Farmitalia), pirenperone base (Janssen), prazosin HCl (Pfizer), 5-[2-[2-(2-ethoxyphenoxy)ethyl]-amino|propyl]-2-methoxybenzenesulphonamide HCl (YM-12617) (Yamanouchi Pharm. Co.), phenotamine methanesulphonate (Ciba-Geigy), remoxipride HCl (Astra Läkemedel AB) and 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) base (Sigma).

Results

Effects of 5-MeODMT in control animals

5-MeODMT (3 mg kg⁻¹ i.p.) induced an ejaculatory response within 5–10 min. The seminal material was a
Table 1 Effect of various receptor blocking agents on the ejaculation induced by 5-MeODMT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg kg⁻¹ i.p.)</th>
<th>Type of receptor antagonism</th>
<th>Number of rats with ejaculation</th>
<th>Weight of the seminal material per rat (mg)</th>
<th>Inhibition of the ejaculatory response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td></td>
<td></td>
<td>270</td>
<td>43 ± 2.3</td>
<td>88</td>
</tr>
<tr>
<td>Methergoline</td>
<td>0.5</td>
<td>S₁,S₂,D</td>
<td>10</td>
<td>1</td>
<td>5*</td>
</tr>
<tr>
<td>Pirenperone</td>
<td>0.1</td>
<td>S₂</td>
<td>10</td>
<td>8</td>
<td>4.3 ± 1.0*</td>
</tr>
<tr>
<td>Prazosin</td>
<td>0.1</td>
<td>α₁</td>
<td>10</td>
<td>6</td>
<td>4.7 ± 0.8*</td>
</tr>
<tr>
<td>YM-12617</td>
<td>0.05</td>
<td>α₁</td>
<td>10</td>
<td>5</td>
<td>4.0 ± 1.0*</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>0.1</td>
<td>α₁,α₂</td>
<td>10</td>
<td>10</td>
<td>5.8 ± 1.0*</td>
</tr>
<tr>
<td>Remoxipride</td>
<td>2.0</td>
<td>D₂</td>
<td>20</td>
<td>20</td>
<td>34.0 ± 10%</td>
</tr>
</tbody>
</table>

General conditions as described in method. The receptor antagonists were injected 60 min before 5-methoxy-N,N-dimethyltryptamine (3 mg kg⁻¹ i.p.). S = 5-hydroxytryptamine; D = dopamine; α = α-adrenoceptor. *P<0.001 compared with saline (Student’s t test). n.s. = not significant. The weight of seminal material represents the mean ± s.e.mean for the group. Five control rats (housed singly) were scored alternately with 5 treated rats.

Fully formed plug with a mean (± s.e.mean) weight of 43 ± 2.3 mg (27 × 10 rats). Ninety-nine % of the 270 rats ejaculated during the first 5 min. Twenty-three % of the rats produced one additional plug between 5 and 10 min. No rats ejaculated after 10 min.

Figure 1 Time-dependent effect of acute doses of different selective inhibitors of 5-hydroxytryptamine (5-HT) uptake on the 5-methoxy-N,N-dimethyltryptamine (5-MeODMT)-induced ejaculatory response. Fluoxetine (10 mg kg⁻¹; stippled columns), zimeldine (10 mg kg⁻¹; open columns), alaproclate (20 mg kg⁻¹; horizontally hatched columns) and citalopram (10 mg kg⁻¹; diagonally hatched columns) were administered at different times before acute injections of 5-MeODMT (3 mg kg⁻¹ i.p.). In a separate experiment, (a), alaproclate (20 mg kg⁻¹) and citalopram (5 mg kg⁻¹) were administered twice within 4 h and 48 h before 5-MeODMT (3 mg kg⁻¹ i.p.). Five control rats (housed singly) were scored alternately with five treated rats. The weight of the seminal material is shown (mean ± s.e.mean % of mean) as % of the control value. Numbers in the columns give the percentage of rats with ejaculations, n = 10–20 rats in each experiment. P<0.05, **P<0.02, ***P<0.001 vs control rats (Mann-Whitney U-test).

Effect of various receptor blocking agents on the ejaculations induced by 5-MeODMT

The non-selective 5-HT receptor antagonist methergoline, the selective 5-HT₂ receptor antagonist piren-
perone (Janssen, 1982), the selective $\alpha_{1}$-adrenoceptor antagonists prazosin and YM-12617 (Takenaka et al., 1984), and the non-selective $\alpha$-adrenoceptor antagonist phentolamine significantly antagonized the ejaculatory response at small doses. Remoxipride, a selective dopamine$_{2}$-receptor antagonist (Florvall & Ögren, 1982), had no significant effect even at a large dose (Table 1).

**Time-dependent effect of acute doses of various selective 5-HT uptake inhibitors on the 5-MeODMT-induced ejaculatory response**

The doses used for studying the effect of acute doses of various 5-HT uptake inhibitors on the ejaculatory response induced by 5-MeODMT were based on the respective $ED_{50}$ values for uptake inhibition (Rényi & Ross, 1985). All the drugs were administered at about equipotent doses for inhibition of 5-HT uptake. Fluoxetine (10 mg kg$^{-1}$) and zimeldine (10 mg kg$^{-1}$) had, at 1 h, no effect on the ejaculatory response, whereas they caused a marked decrease in the weight of seminal material at 4 h and 48 h (Figure 1). The response returned to the control level on day 4. On day 7, the response was remarkably enhanced by fluoxetine and this enhanced response was still at the same level on day 14. On day 24 the effect on the ejaculatory response caused by fluoxetine had diminished and the response was back to the control level (Figures 1 and 4). Zimeldine caused a small non-significant enhancement on day 7. No sensitization of the ejaculatory response by zimeldine was observed on day 14 (Figure 1). Acute doses of alaproclate (20 mg kg$^{-1}$) and citalopram (10 mg kg$^{-1}$) had a significantly inhibitory effect (34–46%) on the ejaculatory response at 1 h. The values had returned to the control level at 4 h and remained there during the whole observation period: 48 h – day 7 (Figure 1). Neither alaproclate (20 mg kg$^{-1}$) nor citalopram (5 mg kg$^{-1}$) inhibited the ejaculatory response when they were administered twice within 4 h and 48 h before 5-MeODMT (3 mg kg$^{-1}$ i.p., Figure 1).

**Effect of methergoline on the inhibitory effect of acute administration of fluoxetine and zimeldine on the ejaculatory response induced by 5-MeODMT**

The postsynaptic 5-HT receptor antagonist methergoline (2.5 mg kg$^{-1}$ i.p.) blocked completely the ejaculatory response when given 1 h before 5-MeODMT. The blockade had disappeared after 48 h. Methergoline given twice 0.5 h and 3.5 h after fluoxetine (5 mg kg$^{-1}$) or zimeldine (10 mg kg$^{-1}$) counteracted the decrease of the ejaculatory response produced by acute doses of fluoxetine and zimeldine (Figure 2). Methergoline injected only once – 4 h after fluoxetine – did not counteract the decrease of the response (Figure 2).

**Effect of repeated treatment (every second day) with different 5-HT uptake inhibitors on the ejaculatory response induced by 5-MeODMT**

Figure 3 shows the effect of repeated treatment of rats with fluoxetine, zimeldine, alaproclate and citalopram on the ejaculatory response induced by 5-MeODMT. An acute dose of either fluoxetine (5 mg kg$^{-1}$) or zimeldine (10 mg kg$^{-1}$) caused a strong inhibitory effect on the 5-MeODMT-induced ejaculatory response at 48 h (Figure 3). The administration of these drugs was therefore carried out every second day, 5 times over 9 days. Repeated treatment of the rats with either fluoxetine (5 mg kg$^{-1}$) or zimeldine (10 mg kg$^{-1}$) did not further block the ejaculatory response as regards the weight of the seminal material, but the duration, at least after repeated treatment with fluoxetine, was considerably longer compared with that after an acute dose (Figures 1 and 3). On day 9 after the final dose the inhibition was still high, on day 14 the response was back to the control level, while on day 24, there appeared a marked, significant, enhancement of the ejaculatory response. On day 42 the response was again back to the control level (Figures 3 and 4). After repeated treatment with zimeldine, the
5-HT UPTAKE INHIBITORS AND EJACULATORY RESPONSE

Figure 3  Effect of repeated treatment with different selective 5-hydroxytryptamine (5-HT) uptake inhibitors on the 5-methoxy-N,N-dimethyltryptamine (5-MeODMT)-induced ejaculatory response. Fluoxetine (F; stippled columns), zimeldine (Z; open columns), alaproclate (A; horizontally hatched columns) and citalopram (C; diagonally hatched columns) were given every second day, five times over 9 days. The doses were as follows: F: 5 mg kg\(^{-1}\), Z: 10 mg kg\(^{-1}\), A: 20 mg kg\(^{-1}\), C: 5 mg kg\(^{-1}\); 5-MeODMT (3 mg kg\(^{-1}\) i.p.) was injected at different times after the last administration of the drugs. Five control rats (housed singly) were scored alternately with five treated rats. The weight of the seminal material is shown (mean ± s.e.mean % of mean) as % of the control value. Numbers in the columns give the percentage of rats with ejaculations, \(n = 10–20\) rats in each experiment. *\(P < 0.05\), **\(P < 0.02\), ***\(P < 0.001\) vs control rats (Mann-Whitney U-test).

Figure 4  Development of functional receptor supersensitivity after acute and repeated treatment with fluoxetine. Fluoxetine was administered either acutely (10 mg kg\(^{-1}\)) (O) or every second day (5 mg kg\(^{-1}\)) 5 times for 9 days (□) and 10 times for 19 days (▽). 5-Methoxy-N,N-dimethyltryptamine (5-MeODMT; 3 mg kg\(^{-1}\), i.p.) was injected at different time points after the last administration of fluoxetine. Five control rats (housed singly) were scored alternately with five treated rats. The weight of the seminal material is shown (mean ± s.e.mean % of mean) as % of the control value. Numbers above the curves give the percentage of rats with ejaculations, \(n = 10–20\) rats in each experiment. **\(P < 0.02\), ***\(P < 0.001\) vs control rats (Mann-Whitney U-test).
Table 2 Effect of repeated treatment (every second day over 9 days) with different selective inhibitors of 5-hydroxytryptamine (5-HT) uptake on some 5-HT-mediated behaviours induced by 5-methoxy-N,N-dimethyltryptamine (5-MeODMT)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Hind limb abduction (min–max)</th>
<th>Forepaw treading</th>
<th>Straub tail</th>
<th>Hind limb abduction (%)</th>
<th>Forepaw treading</th>
<th>Straub tail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>10</td>
<td>10.1 (9–12)</td>
<td>10.5 (9–12)</td>
<td>6.8 (4–10)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10</td>
<td>8.7 (7–10)</td>
<td>7.7 (6–11)</td>
<td>5.1 (1–8)</td>
<td>86**</td>
<td>73*</td>
<td>75</td>
</tr>
<tr>
<td>Saline</td>
<td>10</td>
<td>10.2 (8.5–11.5)</td>
<td>10.6 (8–12)</td>
<td>6.5 (5–8)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fluoxetine*</td>
<td>10</td>
<td>4.5 (2–10.5)</td>
<td>5.6 (3–12)</td>
<td>1.9 (1–6)</td>
<td>44***</td>
<td>53***</td>
<td>29***</td>
</tr>
<tr>
<td>Saline</td>
<td>10</td>
<td>8.9 (7–10.5)</td>
<td>9.8 (7–12)</td>
<td>6.1 (3–12)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Zimeldine</td>
<td>10</td>
<td>6.3 (2–10)</td>
<td>6.5 (4–10)</td>
<td>3.3 (1–7)</td>
<td>71**</td>
<td>66**</td>
<td>54**</td>
</tr>
<tr>
<td>Saline</td>
<td>10</td>
<td>9.3 (8–10)</td>
<td>9.4 (7–12)</td>
<td>5.6 (4–8)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alaproclate</td>
<td>10</td>
<td>8.7 (4–10.5)</td>
<td>9.3 (5–12)</td>
<td>5.8 (4–7)</td>
<td>94</td>
<td>99</td>
<td>104</td>
</tr>
<tr>
<td>Saline</td>
<td>10</td>
<td>9.2 (8–10)</td>
<td>9.6 (6–12)</td>
<td>6.0 (1–10)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10</td>
<td>9.5 (8–10)</td>
<td>9.4 (7–12)</td>
<td>6.5 (3–8)</td>
<td>103</td>
<td>98</td>
<td>108</td>
</tr>
</tbody>
</table>

Fluoxetine (5 mg kg⁻¹), alaproclate (20 mg kg⁻¹) and citalopram (5 mg kg⁻¹) were given orally every second day, 5 times over 9 days; zimeldine (10 mg kg⁻¹), 6 times over 11 days. In a separate experiment fluoxetine was administered 10 times during 19 days. 5-MeODMT (3 mg kg⁻¹) was injected 48 h after the last administration of the drugs. Scoring procedures are described in Methods. *P < 0.05, **P < 0.02, ***P < 0.001 vs control rats (Mann-Whitney U-test).

Effects of repeated treatment with different selective 5-HT uptake inhibitors on some 5-HT-mediated behavioural responses (hind limb abduction, forepaw treading, and Straub tail) induced by 5-MeODMT

5-MeODMT (3 mg kg⁻¹) produced a pronounced behavioural syndrome with several different components. In the present study, three of these components, e.g. hind limb abduction, forepaw treading, and Straub tail, were investigated after repeated treatment of the rats with different uptake inhibitors. Orally administered acute doses of fluoxetine (10 mg kg⁻¹), zimeldine (10 mg kg⁻¹), alaproclate (20 mg kg⁻¹) and citalopram (10 mg kg⁻¹) given 48 h before 5-MeODMT (3 mg kg⁻¹) had no effect on the 5-MeODMT-induced behavioural syndrome (data not shown). Repeated treatment (every second day) of the rats with fluoxetine (5 mg kg⁻¹) or zimeldine (10 mg kg⁻¹) significantly decreased the 5-MeODMT-induced behavioural syndrome (Table 2) except for the Straub tail where no significance was attained after 9 days of treatment with fluoxetine. In a separate experiment fluoxetine, zimeldine, alaproclate and citalopram were given twice daily 15 times for 8 days. 5-MeODMT (3 mg kg⁻¹ i.p.) was injected 48 h after the last administration of the drugs. Five control rats (housed singly) were scored alternately with five treated rats. *P < 0.02, **P < 0.001 vs control rats (Mann-Whitney U-test).

Table 3 Effect of repeated treatment (twice daily) with different 5-hydroxytryptamine (5-HT) uptake inhibitors on the ejaculatory response induced by 5-methoxy-N,N-dimethyltryptamine (5-MeODMT)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg kg⁻¹ p.o.)</th>
<th>n</th>
<th>Rats with ejaculation (%)</th>
<th>Ejaculatory response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>2.5</td>
<td>10</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Zimeldine</td>
<td>5</td>
<td>10</td>
<td>100</td>
<td>110</td>
</tr>
<tr>
<td>Alaproclate</td>
<td>10</td>
<td>10</td>
<td>100</td>
<td>121</td>
</tr>
<tr>
<td>Citalopram</td>
<td>2.5</td>
<td>10</td>
<td>100</td>
<td>105</td>
</tr>
<tr>
<td>Repeated doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>15 × 2.5</td>
<td>10</td>
<td>40</td>
<td>44**</td>
</tr>
<tr>
<td>Zimeldine</td>
<td>15 × 5</td>
<td>10</td>
<td>40</td>
<td>27*</td>
</tr>
<tr>
<td>Alaproclate</td>
<td>15 × 10</td>
<td>10</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Citalopram</td>
<td>15 × 2.5</td>
<td>10</td>
<td>100</td>
<td>84</td>
</tr>
</tbody>
</table>

Fluoxetine, zimeldine, alaproclate and citalopram were given twice daily 15 times for 8 days. 5-MeODMT (3 mg kg⁻¹ i.p.) was injected 48 h after the last administration of the drugs. Five control rats (housed singly) were scored alternately with five treated rats. *P < 0.02, **P < 0.001 vs control rats (Mann-Whitney U-test).
experiment, fluoxetine was administered 10 times over 19 days. The behavioural response induced by 5-MeODMT decreased significantly for all three components compared with the 5 times over a 9 day observation period (Table 2). Repeated treatment (every second day over 9 days) of the rats with alaproclate (20 mg kg\(^{-1}\)) and citalopram (5 mg kg\(^{-1}\)) did not affect the components of the 5-HT syndrome investigated in the study (Table 2).

**Discussion**

The present study supports previous findings (Rényi, 1983) that the 5-MeODMT-induced ejaculatory response is probably mediated by 5-HT\(_2\)-receptors as defined by Peroutka & Snyder (1979) but also involves a tonic noradrenergic input (Rényi, 1985). A dual site of action is implicated by the following results. (1) 5-HT\(_2\)-receptors: the response was not produced by the 5-HT\(_1\)-receptor agonist 8-hydroxy-2-(di-N-propylamino)-tetralin (8-OHDPAT) (Midlemiss & Fozard, 1983; Rényi, 1985). Furthermore, the selective 5-HT\(_2\)-receptor antagonist pirenperone inhibited the response at low doses, selective for the 5-HT\(_2\)-receptors (Pawlowski et al., 1983; Rényi, 1985). (2) Adrenoceptors: the involvement of \(\alpha_1\)-adrenoceptors in the ejaculatory response, as proposed previously (Rényi, 1985), was confirmed in the present study since the selective \(\alpha_1\)-adrenoceptor antagonists prazosin and YM-12617 were potent inhibitors of the response. The noradrenergic input seems to be peripheral as phen tolamine, a non-selective and mainly peripherally acting \(\alpha\)-adrenoceptor antagonist, was also a potent inhibitor of the response (Rényi, 1985). Remoxipride, a selective dopamine-receptor antagonist (Florvall & Ögren, 1982), did not antagonize the 5-MeODMT-induced ejaculatory response.

Taking these results into consideration and the fact that the method is objective and reproducible, the drug-induced ejaculatory response seems to be a suitable model to examine changes to 5-HT\(_2\)-receptors occurring following antidepressant treatment.

The 5-HT uptake inhibitors investigated in the study affected the ejaculatory response induced by 5-MeODMT differently, suggesting different mechanisms of action at pre- or post-synaptic sites.

High acute doses of alaproclate and citalopram blocked the ejaculatory response 1 h after their administration, but fluoxetine and zimeldine failed to do so. The reason for this blockade is unknown but might indicate that alaproclate and citalopram block the response somewhere in the chain of neurones involved in the transmission of the response. Except at 1 h, alaproclate and citalopram administered at different time points before 5-MeODMT did not inhibit the ejaculatory response. Thus it is obvious that the inhibition of 5-HT uptake, in itself, is insufficient to cause the decreased response, possibly because of receptor subsensitivity (Maggi et al., 1980) which, however, developed rapidly within 4 h after the administration of a single dose of fluoxetine and zimeldine. This is surprising since equipotent doses for the 5-HT uptake were used and the increase in 5-HT in the synaptic cleft should be about the same. One explanation could be the short half-lives of alaproclate and citalopram (Arnt et al., 1984; Jostell, K.G., personal communication). However, the ejaculatory response was not inhibited by two administrations of alaproclate and citalopram within 4 h when the response was induced by 5-MeODMT 48 h after the second administration. During this time the uptake inhibition was constant (own unpublished results).

One possible explanation for the differences in the effect of the 5-HT uptake inhibitors on the 5-MeODMT-induced ejaculatory response could be different regional actions of the drugs (cf. Ögren et al., 1984). The development of the long-lasting decrease of the ejaculatory response after a single dose of fluoxetine or zimeldine may also be explained by an influence of these drugs on the postsynaptic receptors involved in the ejaculatory response. This view is supported by the finding that the process was counteracted by methergoline when it was given twice within 4 h after fluoxetine or zimeldine. This result suggests that changes of the 5-HT receptors occur at the postsynaptic level since methergoline seems to possess mainly 5-HT postsynaptic activity without any effect on adrenoceptors (Fuxe et al., 1978). Methergoline, injected only once 4 h after fluoxetine or zimeldine, could not counteract the development of the functional subsensitivity of the receptors which, once established, lasted for a long time, from 48 h to at least 12 days. These observations show that the long-lasting effects of these uptake inhibitors are triggered during the first 4 h after the administration.

The findings, that prolonged functional blockade of the 5-HT receptors results in functional supersensitivity of the same receptors (Samanin et al., 1980; Stolz & Marsden, 1982; Stolz et al., 1983), are confirmed in the present study since the enhancement of the ejaculatory response was obtained on withdrawal from fluoxetine and possibly also from zimeldine. The results, after acute and chronic administration of fluoxetine, indicate that the time point of the appearance of the functional supersensitivity of the receptors may depend mostly on the span of time of administration, i.e. the length of the functional receptor blockade (Antelman et al., 1983; Lace & Antelman, 1983). The total dose given may play a less significant role. It is hardly credible that the enhancement of the total dose of fluoxetine from 25 to 50 mg kg\(^{-1}\) (in the 19 days' experiment) should delay...
the development of the supersensitivity from 24 to 42–56 days.

It has to be taken into consideration that besides the stimulation of 5-HT receptors a noradrenergic input, probably peripheral, seems to be involved in the ejaculatory response (Rényi, 1985). Thus, it is possible that because of the initial blockade of the ejaculatory response, mediated mainly by central 5-HT₂-receptors, the enhancement of the response develops with the involvement of some peripheral adrenoceptor sites.

The observations that chronic treatment with fluoxetine or zimeldine also attenuated the evidently 5-HT₂-receptor mediated behavioural response (reviewed by Green, 1984; Green & Heal, 1985) induced by 5-MeODMT and that the response decreased further with prolonged treatment, support the hypothesis that the receptors which are involved in the changes of the ejaculatory response are also 5-HT₂-receptors. The reason why no decrease of the 5-MeODMT-induced behavioural syndrome could be observed following acute doses of fluoxetine or zimeldine may be that the ejaculatory response is a more sensitive model for examining receptor changes following different drug treatments. The fact that α₁-adrenoceptors also seem to be involved in the ejaculatory response may not be such a disturbing factor since almost all components of the 5-HT syndrome are influenced by different catecholamine receptor activities (Handley & Brown, 1982; Dickinson & Curzon, 1983; Arnt et al., 1984). Furthermore, the way the functional receptor sub- and supersensitivity were produced in this study is suitable in one respect: 48 h after low single doses of fluoxetine or zimeldine and 42–56 days after repeated treatment with fluoxetine there is, in all probability, no residual drug present in the brain (Parli & Hicks, 1974; Heel et al., 1982).

The biochemical mechanism underlying the time-dependent changes in the ejaculatory response are at present unknown. Conflicting results have been published concerning the changes in postsynaptic 5-HT₂-receptor binding sites after chronic treatment with alaproclate (Hall & Wedel, 1985; Ögren et al., 1985) but hitherto, with one exception (Archer et al., 1985), no behavioural effects have been reported after acute or repeated treatment with alaproclate. Long-term treatment with citalopram did not affect the postsynaptic 5-HT₂ binding sites (Hyttel et al., 1984), but it decreased the head shake response induced by 5-HTP or quipazine (Arnt et al., 1984).

Chronic treatment with fluoxetine and zimeldine resulted in a decrease of the 5-HT₂ binding sites mainly in the frontal cortex (Ögren et al., 1982) and in an attenuation or enhancement of 5-HT₂-receptor mediated behavioural changes (Fuxe et al., 1981; Wong & Bymaster, 1981; Hall et al., 1982; Stolz et al., 1983; Ögren et al., 1985), but no decrease or increase of the 5-HT₂ binding sites were found after single doses of fluoxetine or zimeldine. Nevertheless, current data have demonstrated a rapid down-regulation of the 5-HT₂ receptors (within 3 h) and a simultaneous waning of the wet dog shake response in rats treated with a combination of a monoamine oxidase inhibitor and an inhibitor of 5-HT uptake (Koshikawa et al., 1985). In all probability the number of postsynaptic 5-HT receptors involved in the ejaculatory response is large enough to be detectable by ligand-receptor binding studies.

In conclusion, the data presented in this study have shown that selective inhibitors of the uptake of 5-HT differently affect the ejaculatory response and also other components of the 5-HT syndrome induced by 5-MeODMT. Further biochemical and functional investigations are necessary to elucidate whether the time-dependent receptor subsensitivity or supersensitivity is related to the clinical action and/or to possible side-effects of these drugs.

References


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