Br. J. Pharmac. (1986), **88**, 827–835

The effects of monoamine oxidase inhibitors on the ejaculatory response induced by 5-methoxy-N,N-dimethyltryptamine in the rat

Lucy Rényi

Astra Läkemedel AB, Research and Development Laboratories, S-151 85 Södertälje, Sweden.

1 The ejaculatory response and other components of 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 single and repeated treatment of rats with eight different monoamine oxidase (MAO) inhibitors. Single and repeated treatment with the 5-HT agonist 5-MeODMT, and with low doses of the potent releaser of 5-HT, *p*-chloroamphetamine (PCA) were also included in the study.

2 Repeated but not single treatment with 5-MeODMT reduced strongly but reversibly the ejaculatory response and the behavioural responses.

3 Repeated but not single treatment with the nonselective and irreversible MAO inhibitors nialamide and pargyline reduced markedly the ejaculatory response but only slightly the 5-HT behavioural responses.

4 Repeated treatment with the irreversible MAO-B inhibitor (−)-deprenyl, with the irreversible MAO-A inhibitor, clorgyline, with the reversible MAO-A inhibitor moclobemide, and with low doses of PCA did not affect either of the responses.

5 Repeated but not single combined treatment with clorgyline plus PCA caused an almost complete blockade of all the four responses. The selective and reversible MAO-A inhibitors (as well as 5-HT releasers) amiflamine, α-ethyltryptamine, and α-methyltryptamine reduced markedly the ejaculatory response after both single and repeated treatments. The behavioural responses were blocked only after repeated treatment.

6 It is concluded that single and repeated treatments of rats with different MAO inhibitors do not produce a common alteration in 5-HT_2 receptor functions. Repeated treatment with 5-MeODMT caused a blockade of 75–95% of the ejaculatory response and 5-HT behavioural responses. A similar strong blockade was only produced by the combined effect of MAO-A inhibition and 5-HT release.

Introduction

The observation that drugs which stimulate postsynaptic 5-hydroxytryptamine (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) induce dose- and time-dependent ejaculations in the rat initated studies to characterize this response (Rényi, 1985, 1986a). It was found that 5-HT_2 receptors in the CNS seem to mediate the ejaculatory response, but that α_1-adrenoceptors, probably peripherally localized, are also involved (Rényi, 1986a). The ejaculatory response was produced in parallel with the 5-HT syndrome, and it was suggested that the response is a part of this syndrome. Since the amount of seminal material produced can be quantified, the drug-induced ejaculatory response may become a valuable pharmacological model for studies of central 5-HT_2 receptors, e.g. to follow the development of up and down regulation of the 5-HT systems in the brain induced by various compounds that affect 5-HT neurotransmission.

In previous work (Rényi, 1986a), the acute and long-term effects of four selective 5-HT uptake inhibitors were investigated on the ejaculatory response and on other components of the 5-HT syndrome. It was observed that fluoxetine caused an attenuation of the ejaculatory response after an acute dose when tested 48 h later by 5-MeODMT. The blockade was followed by an enhancement of the response which lasted at least 14 days. These effects may be explained

by an initial down regulation followed by a compensatory sensitization of the systems involved in the ejaculatory response.

Another class of antidepressant compound which also affects the 5-hydroxytryptaminergic system in the brain is the monoamine oxidase (MAO) inhibitors. The inhibition of 5-HT catabolism increases the concentration of 5-HT and thereby also the release of this transmitter. Several studies have reported that repeated treatment of rats with MAO inhibitors causes changes in the density of the 5-HT receptors in the brain (Peroutka & Snyder, 1980; Savage *et al.*, 1980a, b). It was therefore of interest to examine whether the MAO inhibitors also influence the sensitivity of the ejaculatory response induced by 5-MeODMT.

In the present study, the acute and long term effects of eight different monoamine oxidase (MAO) inhibitors were investigated on the ejaculatory response induced by 5-MeODMT. 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-HT_2 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 enzyme MAO exists in two different forms: A and B (Johnston, 1968; Knoll & Magyar, 1972). These two forms seem to have different importance for the regulation of the transmitter amines, 5-HT, noradrenaline and dopamine. In the rat brain, all three amines are mainly metabolized by the A form of MAO (Johnston, 1968; Waldmeier *et al.*, 1976; Garrick & Murphy, 1981).

This study included both the irreversible nonselective MAO inhibitors, nialamide and pargyline, the irreversible selective MAO inhibitors, clorgyline (MAO-A) and (−)-deprenyl (MAO-B), and the reversible selective MAO-A inhibitors, amiflamine, α-ethyltryptamine, α-methyltryptamine, and moclobemide (for review, see Fowler & Ross, 1982; Willner, 1985). In order to evaluate the effects of prolonged stimulation of the 5-HT receptors on the functional responses, repeated high doses of 5-MeODMT were administered to rats.

Parts of this work were presented at the Proceedings of the 14th Collegium Internationale Neuro-Psychopharmacologicum, Florence (Rényi, 1984).

Methods

Sprague-Dawley rats, (Anticimex, Sollentuna, Sweden), 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 softly lighted, quiet room at 20–22°C. The drugs were dissolved in saline, except nialamide (diluted HCl, pH 3.0), 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) and α-methyltryptamine (0.5% ascorbic acid). Except for nialamide (2.0 ml kg^{-1} body weight) the drugs were administered in 1.0 ml kg^{-1} body weight. The animals were deprived of food for 16 h before the acute doses or before the first dose by repeated treatment, but water was supplied *ad libitum*. One h after the administration of the drugs, the rats were again supplied with food.

Ejaculatory response

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 removal 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 the 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 was 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

Behaviours (hind limb abduction, forepaw treading, and Straub tail) were scored individually. Singly housed rats 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 removal exactly 3 min before the first observation period. The behaviours were assessed on a 0–4 scale.

(I) *Hind limb abduction:* 0 – absent, 1 – rigid posture, occasional and slow forward movements, 2 – rigid posture, somewhat 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').

(II) *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.

(III) *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 degrees to the bottom of the cage, 3 – the angle is 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. A maximum total score obtainable was $3 \times 4 = 12$.

Single and repeated treatment with 5-MeODMT

Repeated treatment of rats with 5-MeODMT (8 mg kg^{-1} i.p.) twice daily was performed for 7 days. The control animals were injected with a saline solution (2×1 ml kg^{-1}, i.p.) during the same period. The first test dose of 5-MeODMT (3 mg kg^{-1}, i.p.) was given 48 h after a single dose of 5-MeODMT (8 mg kg^{-1}, i.p.) or after the last repeated injection. The same animals were thereafter tested again 10, 28, and 42 days after the last repeated dose (8 mg kg^{-1}, i.p.). The ejaculatory and behavioural responses after the challenge dose of 5-MeODMT were measured as described above.

Single and repeated treatment with irreversible MAO inhibitors

The irreversible MAO inhibitors nialamide (40 mg kg^{-1}, s.c.), pargyline (25 mg kg^{-1}, s.c.), (−)-deprenyl (1 mg kg^{-1}, s.c.), and clorgyline (0.1 mg kg^{-1}, s.c.) were injected once daily for 7 days. Single injections of (−)-deprenyl, clorgyline, and pargyline at these doses produce 50–70% inhibition of the brain MAO-A and/or MAO-B (Waldmeier *et al.*, 1981; Fagervall & Ross, 1986). A single injection of nialamide 40 mg kg^{-1}, s.c. caused 65% inhibition of MAO-A in the rat brain when tested 24 h after the injection (Ross, unpublished data). The rats were tested on the ejaculatory and behavioural responses induced by 5-MeODMT (3 mg kg^{-1}, i.p.) 48 h after the single dose or after the last repeated injection of the MAO inhibitors.

Single and repeated treatment with reversible MAO inhibitors

Moclobemide (10 mg kg^{-1}), amiflamine (5 or 10 mg kg^{-1}), α-methyltryptamine (5 mg kg^{-1}) and α-ethyltryptamine (10 mg kg^{-1}) were all administered orally, twice daily for 7 days. The single administration of these doses produces 80 to 100% inhibition of MAO-A within the 5-hydroxytryptaminergic neurones of the rat brain (Ask *et al.*, unpublished data). The ejaculatory and behavioural responses produced by 5-MeODMT (3 mg kg^{-1}, i.p.) were measured 48 h after a single dose or after the last repeated administration of the MAO inhibitors.

Combined treatment with clorgyline plus PCA

Rats were treated for 7 days with clorgyline (0.1 mg kg^{-1}, s.c. once daily) plus PCA (0.5 mg kg^{-1}, orally twice daily) or with saline (1 ml kg^{-1}, s.c.) plus PCA (1.0 mg kg^{-1}, orally twice daily). The ejaculatory and behavioural responses induced by 5-MeODMT (3 mg kg^{-1}, i.p.) were measured 48 h after the last repeated administration or after the single combined treatment.

Drugs

The following drugs were used in the study: amiflamine (+)-hydrogen tartrate, clorgyline HCl, moclobemide (RO 11-1163) synthesized by L. Florvall, Astra Läkemedel AB), (−)-deprenyl HCl (kindly donated by Professor J. Knoll, Semmelweiss University, Budapest, Hungary), *p*-chloroamphetamine HCl (Sigma), α-ethyltryptamine acetate (Sigma), α-methyltryptamine base (Janssen), 5-methoxy-N,N-dimethyltryptamine base (Sigma), nialamide base (Sigma), and pargyline HCl (Abbott).

Results

The ejaculatory response and the 5-HT behavioural response in this study were induced by 5-MeODMT (3 mg kg^{-1}, i.p.) 48 h after an acute dose or after the last dose of the repeated treatment with the drugs studied. Repeated treatment means that the drugs were administered for 7 days. The acute effects of those drugs which after repeated treatment neither affected the ejaculatory response nor the 5-HT behavioural response are not shown.

Effects of repeated treatment of rats with the 5-HT receptor agonist 5-MeODMT on the 5-MeODMT-induced ejaculatory response and 5-HT behavioural response

Repeated (7 days) but not single treatment with 5-MeODMT (2×8 mg kg^{-1}, i.p.) caused a 75–95% blockade both of the ejaculatory response and of the 5-HT behavioural response when tested 48 h after the last repeated dose (Figure 1, Table 1). This effect was reversible (Figure 2). After the blockade of the ejaculatory response on day 10, an enhancement of the

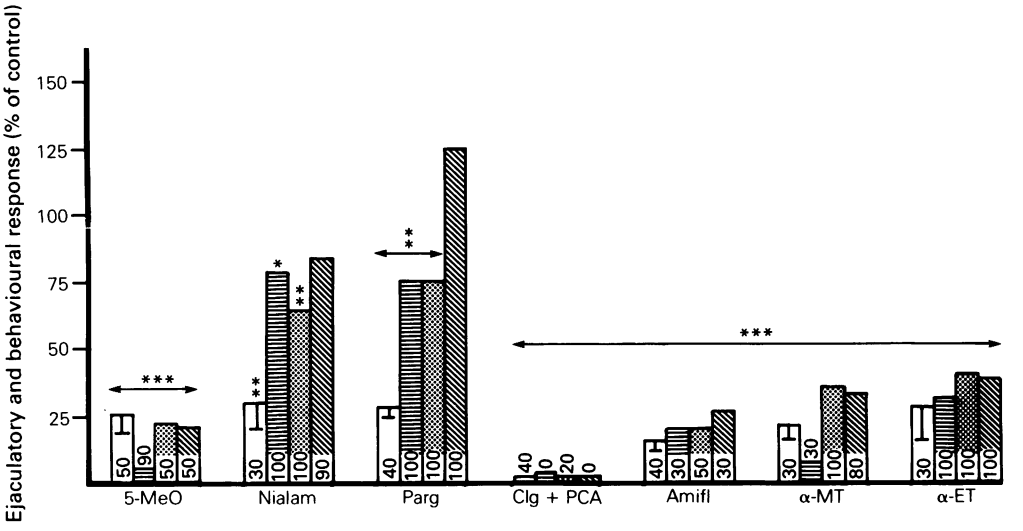

Figure 1 Effects of repeated treatment with two 5-hydroxytryptamine (5-HT) receptor agonists and different monoamine oxidase (MAO) inhibitors on the ejaculatory response and on the 5-HT behavioural response. 5-Methoxy-N,N-dimethyltryptamine (5-MeO, 2 × 8 mg kg^{-1}, i.p.), nialamide (Nialam, 1 × 40 mg kg^{-1}, s.c.), pargyline (Parg, 1 × 25 mg kg^{-1}, s.c.) clorgyline (Clg, 1 × 0.1 mg kg^{-1}, s.c.) plus *p*-chloroamphetamine (PCA, 2 × 0.5 mg kg^{-1}, orally), amiflamine (Amifl, 2 × 10 mg kg^{-1}, orally), α-methyltryptamine (α-MT, 2 × 5 mg kg^{-1}, orally), and α-ethyltryptamine (α-ET, 2 × 10 mg kg^{-1}) were administered for 7 days. The ejaculatory response and the 5-HT behavioural response were induced by 5-MeODMT (3 mg kg^{-1}, i.p.) 48 h after the last administration of the drugs. In the ejaculatory response test, 5 singly housed control rats were scored alternately with 5 treated rats. In the 5-HT behavioural response test, control and treated animals were scored in parallel. Ejaculatory response, open columns; abduction, horizontally hatched columns; forepaw treading, stippled columns; Straub tail, diagonally hatched columns. The weight of the seminal material is shown (mean ± s.e.mean as % of mean) as % of the control value. The 5-HT behavioural response is shown as % of the control value. Numbers in the columns give the percentage of rats with positive response, $n = 10$ rats in each experiment (column). $^{*}P < 0.05$, $^{**}P < 0.02$; $^{***}P < 0.001$ vs control rats (Mann-Whitney U-test).

Table 1 Effect of single treatment with nonselective and irreversible monoamine oxidase (MAO) inhibitors and 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) itself on the ejaculatory response induced by 5-MeODMT

Treatment	n	*Dose* (mg kg^{-1})	*Weight of the seminal material* (mg) ± (min–max)	*Ejaculatory response* (% of control)
Saline	10		36 (6– 83)	
Nialamide	10	40 s.c.	45 (14– 98)	125
Pargyline	10	25 s.c.	40 (4–146)	111
Saline	10		40 (11– 65)	
5-MeODMT	10	8 i.p.	32 (6– 93)	80

5-MeODMT (3 mg kg^{-1}, i.p.) was injected 48 h after the administration of the drugs. The seminal material produced during 10 min after the injection of 5-MeODMT was collected and weighed as described under Methods. The values are means with the ranges in parentheses.

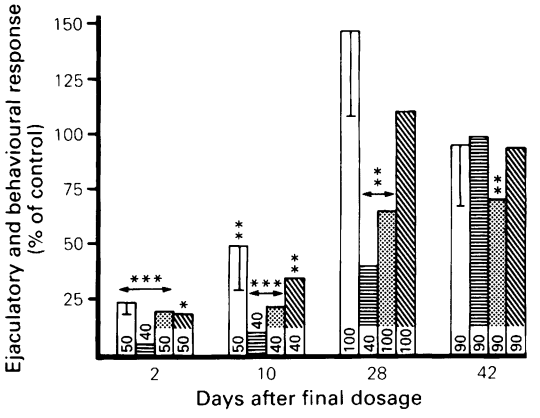

Figure 2 The recovery of the ejaculatory response and the 5-hydroxytryptamine (5-HT) behavioural response after repeated treatment with 5-methoxy-N,N-dimethyltryptamine (5-MeODMT, 2×8 mg kg^{-1}, i.p.) for 7 days. The response was induced by an acute dose of 5-MeODMT (3 mg kg^{-1}, i.p.) at different times after the last administration. In the ejaculatory response test, 5 singly housed control rats were scored alternately with 5 treated rats. In the 5-HT behavioural response test, control and treated animals were scored in parallel. Ejaculatory response, open columns; abduction, horizontally hatched columns; forepaw treading, stippled columns; Straub tail, diagonally hatched columns. The weight of the seminal material is shown (mean ± s.e.mean as % of mean) as % of the control value. The 5-HT behavioural response is shown as % of the control value. Numbers in the columns give the percentage of rats with positive response, $n = 10$ rats in each experiment (column). $^{*}P < 0.05$; $^{**}P < 0.02$; $^{***}P < 0.001$ vs control rats (Mann-Whitney U-test).

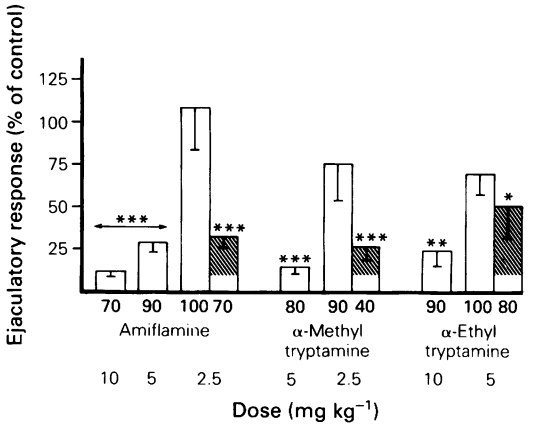

Figure 3 Effects of acute (open columns) and repeated treatment for 7 days (hatched columns) with some reversible monoamine oxidase-A (MAO-A) inhibitors on the ejaculatory response. The response was induced by 5-methoxy-N,N-dimethyltryptamine (5-MeODMT, 3 mg kg^{-1}, i.p.) 48 h after an acute dose of the drugs or after the last dose of the repeated treatment. Five singly housed control rats were scored alternately with five treated rats. The weight of the seminal material is shown (mean ± s.e.mean as % of mean) as % of the control value. Numbers under the columns give the percentage of rats with ejaculations, $n = 10$ rats in each experiment (column). $^{*}P < 0.05$; $^{**}P < 0.02$; $^{***}P < 0.001$ vs control rats (Mann-Whitney U-test).

same response occurred on day 28 which, however, failed to reach significance. On day 42, the ejaculatory response, the hind limb abduction, and the Straub tail were back to the control level. The forepaw treading was still significantly blocked (30%).

Effect of the nonselective and irreversible MAO inhibitors, on the 5-MeODMT-induced ejaculatory response and on the 5-HT behavioural response

Repeated (7 days) but not acute treatment with nialamide (1×40 mg kg^{-1}, s.c.) and pargyline (1×25 mg kg^{-1}, s.c.) produced 77 and 78% blockade of the ejaculatory response, respectively, when tested 48 h after the last repeated dose and between 24 and 37% blockade of the hind limb abduction and forepaw treading, respectively, but had no effect on the Straub tail response (Figure 1, Table 1). However, the selective MAO-A inhibitor clorgyline (1×0.1 mg kg^{-1}, s.c.) or the MAO-B inhibitor (−)-deprenyl ($1 \times$ mg kg^{-1}, s.c.) did not affect either the ejaculatory response (Table 2) or the 5-HT behavioural response (data not shown). These compounds also had no effects after single injections.

Effects of some selective and reversible MAO-A inhibitors on the 5-MeODMT-induced ejaculatory response and on the 5-HT behavioural response

Repeated treatment (for 7 days) with the MAO-A inhibitor moclobemide (2×10 mg kg^{-1}, orally) did not affect either the 5-MeODMT-induced ejaculatory response (Table 2) or the 5-HT behavioural response (data not shown). Single higher doses of amiflamine (5 and 10 mg kg^{-1}, orally), α-methyltryptamine (5 mg kg^{-1}, orally), and α-ethyltryptamine (10 mg kg^{-1}, orally) reduced the ejaculatory response by 75–90% (Figure 3) but not the 5-HT behavioural response (data not shown). Repeated treatment for 7 days of the rats with the same high doses also reduced the 5-HT behavioural response and reinforced the blockade of the ejaculatory response (Figure 1). These effects were dose-dependent (Figures 1 and 3).

Table 2 Effect of repeated treatment with monoamine oxidase (MAO)-inhibitors and a low dose of *p*-chloroamphetamine (PCA) on the 5-methoxy-N,N-dimethyltryptamine (5-MeODMT)-induced ejaculatory response

Treatment	n	*Dose* ($mg\,kg^{-1}$)	*Weight of the seminal material* (mg) ± (min–max)	*Ejaculatory response* (% of control)
Saline	10		48 (10–177)	
Moclobemide	10	2 × 10 p.o.	50 (2–142)	104
Saline	10		40 (6– 97)	
(−)-Deprenyl	10	1 × 1.0 s.c.	51 (3–112)	128
Saline	10		53 (8–136)	
Clorgyline	10	1 × 0.1 s.c.	64 (8–165)	121
Saline	10		31 (11– 78)	
PCA	10	2 × 1.0 p.o.	29 (7– 68)	94

The drugs were administered for 7 days. 5-MeODMT (3 $mg\,kg^{-1}$, i.p.) was injected 48 h after the last administration of the drugs. The seminal material produced during 10 min after the injection of 5-MeODMT was collected and weighed as described under Methods. The values are means with the ranges in parentheses.

Effect of combined treatment with clorgyline plus PCA

Since the reversible MAO-A inhibitors, amiflamine, α-methyltryptamine, and α-ethyltryptamine, which also release 5-HT, strongly reduced the ejaculatory response, the contribution of the 5-HT release to this effect was tested by the combined treatment of the rats for 7 days with clorgyline (0.1 $mg\,kg^{-1}$, s.c. once daily) plus the 5-HT releasing compound, PCA (0.5 $mg\,kg^{-1}$, orally twice daily). Other rats were treated with saline plus PCA (1.0 $mg\,kg^{-1}$, orally twice daily) for 7 days. The ejaculatory and behavioural responses induced by 5-MeODMT (3 $mg\,kg^{-1}$, i.p.) 48 h after the last repeated combined treatment were almost abolished (Figure 1) whereas repeated treatment with PCA alone or the single combined treatment did not change the responses (Table 2).

Dose-response and time curves of ejaculation induced by amiflamine

Since amiflamine itself induced ejaculation in the rat, the dose-response and time curves for this compound were examined. Like PCA (Rényi, 1985) amiflamine caused a dose-dependent, bell-shaped ejaculatory response curve (Figure 4). The seminal material collected after 40 $mg\,kg^{-1}$, i.p. was significantly ($P<0.001$) less than after 20 $mg\,kg^{-1}$, i.p. The production of the ejaculate was optimal at 90 min ($P<0.05$ vs 15 min). However, 90% of the rats still ejaculated at 150 min with a low weight of the seminal material (Figure 5).

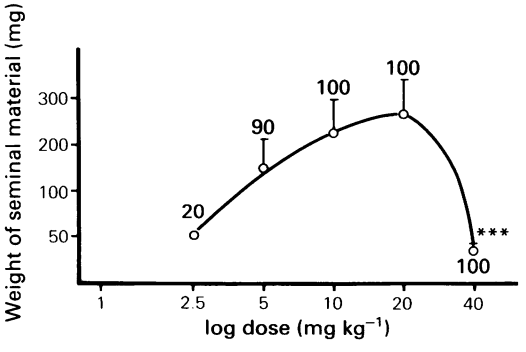

Figure 4 Dose-dependent effect of amiflamine on the weight of seminal material. Each value is the mean of the weights of seminal material produced during 2 h for 10–20 separate rats. The vertical bars represent s.e.mean. Values above the doses represent the number of rats per group showing ejaculatory response. ***$P<0.001$ compared with 20 $mg\,kg^{-1}$, i.p. of amiflamine (Student's *t* test).

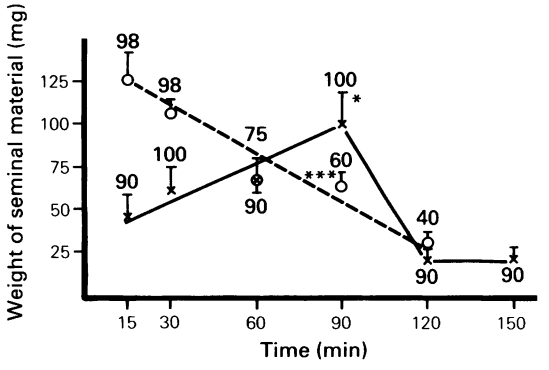

Figure 5 Time curve of the production of the seminal material after amiflamine (20 mg kg^{-1}, i.p., ×) and *p*-chloroamphetamine (2.5 mg kg^{-1}, i.p., O). Each value is the mean ± s.e.mean (vertical bars) from at least 10 rats. The values above the points represent the percentage of rats per group showing the ejaculatory response. $^{*}P < 0.05$; $^{***}P < 0.001$ compared with the weights at 15 min (Student's *t* test). *p*-Chloroamphetamine results from Rényi (1985).

Discussion

As shown previously (Rényi, 1984), repeated treatment of rats with 5-MeODMT produces an almost complete blockade of the ejaculatory response and three other components of the 5-HT syndrome induced by an acute dose of the same drug 48 h after final dosage. Development of tolerance toward this drug has also been reported by Archer *et al.* (1985b), Sills *et al.* (1985) and Trulson & Keltch (1985).

A possible explanation of this phenomenon is a functional down-regulation of some 5-HT (5-HT$_2$) receptors due to prolonged stimulation of the postsynaptic receptors by the directly acting 5-HT agonist, 5-MeODMT (Fuxe *et al.*, 1972). Present findings, i.e. that the reversible MAO-A inhibitors, amiflamine (FLA 336(+)), α-ethyltryptamine, and α-methyltryptamine (Ask *et al.*, 1982) which also release 5-HT (Rényi & Ross, 1985; Ask & Ross, 1985) produced a similar strong blockade of the 5-MeODMT-induced responses, give support to this hypothesis. Thus, although 5-MeODMT does not release 5-HT (A.-L. Ask, personal communication), it produces as strong a stimulation of the post-synaptic 5-HT receptors as the 5-HT released by the reversible MAO-A inhibitors.

The long period for recovery of the ejaculatory response following repeated 5-MeODMT treatment is in accordance with previous findings i.e. that the response is still changed (decreased and/or increased) at a time when the presynaptic content of 5-HT presumably has returned to normal (Rényi, 1986a, b).

MAO-A inhibition in itself is obviously not enough to affect the responses since clorgyline at a dose producing an almost complete inhibition of MAO-A in the rat brain following repeated administration (Waldmeier *et al.*, 1981) had no effect. At this dose the MAO-A selectivity of clorgyline remained constant during two weeks repeated treatment (Waldmeier *et al.*, 1981). However, combined with a low dose of PCA which releases 5-HT (Rényi, 1985) clorgyline caused a complete blockade of all four responses induced by 5-MeODMT. In accordance with this view, moclobemide, a reversible MAO-A inhibitor which does not release 5-HT (A.-L. Ask, personal communication), had no effect.

The observation that nialamide and pargyline produced a pronounced decrease in the 5-MeODMT-induced ejaculatory response may indicate that inhibition of both A and B forms of MAO is necessary to alter 5-HT receptor functions (Green & Youdim, 1975). Although the MAO-B selectivity of (−)-deprenyl at the dose used is partially lost during repeated treatment (Waldmeier *et al.*, 1981) the inhibition of the A form may be too low to induce, together with MAO-B inhibition, receptor changes. Further experiments combining clorgyline and (−)-deprenyl treatment will elucidate this question. Alternatively, nialamide and pargyline may cause some release of 5-HT. Several authors reported changes of the 5-HT behavioural responses after combining MAO inhibitor treatment with 5-HT uptake inhibitors (Ashkenazi *et al.*, 1983; Koshikawa *et al.*, 1985) or with 5-HT releasing compounds (Archer *et al.*, 1985a). The possibility of such a combined effect of these non-selective MAO-inhibitors may not be excluded. The three behavioural components induced by 5-MeODMT were much less affected by nialamide and pargyline. These findings are in contrast to those reported by Lucki & Frazer (1982) who found an almost complete down-regulation of the 5-HT syndrome induced by 5-MeODMT. The discrepancy may be explained by the differences in the method (doses) used for the evaluation of the behavioural changes.

The functional blockade of the 5-MeODMT-induced ejaculatory response and the three other components of the 5-HT syndrome observed in the present study may be due to changes in the density of the 5-HT (probably 5-HT$_2$) receptors mediating the responses. However, although decreased density of 5-HT$_2$ and 5-HT$_1$ receptors has been reported after repeated treatment with pargyline (Peroutka & Snyder, 1980; Kendall *et al.*, 1982), no such effect could be found after repeated amiflamine treatment (Hall & Wedel, 1985; Ögren *et al.*, 1985). Clorgyline has been reported to reduce the number of 5-HT$_1$ receptors (Savage *et al.*, 1980a, b), but had no effect on the functional changes

examined in this study. Thus, there is no obvious correlation between drug-induced 5-HT-mediated behavioural changes and 5-HT receptor density which is in accordance with the results obtained by others (for review, see Willner, 1985).

A possible explanation for this lack of relationship is that while the receptors have been analysed in the cerebral cortex, the 5-HT-mediated behavioural changes appear to be localized in the hind brain and/or spinal cord (Jacobs & Klemfuss, 1975; Deakin & Green, 1978; Dickinson *et al.*, 1984). It is also possible that the functional receptors are so few that a decrease in the number of these receptors is not detectable when measuring the total number of receptors. A third possibility is that the responses triggered by stimulation of 5-HT receptors are mediated through other neurone systems.

The 5-MeODMT-induced ejaculatory response appears to be more sensitive to down-regulation than the three other components of the 5-HT syndrome examined since acute high doses of the reversible MAO-A inhibitors caused a strong inhibition of the ejaculatory response but not of the behavioural responses induced 48 h later by 5-MeODMT. Furthermore, nialamide and pargyline had a greater effect on the ejaculatory response than on the behavioural response.

Amiflamine itself produced a dose-dependent ejaculatory response which, like that produced by PCA or 5-MeODMT, follows a bell-shaped course (Rényi, 1985). This effect is probably due to a simultaneous release of 5-HT plus noradrenaline (but not dopamine) by the drug (Ask & Ross, 1985; Rényi & Ross, 1985). The difference in the time curve for PCA and amiflamine may depend on the fact that the optimal balance for the level of 5-HT and noradrenaline at postsynaptic sites which seems to be necessary to elicit the ejaculatory response occurs at different time points, possibly because of contributions to the effect by metabolites of amiflamine (Rényi & Ross, 1985).

In summary, the results obtained show that acute and repeated treatments of rats with different MAO inhibitors do not produce a common alteration in 5-HT receptor functions. Repeated stimulation of 5-HT receptors by 5-MeODMT or by inhibition of MAO-A combined with 5-HT release induces a strong blockade of the ejaculatory response and of the other three components of the 5-HT syndrome due probably to the down-regulation of some 5-HT (5-HT_2) receptors. Nonselective MAO inhibitors produced marked inhibition of the 5-HT-mediated ejaculatory response but they had less effect on the behavioural responses. Selective inhibition of MAO-A (clorgyline and moclobemide) or MAO-B (−)-deprenyl) did not produce any alteration in 5-HT_2 receptor functions.

I am grateful to Professor S. Ross for stimulating discussions and to Dr A.-L. Ask for allowing me to use unpublished results.

References

ARCHER, T., FOWLER, C.J., FREDRIKSSON, A., LEWANDER, T., MAGNUSSON, O., MOHRINGE, B. & SÖDERBERG, U. (1985a). Increased total activity in the rat after L-tryptophan plus the monoamine oxidase-A inhibitor amiflamine but not after L-tryptophan plus clorgyline. *Br. J. Pharmac.*, **85**, 581–590.

ARCHER, T., TANDBERG, B., RÉNYI, L. & ROSS, S.B. (1985b). Antagonism of 5-methoxy-N,N-dimethyltryptamine-induced changes in postdecapitation convulsios by repeated treatment with drugs (enhancing 5-hydroxytryptamine neurotransmission). *J. Pharm. Pharmac.*, **37**, 648–650.

ASHKENAZI, R., FINBERG, J.P.M. & YOUDIM, M.B.H. (1983). Behavioural hyperactivity in rats treated with selective monoamine oxidase inhibitors and LM 5008, a selective 5-hydroxytryptamine uptake blocker. *Br. J. Pharmac.*, **79**, 765–770.

ASK, A.-L., HÖGBERG, K., SCHMIDT, L., KIESSLING, H. & ROSS, S.B. (1982). (+)-4-Dimethylamino-2,α-dimethylphenethylamine (FLA 336(+)), a selective inhibitor of the A form of monoamine oxidase in the rat brain. *Biochem. Pharmac.*, **31**, 1401–1406.

ASK, A.-L. & ROSS, S.B. (1985). Release of ^{3}H-5-hydroxytryptamine by amiflamine and related compounds in rat occipital cortex slices. *Ninth European Neuroscience Congress*, Oxford, September 8–12, 1985.

DEAKIN, J.F.W. & GREEN, A.R. (1978). The effects of putative 5-hydroxytryptamine antagonists on the behaviour produced by administration of tranylcypromine and L-DOPA to rats. *Br. J. Pharmac.*, **64**, 201–209.

DICKINSON, S.L., ANDREWS, C.D. & CURZON, G. (1984). The effects of lesions produced by 5,7-dihydroxytryptamine on 5-hydroxytryptamine-mediated behaviour induced by amphetamine in large doses in the rat. *Neuropharmacology*, **23**, 4, 423–429.

FAGERVALL, I. & ROSS, S.B. (1986). Inhibition of monoamine oxidase in monoaminergic neurones in the rat brain by irreversible inhibitors. *Biochem. Pharmac.*, **35**, 1381–1387.

FOWLER, C.J. & ROSS, S.B. (1984). Selective inhibitors of monoamine oxidase A and B: biochemical, pharmacological, and clinical properties. *Medicinal Research Reviews*, **4**, (3), 323–358.

FUXE, K., HOLMSTEDT, B. & JONSSON, G. (1972). Effects of 5-methoxy-N,N-dimethyltryptamine on central monoamine neurons. *Eur. J. Pharmac.*, **19**, 25–34.

GARRICK, N.A. & MURPHY, D.L. (1981). Differences in the preferential deamination of l-norepinephrine, dopamine and serotonin by MAO in rodent and primate brain. In *Function and Regulation of Monoamine Enzymes. Basic and Clinical Aspects*. Usdine, E., Weiner, N. & Youdim,

M.B.H. (eds). pp. 517–525. London and Basingstoke: Macmillan.

GREEN, A.R. (1984). 5-HT-mediated behaviour. Animal studies. *Neuropharmacology*, **23**, 1521–1528.

GREEN, A.R. & HEAL, D.J. (1985). The effects of drugs on serotonin-mediated behavioural models. In *Neuropharmacology of Serotonin*, pp. 326–355. Oxford: University Press.

GREEN, A.R. & YOUDIM, M.B.H. (1975). Effect of monoamine oxidase inhibition by clorgyline, deprenyl and tranylcypromine on 5-hydroxytryptamine concentration in rat brain and hyperactivity following subsequent tryptophan administration. *Br. J. Pharmac.*, **55**, 415–422.

HALL, H. & WEDEL, I. (1985). The effects of manipulation of presynaptic 5-HT nerve terminals on postsynaptic 5-HT_1 and 5-HT_2 binding sites of the rat brain. *J. Neural Transmiss.*, **64**, 129–143.

JACOBS, B.L. & KLEMFUSS, H. (1975). Brainstem and spinal cord mediation of serotonergic behavioural syndrome. *Brain Res.*, **100**, 450–457.

JOHNSTON, J.P. (1968). Some observations upon a new inhibitor of monoamine oxidase in brain tissue. *Biochem. Pharmac.*, **17**, 1285–1297.

KENDALL, D.A., DUMAN, R., SLOPIS, J. & ENNA, S.J. (1982). Influence of adrenocorticotropin hormone and yohimbine on antidepressant-induced declines in rat brain neurotransmitter receptor binding and function. *J. Pharmac. exp. Ther.*, **22**, 566–571.

KNOLL, J. & MAGYAR, K. (1972). Some puzzling pharmacological effects of monoamine oxidase inhibitors. *Adv. Biochem. Psychopharmac.*, **5**, 393–408.

KOSHIKAWA, N., SMOCKUM, R.W.J. & STEPHENSON, J.D. (1985). Is waning of a 5-hydroxytryptamine (5-HT)-mediated syndrome due to 5-HT_2 receptor down-regulation? *Neurosci. Letts*, **55**, 279–282.

LUCKI, I. & FRAZER, A. (1982). Prevention of the serotonin syndrome in rats by repeated administration of monoamine oxidase inhibitors but not tricyclic antidepressants. *Psychopharmacology*, **77**, 205.

ÖGREN, S.O., FUXE, K., AGNATI, L.F. & CELANI, M.F. (1985). Effects of antidepressant drugs on cerebral serotonin receptor mechanisms. *Acta Pharmac. Tox.*, **56**, Suppl 1, 105–127.

PEROUTKA, S.J. & SNYDER, S.H. (1980). Long-term antidepressant treatment decreases spiroperidol-labelled serotonin receptor binding. *Science*, **210**, 88.

RÉNYI, L. (1984). Blockade of the serotonin syndrome induced by 5-methoxy-N,N-dimethyl-tryptamine after repeated treatment of rats with amiflamine and some other monoamine oxidase inhibitors. *Abstr 14th CINP*, Florence, p. 409.

RÉNYI, L. (1985). Ejaculations induced by p-chloroamphetamine in the rat. *Neuropharmacology*, **24**, 697–704.

RÉNYI, L. (1986a). The effect of selective 5-hydroxytryptamine uptake inhibitors on 5-methoxy-*N,N*-dimethyltryptamine-induced ejaculation in the rats. *Br. J. Pharmac.*, **87**, 639–648.

RÉNYI, L. (1986b). Long-lasting 5-HT mediated behavioural supersensitivity following monoamine depletion in the rat brain. *Acta pharmac. tox.*, (in press).

RÉNYI, L. & ROSS, S.B. (1985). Effects of amiflamine and related compounds on the accumulation of biogenic monoamines in rat brain slices in vitro and ex vivo in relation to their behavioural effects. *Acta pharmac. tox.*, **56**, 416–426.

SAVAGE, D.D., MENDELS, J. & FRAZER, A. (1980a). Decrease in ^{3}H-serotonin binding in rat brain produced by the repeated administration of either monoamine oxidase inhibitors or centrally acting serotonin agonists. *Neuropharmacology*, **19**, 1063.

SAVAGE, D.D., MENDELS, J. & FRAZER, A. (1980b). Monoamine oxidase inhibitors and serotonin uptake inhibitors: Differential effects on ^{3}H-serotonin binding sites in rat brain. *J. Pharmac. exp. Ther.*, **212**, 259–263.

SILLS, M.A., LUCKI, I. & FRAZER, A. (1985). Development of selective tolerance to the serotonin behavioural syndrome and suppression of locomotor activity after repeated administration of either 5-MeODMT or mCPP. *Life Sciences*, **36**, 2463–2469.

TRULSON, M.E. & KELTCH, G.F. (1985). Development of tolerance to repeated administration of 5-methoxy-N,N-dimethyltryptamine in rats. *Eur. J. Pharmac.*, **108**, 33–37.

WALDMEIER, P.C., DELINI-STULA, A. & MAITRE, L. (1976). Preferential deamination of dopamine by an A type monoamine oxidase in rat brain. *Naunyn-Schmiedebergs Arch. Pharmac.*, **292**, 9–14.

WALDMEIER, P.C., FELNER, A.E. & MAITRE, L. (1981). Long-term effects of selective MAO inhibitors on MAO activity and amine metabolism. In *Monoamine-Oxidase Inhibitors – The State of the Art*. Youdim, M.B.H. & Paykel, E.S. (eds). pp. 87–102. London: John Wiley & Sons Ltd.

WILLNER, P. (1985). Antidepressants and serotonergic neurotransmission: an integrative review. *Psychopharmacology*, **85**, 387–404.

(Received December 17, 1985.
Revised April 4, 1986.
Accepted April 11, 1986.)