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Serotonergic drugs and masculine sexual behavior in laboratory rats and men

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Introduction

The neurotransmitter serotonin (5-HT) has been known for its involvement in sexual behavior since the late sixties [1]. By now, there is quite an extensive literature on the effects of serotonergic agents, especially the agonists, on sexual behavior of rats [reviews: 2-5].

In recent years we have studied the effects of serotonin agonists on sexual behaviors in rats. We investigated the effects of 8-OH-DPAT (a selective 5-HT_{1A} receptor agonist) in male and female rats [6-8] and the effects of flesinoxan, also a selective 5-HT_{1A} agonist [9] on masculine sexual behavior in male rats. In the human we studied the effects of clomipramine, a tricyclic antidepressant with selective serotonin reuptake inhibitor properties [10], in men with ejaculatory and erectile dysfunctions and in a group of control men without sexual dysfunction.

In this paper we present recent [7-8] and new rat data, and hitherto unpublished human data.

ANIMAL STUDIES

General method

Animals and laboratory conditions

Albino Wistar rats were used, except the male rats in Exp. 2 and 3, which were F_1-hybrids of two inbred Wistar strains (RxU). The animals were housed 2 to 3 to a cage, of the same sex and treatment. Water and food were available *ad lib*. The day-night cycle was artificially maintained (dark 7:30 am - 5:30 pm) and the temperature in the climate-controlled room ranged from 22 to 24 °C.

Drugs

Ovariectomized stimulus females were brought into behavioral estrus by injecting 30 μg estradiol benzoate (EB) in 0.15 ml olive oil 48-24 h prior to testing, followed by 2.5 mg progesterone (P) in 0.1 ml olive oil 3 h before testing.

Fresh solutions of 8-OH-DPAT ((±)-8-hydroxy-2-(di-n-propylamino) tetralin•HBr) and flesinoxan (Solvay Duphar, Weesp, The Netherlands) were dissolved in 0.9% NaCl approximately 1 h before testing. 8-OH-DPAT solution was administered by SC injection in the neck, flesinoxan by IP injection, both 30 min before testing.

Behavioral tests

Behavioral testing (pair-tests with estrous female, duration 15 min) started about 2 hr after the onset of the dark cycle with 15 min adaptation to the test cage. Testing was carried out in a semicircular arena, measuring 62x40x36 cm, with a wire mesh floor and a transparent front. The test room was dimly illuminated with indirect white light (60 W).

The following male sexual behavioral data were collected: number of mounts with pelvic thrusts (MF), intromissions (IF) and ejaculations (EF), time from the start of test to first mount (ML), to first intromission (IL), to first ejaculation (EL), and the number of intromissions before first ejaculation (ITE).

Experiment 1: Does 8-OH-DPAT affect sexual behavior in middle-aged male rats?

It has been shown earlier that 8-OH-DPAT increased ejaculatory frequencies in male rats [11-14]. Such studies employed males that were approximately 6 months old, i.e. relatively young. We thought it to be of interest to investigate the acclaimed sexually stimulatory properties of the drug in middle-aged male rats, particularly because such rats are assumed to be less sexually active [15].

Method

Twelve middle-aged rats (12-14 months old at the start of the study; body weights between 540 and 695 g) were tested for masculine sexual behavior. These animals had no heterosexual experience for at least 4 months prior to testing. Following the first 15-min pair-test two groups were formed on the basis of their sexual performance: an "active" group (n=7): males that ejaculated at least once, and an "inactive" group (n=5): males that did not ejaculate.

The animals were tested once a week with an estrous female for 7 consecutive weeks. When a stable level of sexual behavior was found (i.e. tests 3 and 4), treatment with 8-OH-DPAT or saline was started. In tests 5, 6 and 7 the animals were treated with saline (2 ml/kg), 8-OH-DPAT (0.2 mg/kg) and saline (2 ml/kg), respectively. Finally, test 8 (saline) was given 4 weeks following test 7.

Results

As can be seen in Figure 1, with 8-OH-DPAT treatment there was a increase in ejaculation frequency (EF) in both groups of males. ANOVA [16, 17] on tests -1 to +5 revealed an effect of tests, $p<0.001$, a borderline significant effect of groups, $p<0.07$, and no significant interaction. From looking at the figure it is clear that during 8-OH-DPAT treatment all males of both groups ejaculated with high frequencies. With 8-OH-DPAT males of both groups no longer differed in EF.

Statistical analysis of other sexual behavioral data revealed the following. For mounting: both groups of males showed lowest frequencies (MF) during tests with 8-OH-DPAT treatment (groups, n.s.; tests, $p<0.02$; groups x test interaction, n.s.). For

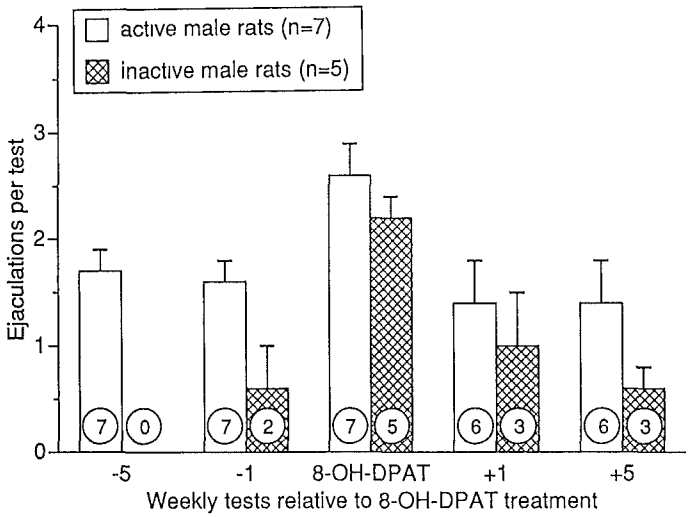

Figure 1. Mean (± SEM) ejaculation frequency of initially active (open bars) and inactive (hatched bars) middle-aged male rats before and after 0 2 mg/kg 8-OH-DPAT treatment. Males were tested weekly for 7 consecutive weeks; the result of the 1st (-5), 5th through 7th (-1; 8-OH-DPAT; +1) and 8th (+5) are depicted. Asterisks indicate a significant difference from tests before and after treatment. Also indicated is the number of animals per test that ejaculated at least once (after: [7]).

intromission frequencies (IF) similar results were found, i.e., lowest frequencies with 8-OH-DPAT (groups, n.s.; tests, n.s.; groups x test interaction, $p=0.04$). Furthermore, the number of intromissions to first ejaculation (ITE) did not seem to differ between the two groups of males; lowest numbers were found during 8-OH-DPAT treatment (see also Experiment 2).

Latency to first mount (ML) revealed a weak difference for groups, with shorter latencies for active males ($p=0.096$), and no differences for tests and groups x test interaction. Latency to first ejaculation (EL) differed over the tests ($p<0.001$), but the groups of males did not differ, and there was no significant interaction. Thus, both groups showed shortest latencies to ejaculation with 8-OH-DPAT treatment.

In summary, 8-OH-DPAT treatment increased ejaculation frequency in "middle-aged" (± 15 months old) male rats, both in initially sexually active and inactive animals. 8-OH-DPAT made both groups equally sexually active.

Experiment 2: "Premature ejaculation" caused by 8-OH-DPAT.

It has long been known that with a high dose of 8-OH-DPAT male rats can ejaculate following just the first or second intromission [11]. This unusual phenomenon for normal rats may be analogous to premature ejaculation in the human and therefore warranted further investigation. Questions studied were 1. the details of the sexual behavior, 2. the quality of the ejaculate, whether or not it contained mobile spermatozoa, and 3. where the semen was deposited, i.e. intra- or extravaginally.

Method

Twenty heterosexually naive male rats, approximately 6 months old, were pair-tested for sexual behavior untill one ejaculation had occured. Immediately after ejaculation the female was removed from the test-cage and a vaginal smear was taken, which was subsequently studied microscopically. The test cage was searched for the presence of a seminal plug; both animals were also inspected for possible ejaculate coagulated on their fur.

Five consecutive weekly tests were carried out with the following treatment: saline (2 ml/kg), a low dose 8-OH-DPAT (0.2 mg/kg), a higher dose 8-OH-DPAT (0.4 mg/kg), saline (2 ml/kg) and again the higher dose 8-OH-DPAT (0.4 mg/kg).

Table 1. Sexual behavior parameters (Means ± SEM) in male rats (n=20) tested till ejaculation. Five weekly tests, with 8-OH-DPAT or saline treatment 30 min prior to testing (after: [7])

	Test 1 saline	Test 2 DPAT 0 2 mg/kg	Test 3 DPAT 0 4 mg/kg	Test 4 saline	Test 5 DPAT 0 4 mg/kg	Statistics (1-way anova) F(4,76), p LSD(5%)
Intromissions						
Latency (sec)	76 ± 24	29 ± 10	7 ± 1	15 ± 2	12 ± 4	6 05, <0 001 27 0
Number	12 7 ± 6	2 4 ± 6	1 6 ± 4	14 0 ± 1 1	1 8 ± 3	7 54, <0 001 1 5
Ejaculations						
Latency (sec)	505 ± 52	123 ± 47	36 ± 13	289 ± 28	39 ± 9	37 0, <0 0001 7 4
"Premature" ejaculation*	0% (n=0)	45% (n=9)	55% (n=11)	0% (n=0)	50% (n=10)	
Ejaculate						
intravaginal	16	15	10	19	14	
extravaginal	1	1	7	1	5	
combined	2	1	2	0	0	
not found	1	3	1	0	1	

* Number of males ejaculating at first or second intromission

Results

The main findings (see Table 1) were that latency to ejaculation was significantly shorter with 8-OH-DPAT. Mean number of intromissions prior to ejaculation (ITE) and latency to first intromission (IL) decreased significantly with 8-OH-DPAT

treatment. Although lowest intromission frequencies (IF) were found with the higher dose, this was not significantly different from the lower dose of 8-OH-DPAT. "Premature" ejaculations were never observed following saline injection (tests 1 and 4). With the low dose of 8-OH-DPAT one male ejaculated during the first, and 8 during the second intromission. With the higher dose (tests 3 and 5), 11 and 10 males, respectively, ejaculated during the first or second intromission.

The location of the semen was usually in the vagina. However, with the higher dose 8-OH-DPAT (tests 3 and 5) 7 and 5 animals, respectively, ejaculated extravaginally. Surprisingly, this was also observed in one male in test 1 and one other male in test 4 (saline treatment).

The quality of the ejaculate, as judged by microscopic inspection revealed no systematic differences between the different tests. Live spermatozoa were always found.

Thus, 8-OH-DPAT induced a high percentage (45-55%) of males to ejaculate "prematurely", i.e. at the first or second intromission. Latency to ejaculation decreased. With the higher dose 8-OH-DPAT (0.4 mg/kg) 25-35% of the males ejaculated extravaginally.

Experiment 3: Is testosterone required for the effects of 8-OH-DPAT on male rat sexual behavior?

In *female* rats, we had found that 8-OH-DPAT increased the frequencies of mounting (MF) only when the animals recieved a longterm treatment with testosterone (T) [7]. Ahlenius *et al.* reported a significant stimulation in *male* rat sexual behavior (increase in MF and IF) at about 5 weeks after castration and suggested that 8-OH-DPAT did not require T to stimulate sexual behavior [11]. The present experiment was carried out to address the question whether or not T was required for 8-OH-DPAT to affect the copulatory behavior of castrated male rats.

Method

Twelve heterosexually experienced male rats were pair-tested with an estrous female twice weekly for 25 weeks and once weekly during a final 7 weeks. After week 2, the males were castrated. Following postcastration week 18, a T-filled Silastic capsule (inner diameter 1.5 mm, outer diameter 2.1 mm, length 5 mm) was implanted SC in the neck. Blood was collected (from the orbital plexus) in post-castration weeks 19, 23, 46 and 52. Serum T levels were estimated by radioimmunoassay, without chromatography, using the prevailing method in our laboratory [18]. The intraassay and interassay coefficients of variation were 3 and 5%, respectively.

Results

For detailed presentation and statistical analyses of the various data, refer to Haensel *et al.* [8]. Male rats displayed a relatively high ejaculatory frequency (EF) for several weeks after castration (see Figure 2). A low EF was found during post-

castration week 6. The effects of 8-OH-DPAT, in doses of 0.2 and 0.4 mg/kg body weight, were studied during weeks 8-12.

For weeks 1-6 after castration, one-way ANOVA revealed a significant decrease in the frequency of mounts (MF; $p<0.04$), intromissions (IF; $p<0.001$) and ejaculations (EF; $p<0.001$), and a significant increase in the latency to first mount (ML; $p<0.001$), to first intromission (IL; $p<0.001$) and to first ejaculation (EL; $p<0.001$) compared to the results obtained before the rats were castrated.

8-OH-DPAT moderately stimulated these parameters of sexual behavior (compared to saline tests) 2-3 months after castration. The lower dose of 8-OH-DPAT significantly reduced the number of intromissions before first ejaculation (ITE; $p<0.01$) and EL ($p=0.02$). MF and IF showed a non-significant decrease ($p=0.08$). The higher dose of 8-OH-DPAT induced a significant decrease in IL ($p<0.04$) and EL ($p<0.01$), and also in ITE ($p<0.01$). There was a non-significant ($p=0.06$) stimulatory effect on EF and a non-significant ($p=0.06$) decrease in EL.

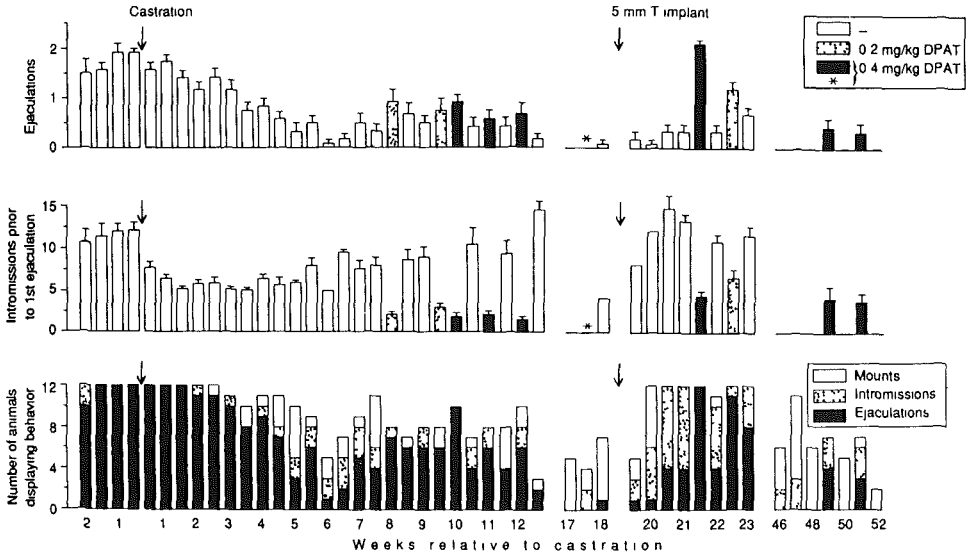

Figure 2 Three parameters (mean ± SEM) of sexual behavior of male Wistar rats (n=12) before and after castration Animals were tested with an estrous female (15 min, twice weekly up to week 23 after castration, once weekly for the final 7 weeks) The behavioral effects of 0 2 and 0 4 mg/kg were studied. A 5 mm Silastic testosterone-filled tube, implanted in postcastration week 19, resulted in subnormal serum testosterone levels, ranging from 4 6 nmol/l 20 weeks after castration to 0 6 nmol/l after 52 weeks From week 7 onwards animals were injected with saline or 8-OH-DPAT 30 min before testing (after [8])

In weeks 17 and 18 after castration, the higher dose 8-OH-DPAT no longer affected male sexual behaviors. A small T-filled Silastic capsule was then implanted, resulting in serum T levels of 4.6 ± 0.4 nmol/l (mean ± SEM). The levels are lower than those of normal male rats [19]. Under these conditions, clearcut effects of 8-OH-

DPAT compared to saline were found. There was a significant increase in EF ($p<0.001$), a decrease in ITE ($p<0.005$), and a decrease in IL ($p<0.05$) and EL ($p<0.001$). Serum T levels 4 weeks after capsule implantation were 4.1 ± 0.4 nmol/l.

After 5 months without behavioral tests, T levels ranged from 0.9 ± 0.1 nmol/l (postcastration week 46) to 0.6 ± 0.1 nmol/l (week 52). 8-OH-DPAT (0.4 mg/kg), compared to saline, significantly increased the IF ($p<0.03$) and EF ($p<0.05$) and decreased the IL ($p<0.05$) and EL ($p<0.07$).

Therefore, in the absence of testosterone between 8-12 weeks after castration, 8-OH-DPAT marginally increases the ejaculation frequency of male rats. Major effects of 8-OH-DPAT on sexual behavior, i.e. increase in ejaculation frequency, decrease in ejaculation latency and in intromissions to first ejaculation, in castrated male rats tested 17-52 weeks after castration appeared to require circulating testosterone. Levels as low as 0.6 nmol/l were sufficient.

Experiment 4: Flesinoxan and sexual behavior of adult male rats neonatally treated with the aromatase inhibitor ATD.

Neonatal administration of an aromatase inhibitor, 1,4,6-androstatriene-3,17-dione (ATD; blocks conversion of endogenous testosterone to estradiol) impairs the *de*feminization and masculinization of the developing male rat [20, 21]. Such ATD-males showed markedly reduced ejaculation frequencies when pair-tested with an estrous female [6, 20]. There also appeared to be a nocturnal rhythm: early in the dark phase few or no ejaculations occurred, late in the dark phase higher ejaculation frequencies were found [22]. It was earlier reported that 8-OH-DPAT increased ejaculation frequencies in ATD-males [6].

In this experiment the effects of flesinoxan, also a 5-HT_{1A}agonist [9, 23] on male sexual behavior of ATD-males and controls were studied.

Method

Within 3 h after birth male pups received SC in the neck under hypothermic anesthesia a Silastic implant (inner diameter 1.5 mm, outer diameter 2.1 mm, effective length 5 mm) filled with ATD ($n=11$) or an empty implant (controls; $n=12$). At 21 days of age, the implants were removed and the animals were weaned. The male rats were used in earlier behavioral experiments [24].

In the six weekly pair-tests (early in the dark phase) the rats received saline, saline, 0.3 mg/kg flesinoxan, saline, 1.0 mg/kg flesinoxan and saline, respectively. The drug or vehicle was administered IP, in a volume of 2 ml/kg.

Results

For ejaculation frequencies (see Figure 3), two-way ANOVA indicated a significant effect of tests [$F(5,105)=9.90$, $p<0.001$, $LSD(5\%)=0.36$], of groups [$F(1,21)=5.12$, $p=0.034$, $LSD(5\%)=0.52$], and no significant group x test interaction [$F(5,105)=0.34$]. Futhermore, flesinoxan (0.3 and 1.0 mg/kg) significantly increased the number

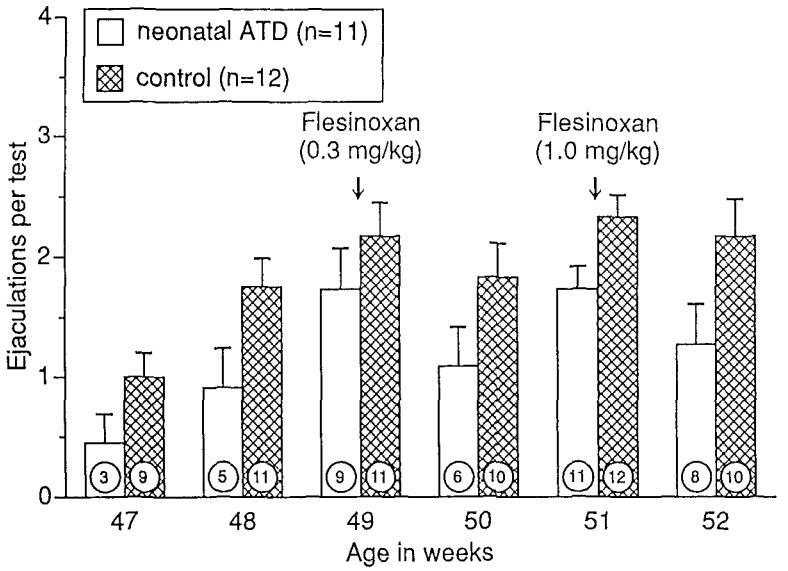

Figure 3. Mean (± SEM) ejaculation frequency of male Wistar rats, neonatally treated with ATD vs. control treatment. Animals were tested with an estrous female (15 min; once weekly) before and after 0.3 and 1.0 mg/kg flesinoxan administration (IP, 30 min before testing). Also indicated is the number of animals per test that ejaculated at least once.

of animals ejaculating in both ATD-males and controls. In the saline tests fewer ATD-males ejaculated than controls.

Frequencies of intromissions, latencies to mounting, to intromission and to first ejaculation (900 sec for non-ejaculators) were not significantly affected by flesinoxan treatment.

In summary, flesinoxan treatment increased ejaculation frequencies in male rats (ATD-males as well as controls). This 5-HT_{1A} agonist, however, is different from 8-OH-DPAT: it did not decrease the number of intromissions prior to ejaculation. With 0.3 or 1.0 mg/kg flesinoxan, no "premature" ejaculations were seen as in Experiment 2.

HUMAN STUDY

Experiment 5: Clomipramine and sexual functioning in sexually dysfunctional and functional men.

Several reports have indicated effective treatment of premature ejaculation with the use of the tricyclic antidepressant and serotonin reuptake inhibitor clomipramine [25-29]. The mechanism through which this drug exerts its effect on ejaculation latency is still to be elucidated.

Since prospective, double-blind, placebo controlled, crossover designed studies on patients and control men are lacking, we initiated and carried out such a study. Here, we present the first preliminary results.

Method

The experimental group consisted of 14 men, 8 with premature ejaculation (PE) and 6 with both PE and erectile dysfunction (PE/ED; inability to achieve or maintain an erection sufficient for sexual intercourse or masturbation). The patients fulfilled the following criteria: 1. age 18 years or more; 2. heterosexual; 3. duration of sexual dysfunction for at least 6 months; 4. premature ejaculation during coitus (or masturbation), defined by self-reported inability to control ejaculation (DSM-IV definition); 5. willing to attempt intercourse or masturbation at least 1 time/week; 6. have the consent of possible sexual partner; 7. no concomitant disease, former surgery or the use of drugs known to affect sexual functioning. A group of 8 healthy, sexually functional volunteers was included; these men indicated no sexual problems.

The experiment was a double-blind, complete crossover design. The study was comprised of two 3-week blocks, clomipramine and placebo. About half of the men started with clomipramine, about half started with placebo (order unknown to both subjects and investigators). Subjects were asked to take the drug (25 mg clomipramine or placebo) between 12-24 hr before anticipated sexual activity (coitus or masturbation), not more than twice a week.

Psychophysiological measurements of erectile response and sexual arousal were taken in the laboratory at the beginning, after 3 and after 6 weeks. During the drug phase subjects were asked to take a capsule 12-24 hr before the planned visit to the lab. In the laboratory the subjects were exposed to two erotic video's (EV) with and

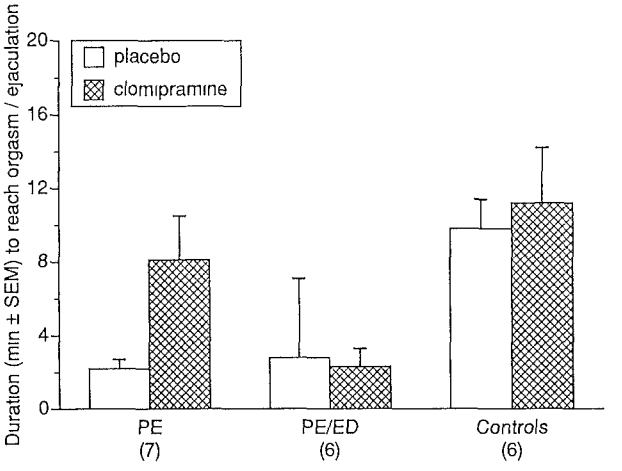

Figure 4. Mean (± SEM) estimated duration in minutes to reach orgasm/ejaculation with sexual activity, when clomipramine (25 mg) or placebo was taken 12-24 hr earlier (double-blind, crossover design). PE (n=7): men with premature ejaculation. PE/ED (n=6): men with both PE and erectile dysfunction. Contr (n=6): volunteers without sexual dysfunction.

without concomitant vibrotactile stimulation (VIB) to the penis [30-32]. Measurements were taken with a Barlow gauge and erectiometer [31, 33, 34]. During these lab visits questionnaires were also filled out about personal, medical and sexual history, and current sexual functioning. At home, short daily logs for sexual activities and feelings of "well-being" were filled out and mailed once a week to the investigators.

Table 2. Some questionnaire (top 4 items) and laboratory data (mean ± SD) during clomipramine and placebo treatment of men with premature ejaculation (PE), PE and erectile dysfunction (PE/ED) and men without sexual difficulties (Contr).

Item & Description	Group	N	Clomipramine	Placebo	Statistics 2-way ANOVA
Judgement of current sex life	PE	8	5.0 ± 1.5	3.8 ± .7	groups: p=.002
1= very bad	PE/ED	6	3.3 ± 1.5	3.5 ± .5	drug: ns
7= excellent	Contr	7	5.3 ± .8	5.3 ± .5	gr x dr: ns
Orgasm sooner than wanted?	PE	8	4.0 ± 2.3	1.1 ± .4	group: p<.001
1= always	PE/ED	6	1.8 ± 1.3	1.8 ± 2.0	drug: p=.025
7= never	Contr	7	5.6 ± 1.7	5.7 ± 1.3	gr x dr: p=.004
With coital intromission: estimated time till orgasm/ejaculation	PE	6	2.8 ± 1.5	1.7 ± .8	group: p<.001
1: < 1 min	PE/ED	5	1.2 ± .4	1.2 ± .4	drug: ns
3: 4-6 min	Contr	5	3.9 ± 1.1	3.8 ± .4	gr x dr: p=.09
5: 11-15 min					
With coital intromission: # of pelvic thrusts till orgasm/ejaculation	PE	6	4.0 ± .0	3.3 ± 1.2	group: p<.001
1: < 5 3: 11-20	PE/ED	5	1.8 ± .8	1.5 ± .8	drug: ns
2: 6-10 4: > 20	Contr	5	3.7 ± .8	4.0 ± .0	gr x dr: ns
During Erotic Video without Vibration: how sexually aroused?					
1: not at all	PE	8	5.9 ± .8	5.6 ± .7	group: p=.085
4: moderate	PE/ED	6	5.3 ± 1.6	5.8 ± 1.2	drug: ns
7: very strong	Contr	8	4.8 ± .7	4.9 ± .6	gr x dr: ns
During Erotic Video without Vibration: how close to ejaculation?					
1: not at all	PE	8	1.9 ± 1.6	2.8 ± 1.9	group: ns
4: moderate	PE/ED	6	3.0 ± 1.7	2.8 ± 2.2	drug: ns
7: very close	Contr	8	1.6 ± 1.1	1.5 ± .8	gr x dr: ns
During Erotic Video with Vibration: how sexually aroused?					
1: not at all	PE	8	6.2 ± 1.2	6.6 ± .7	group: ns
4: moderate	PE/ED	6	5.7 ± 1.4	6.2 ± 1.2	drug: p=.048
7: very strong	Contr	8	5.5 ± 1.2	6.2 ± .7	gr x dr: ns
During Erotic Video with Vibration: how close to ejaculation?					
1: not at all	PE	8	4.5 ± 2.3	2.8 ± 1.8	group: ns
4: moderate	PE/ED	6	5.5 ± 1.6	4.8 ± 2.7	drug: p=.037
7: very close	Contr	8	3.1 ± 2.0	2.9 ± 2.0	gr x dr: ns

Results

Preliminary analysis of the data revealed that clomipramine significantly increased the duration to reach orgasm/ejaculation with sexual activity (coitus or masturbation) in men with PE (from about 2 to 8 min, see Figure 4). There was a non significant increase in controls, and no effect at all in men with PE/ED.

The "positive" effects of clomipramine in men with PE was further found in some other parameters (see Table 2): improved rating of current sex life and the decrease in the occurrence of orgasm sooner than desired. No dramatic effects were found in the psychophysiological data collected in the laboratory.

In summary: from the present study it seems evident that the acute use of clomipramine (25 mg), taken 12-24 before sexual activity, is very effective in increasing ejaculatory latency in men with premature ejaculation. Why there is no such effect in men with both erectile dysfunction and premature ejaculation, remains to be elucidated.

General Discussion

The finding that 8-OH-DPAT increased ejaculation frequencies in middle-aged rats is in line with many other studies using younger rats [11, 13]. The finding that 8-OH-DPAT in longterm castrated rats only increased ejaculatory activity when some testosterone was (still) present, differs from earlier studies of Ahlenius *et al.* [11]. The latter investigators reported that 8-OH-DPAT could completely restore sexual behavior in male rats that had been castrated 1 month earlier. As we have proposed earlier [8], we believe that Ahlenius and co-workers should have waited longer after castration before testing the possible "stimulatory" properties of 8-OH-DPAT.

It is interesting to note that flesinoxan, also a 5-HT_{1A} receptor agonist, seems to act differently from 8-OH-DPAT. The latter compound increases EF, but concomitantly decreases IF and thus has a strong tendency to render male rats "premature" ejaculators. Flesinoxan also increases EF but it does not significantly affect other sexual behaviors (Exp. 4 and [35]).

The view of 8-OH-DPAT as a drug that *stimulates* or *facilitates* male rat sexual behavior is widely accepted. This interpretation depends, however, on how one looks upon the effects of the drug. It clearly increases ejaculation frequency within a set testing period, but at the same time it causes male rats to display abnormal sex behavior: only a few mounts and intromissions, and quite regularly, depending on the dose [12], ejaculation with the first or second intromission (Exp. 2). Furthermore, quite often such ejaculation behavior results in an abnormal deposition of the ejaculate, suggesting that proper penile intromission has not occurred (Exp. 2). Compared to 8-OH-DPAT, flesinoxan seems to be really a prosexual drug: it increases ejaculation frequency in the presence of normal mount and intromission frequencies. From a clinical point of view, it might be preferable to test flesinoxan in men with erectile dysfunction and low libido than 8-OH-DPAT. The latter compound, however, might be effective in men with an inability to ejaculate and experience orgasm.

The clomipramine data of the present study appear promising. In men with pure premature ejaculation, i.e. without erectile dysfunction, the use of 25 mg, 12-24 hr before anticipated sexual activity, was effective in increasing ejaculation latency, yet

had few side-effects. There were, however, no major effects of clomipramine based on psychophysiological measurements taken in the laboratory. Future research might address this lack of effect.

We have recently obtained promising results in men with PE in prescribing clomipramine chronically in a low dose of 10 mg/day. However, we would like to emphasize that a lifelong treatment with clomipramine may not be the ideal therapy in men with PE. Ideally clomipramine should be used on a short-term basis and be accompanied by psychotherapy or counseling. Also self-therapy with clomipramine might be advocated for men with PE and their partner [e.g. 36].

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Discussion - SEROTONERGIC DRUGS AND MASCULINE SEXUAL BEHAVIOR IN LABORATORY RATS AND MEN

J.R. Heiman

I just want to ask you a question about the PE-dependent variable. In the increase in latency, did you group together the masturbation and the partner-related experience? And, on the partner-related experience, did you get any collateral reporting?

A.K. Slob

In the group of men with premature ejaculation there were six that were having a partner in both periods and there was one who had no partner, but I took his estimated time to reach orgasm through masturbation. So it is estimation of duration of coitus and if there is no partner available it is masturbation duration.

K. Demyttenaere

I would be cautious to call clomipramine a selective serotonin reuptake inhibitor because I think it is as well interfering with the noradrenergic system and its metabolite desmethylclomipramine is even more potent in the noradrenergic system than in the serotonergic system. On the other hand, with the use of clomipramine as an antidepressant at doses of 150 mg one of the most under-reported side effects on the sexual behaviour is painful ejaculation. Do you hear about painful ejaculation in these patients on these lower doses?

A.K. Slob

No, absolutely not. Nowadays many patients with premature ejaculation are treated chronically with a very low dose of clomipramine, 10 mg per day, and there are a number of men very enthusiastic about this. There are no side effects and they say it works perfectly.

G. Wagner

I think there is a considerable difference when you say 12 to 24 hours. Could

you separate that in any way or was it so that the same man was running 12 hours ahead in each occasion?

A.K. Slob

It is not so easy as we thought it would be. Sometimes in the morning they would know that they would make love later that day or in the case of other couples they could just talk about it and say let us do it tomorrow and so he would take the drug late at night when they would go to sleep, and I cannot discriminate.

G. Wagner

Even if you have a prediction of what is going to happen, this may not happen and you may have the occasion on the next day. Would there be a cumulative effect included in the studies as well?.

A.K. Slob

No, they were asked to take the drug only twice a week, not more than that. So if they had taken the drug and there was no sexual activity, too bad. They had to wait another two days.

A.J. Riley

That is interesting. We have used clomipramine now for many years in the treatment of premature ejaculation. At one time we gave it on a repeat dosing basis, we now give it on PRN basis, one hour before they want an effect. And it seems to be just as effective then as giving it 12 hours before. I am somewhat hesitant about giving a drug 12 hours before anticipated sex, because in that case there would be a lot of drug taken unnecessarily because sex does not always materialize even if you anticipate it 12 hours in advance.

Another point I would take a slight issue about is that you said that chlomipramine is a treatment for premature ejaculation, I do not think it is a treatment for it, I think it delays ejaculation. The reason why I think so is that we are in the process of analyzing some data on premature ejaculators treated both behaviourally and pharmacologically and of those that were treated pharmacologically, even when

used in combination with behaviour therapy, 75% relapsed within 12 months. I regard treatment as something which affects a long term beneficial effect.

A.K. Slob

I agree.

W. Everaerd

I am just curious about the relationship between the effects of these drugs and time perception. Are there any data on time perception?

A.K. Slob

This is a good question. I do not know. The only thing you should keep in mind is that it was administered in a double-blind manner so no one knew what was happening. And it is also that the men were grouped not on the basis of their performance, they were grouped on the basis of whether or not they would also report erectile difficulties. So, there is no bias in the grouping of the two patient groups.

J. Bancroft

I would like to comment a bit on the differences between 8-OH-DPAT and flesinoxan. You said that both are 5-HT_{1A} agonists. Flesinoxan looks like a very interesting drug, it has quite powerful neuroendocrine effects and I wonder if you could say whether it was different from the other drug in that respect. Am I right in thinking that 8-OH-DPAT is neurotoxic and that would rule out its use in humans? Also, why do you say from your data that flesinoxan might be a drug used for low sexual desire? Is that based in the increase on ejaculation frequency, and is that an appropriate model for sexual desire?

A.K. Slob

That is a good point but if you want to test it you have to take into account that men with erection problems usually also report low sexual desire.

J. Bancroft

In the rat, would you be able to demonstrate the effect on appetitive behaviours using tests such as those involving working for gaining access to the females?

A.K. Slob

We have not done that. But we should do that, I agree.

M. Baum

We (Paredes et al. Psychopharmacol. 114: 591, 1994) studied the effects of 8-OH-DPAT in male ferrets and we found no effects on the appetitive performance. We actually found an inhibitory effect of 8-OH-DPAT on the male ferrets' neck grip mounting patterns. But I might add that the ferret is very different from the multiple mount intromission model that both characterize the rat and the rhesus monkey. This raises the question of whether there may be some fundamental differences in the underlying neurobiology, in the regulatory systems of mating patterns in species which may lead to very different outcomes in terms of the actions of these drugs.

J.T. Clark

I have done a little work with RDS 127, which also has 5-HT_{1A} activity, and in the intact male rat we do not see any effect on motivation, as measured as mounts after general desensitization or mount and intromission latency or things like that, whereas we do see a potent decrease in intromission frequency. However in castrated rats we can induce mounting behaviour 30 days after castration but not 60 days after castration. With RDS 127 we saw emission of a copulatory plug irrespective of whether there was a female there or not, and usually within six minutes after injecting the drug. So if you are waiting until 30 minutes is it possible that the rat has already deposited a number of plugs around the cage prior to introducing the female. Have you ever looked at that?

A.K. Slob

I do not believe this may have happened because, even if we have not specifically studied that, we did a careful search of the cage after the animals were

removed and we never found two or three plugs or more. In the case that you mentioned we should have found plugs in the cage because we inject them before the test and the male is left in the cage and after 30 minutes the oestrous female is introduced into the cage.

J.T. Clark

But there is a complicating variable which is that if the animal deposited two or three plugs then he would still go on and do ejaculatory behaviour but he may not have a plug. We did some of that work with RDS 127 as well so that your failure to find a plug in the vagina may have been due to the fact that it had been on the cage floor.

A.K. Slob

It is a possibility, but we have never found a plug in the vagina and a full-blown plug in the cage so I cannot really deny what you are saying but I do not believe it.

S.M. Pomerantz

I have a question concerning the use of these 5-HT_{1A} agonists in humans. An anxiolytic compound that is currently being widely prescribed is buspirone. It has very potent 5-HT_{1A} activity. I was wondering if anybody is aware of whether it has been reported to have any sexual side effects.

M. Murphy

Yes. They were in fact reviewed in the book that Riley edited. Buspirone has stimulatory effects on human subjects.

D. Vanderschueren

I have a technical question concerning the experiments with the aromatase inhibitor ATD in male rats. How long is the period of administration necessary to impair masculinization? And, do you also impair growth or it is just specifically sexual behaviour that you impair with this aromatase inhibitor?

A.K. Slob

One has to start giving this right after birth. In our case three hours following birth. We gave them a silastic implant containing ATD. Ideally one leaves it in till about day 10, but you can also leave it till day 21 when the animals are weaned and that is our procedure now. They grow up and they look like normal male rats, they have testes. We are discovering now that there might be differences in their endogenous testosterone levels but it is in terms of rhythmicity that we have discovered that these animals are quite different from normal males. But the levels are still well within the limits of what normal rats have, and which are necessary for normal copulatory behaviour. These males are capable of showing absolutely normal male sexual behaviour, but it depends on the time of the night you test them. If you do it early in the night, they switch from female-like behaviours to male-like behaviours but if you test them towards daylight, in the end of the night, they are much more like normal males, they are only interested in oestrous females, they do not want to be mounted by males, etc. So it is very interesting.

J. Herbert

We have to consider the relationship between the effects of manipulating serotonin on sexual behaviour with those on other sorts of function and in particular on things like aggression. I was particularly interested in the results of Slob's work on ejaculation and I tried to put them together with Pfaus' work on pacing. Is it possible that one of the effects of changing serotonin in a male rat is that he is no longer sensitive to the pacing effects of the female and therefore ejaculates more rapidly because he is showing impulse discontrol?

J.G. Pfaus

It is an interesting question. Certainly we have known for a long time that when females pace the males, part of the reason why they are doing that, at least part of the end-points of why they are doing that, is to make the male ejaculate faster, that is, with fewer intromissions. If 8-OH-DPAT is doing that perhaps it could be acting on a system that the pacing itself is acting on normally. Male rats treated with 8-OH-DPAT look very surprised. I hate to be anthropomorphic about it, but when it happens on number 2 they

really do not have the look of a rat who has expected to ejaculate: their arms fly about, they really do look quite surprised. And it is interesting as well when ejaculation comes on number 2 we have a situation where there are fewer intravaginal plugs. On number 2 the female and the male are still getting this together and she is only beginning to pace him and he has not probably aimed his erection properly. You really have a disruption of the ongoing pattern that has not really got off the ground yet, much less reached some degree of fulfilment.

A.K. Slob

The behaviour of the males is also quite different in terms of locomotor behaviour. They can lie down, specially with a higher dose, and what they do is that they mount, intromit and ejaculate and they lie down again.

S.M. Pomerantz

In the rat you are able to see the $5HT_{1A}$ effects at both low and high doses. I think that is important because in monkeys we do not see that. Rather we see a biphasic effect in which low doses of $5\text{-}HT_{1A}$ agonists facilitate ejaculation and high doses interfere with copulation and ejaculation. The point I want to make is that when rats are laying down then the serotonin syndrome is being expressed. This postsynaptic $5\text{-}HT_{1A}$ effect is clearly very different from the purely autoreceptor effect being elicited at lower doses. In the monkeys we only see the premature ejaculation at the lower doses.

M. Baum

Has anyone looked at a situation where the female has complete control over the access to the male?

J.G. Pfaus

Scott Mendelson did these studies in the bilevel chamber. The male simply stayed at the bottom level, and the females would come down and run away repeatedly and sometimes they run behind the male, and mount him. The males would eventually get up and ejaculate and then lie back down again.

A.K. Slob

What we tried to find out was whether male rats treated with 8-OH-DPAT would be more attractive to female rats because they have few intromissions and, if I remember the data correctly, there was not much of a preference for the 8-OH-DPAT treated males versus vehicle-treated males.