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Effects of the 5-HT_{1A} Agonist, 8-OH-DPAT, on Sexual Behaviors of the Proestrous Rat

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UPHOUSE, L., S. MONTANEZ, R. RICHARDS-HILL, M. CALDAROLA-PASTUSZKA AND M. DROGE. *Effects of the 5-HT_{1A} agonist, 8-OH-DPAT, on sexual behaviors of the proestrous rat.* PHARMACOL BIOCHEM BEHAV **39**(3) 635–640, 1991.—The effects of the 5-HT_{1A} agonist, 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), were examined in intact, proestrous rats. Although this compound has been reported to inhibit sexual receptivity of hormonally primed, ovariectomized rats, this is the first report of its effect in intact females. After intraperitoneal treatment with 8-OH-DPAT (0.01 to 0.25 mg/kg), there was a dose-dependent suppression of lordosis behavior. The inhibition occurred within 10–15 min after the higher doses and lasted at least an hour after treatment. When females were treated with 1 mg/kg trifluoromethylphenyl piperazine (TFMPP) 30 min prior to treatment with 0.1 mg/kg 8-OH-DPAT, females recovered more rapidly from the inhibitory effects of 8-OH-DPAT. After bilateral, intrahypothalamic infusion of 50 to 1000 ng 8-OH-DPAT, inhibition of sexual behavior resembled that seen following systemic treatment. Cannula locations in the ventromedial hypothalamus, but not the posterior hypothalamus, produced rapid inhibition of lordosis behavior. Both the frequency and the quality of lordosis behavior were reduced within 5 to 10 min after bilateral infusion of 200 to 1000 ng (but not 50 ng) 8-OH-DPAT, and females often successfully avoided attempted mounts by the male. These results suggest that activation of ventromedial hypothalamic 5-HT_{1A} receptors reduces lordosis behavior.

Serotonin 5-HT_{1A} Lordosis Sexual behavior Intact females Ventromedial hypothalamus

ALTHOUGH the serotonin (5-HT) system is generally agreed to play an important role in female reproduction, there has not always been a consensus about the direction and/or mechanism of serotonin's contribution. Much of the early evidence linking serotonin to reproductive behavior relied upon the use of pharmacological compounds [for review, see (17)] with activity at more than one of the serotonin receptor subtypes. At least three distinct classes (5-HT_1, 5-HT_2 and 5-HT_3) of 5-HT receptors are now recognized, and within each class, there is pharmacological, functional, and anatomical heterogeneity [for review, see (23)]. The introduction of pharmacological agents with more or less specificity for these receptor families and their subtypes has provided new tools for the study of 5-HT and female reproduction.

Based on studies with 8-hydroxy-2-(di-n-propylamino)tetralin, (8-OH-DPAT), a relatively specific 5-HT_{1A} agonist (9,21), it was suggested that activation of this receptor subtype inhibits lordosis behavior (1, 5, 15). In contrast, the use of 5-HT_2 antagonists (14,27) and the use of 5-HT_1 agonists with partial preference for the 5-HT_{1B} subtype (16) led to the suggestion that activation of 5-HT_2 or 5-HT_{1B} receptors facilitates female sexual behavior.

In addition to its postsynaptic location, 5-HT_{1A} receptors function as somal/dendritic autoreceptors in the raphe nuclei, especially the dorsal raphe (24,26). Activation of these 5-HT_{1A} autoreceptors reduces firing of raphe neurons (19,24). Unlike the somal/dendritic autoreceptors, terminal autoreceptors of 5-HT neurons appear to be of the 5-HT_{1B} and not the 5-HT_{1A} subtype (4,11).

The inhibition of sexual behavior by 8-OH-DPAT and the facilitation by 5-HT_{1B}-preferring agonists fit the traditional belief that the ventromedial nucleus of the hypothalamus is important in the control of female sexual behavior (22), and that an increase in 5-HT activity in the medial basal hypothalamus is inhibitory to female sexual behavior (7). However, the effective neural locations for 8-OH-DPAT's suppression of female sexual behavior have not been identified. Moreover, in all the studies in which the effects of 5-HT_{1A} agonists on female sexual behavior have been examined, the drugs have been tested in ovariectomized rats, primed with estradiol or with estradiol and progesterone. To our knowledge, there have been no reports of the effects of 5-HT_{1A} agonists on sexual behavior of intact female rats.

The following studies demonstrate that 8-OH-DPAT can inhibit lordosis behavior in intact female rats and that trifluoromethylphenyl piperazine (TFMPP), which has a 3 to 4 fold preference for the 5-HT_{1B} site relative to the 5-HT_{1A} site (20), can partially attenuate the effects of 8-OH-DPAT. Furthermore, we present evidence that infusion of 8-OH-DPAT into the ventromedial hypothalamus causes a rapid, dose-dependent suppression of lordosis behavior.

METHOD

Materials

Trifluoromethylphenyl piperazine (TFMPP) and 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) were purchased from Research Biochemicals Inc., (Natick, MA). Cranioplastic and

intracranial cannulae were purchased from Plastic Products Inc. (Roanoke, VA).

Animals and Housing Conditions

Adult, female rats (CDF-344) were bred in our laboratory from stock obtained from Charles River Laboratories (Kingston, NY). Rats were weaned into either metal hanging cages or polycarbonate shoebox cages at 21–25 days of age and were housed 3 or 4 per cage with like-sex littermates. The colony room was maintained at 72°F and 55% humidity on a 12-12 h light-dark cycle. Food and water were available ad lib. Beginning when the rats were 60 days of age, they were monitored daily for vaginal cyclicity for at least 2 complete estrous cycles as previously described (25). Only regularly cycling proestrous females were used in the study. Vaginal smears with nucleated cells, or primarily nucleated with a few cornified cells but an absence of leucocytes were judged as proestrous smears. The preceding smear history must also have predicted a proestrous state before the female was included in the study. In addition, sexual receptivity was confirmed by brief mating tests prior to the pharmacological treatments.

Injection Procedures

In the first three experiments, proestrous rats were initially tested for sexual receptivity within one hour after lights off. In the first experiment, after a maximum of 15 mounts by the male, the female was removed, injected with 8-OH-DPAT (0.01 to 0.25 mg/kg) or the saline vehicle and immediately replaced in the male's cage. Behavior was then monitored continuously for 60 additional min. In the second experiment, females were injected IP with saline or with 1.0, 2.5 or 5.0 mg/kg TFMPP after the pretest. In the third experiment, females showing sexual receptivity were injected IP with TFMPP (1.0 mg/kg) or with saline, 30 min prior to treatment with 8-OH-DPAT (0.1 mg/kg). In all three experiments, 8-OH-DPAT and TFMPP were dissolved in 0.9% saline and were administered IP in a volume of 0.1 ml/100 g body weight. In the first experiment, data were recorded in units of 5 mounts, and the data are presented as 5-mount intervals. In the remaining experiments, the data are grouped into equal temporal intervals throughout the testing session.

When females were used for intracerebral (IC) injections, they were anesthetized with 3.5 mg/kg Equithesin and were implanted bilaterally with 22-gauge stainless steel guide cannulae advanced stereotaxically into the ventromedial nucleus of the hypothalamus (VMN). Stereotaxic coordinates (AP 4.38; DV 7.8; ML 0.4) were derived from König and Klippel (12). Guide cannulae were secured with cranioplastic cement and anchored to the skull with 3 stainless steel screws. Stainless steel dummy cannulae (28 gauge) were placed in the guide cannulae at the time of surgery to prevent clogging.

Vaginal smears were monitored daily after surgery until the appearance of nucleated cells in the vaginal smears. At the time of vaginal smearing, the dummy cannulae were gently turned to facilitate their ease of removal at the time of infusion and to adapt the females to the type of handling and manipulation that occurred on the day of testing. On the day that females showed a proestrous smear, they were briefly pretested for sexual receptivity with a sexually experienced male. Testing took place 1–3 hours after lights off (1–4 p.m.). Receptive females had their dummy cannulae replaced with 28-gauge stainless steel internal cannulae (terminating 0.5 mm below the guide cannulae), attached by tubing (i.d. = 0.58 mm; o.d. = 0.96 mm) to a BAS (CMA/100) microinjector. The drug (50–1000 ng/site) or saline was infused in a volume of 0.5 μl, delivered at a rate of 0.25 μl/min. The complete infusion required 2 min. The sexual behavior of the females was tested within the specially designed CMA/120 containment system purchased from BAS.

Sexual Behavior

Following IP treatments, sexual receptivity was recorded as previously described (25) with females placed into the cage of a sexually experienced male. For each mount by the male, the presence or absence of a lordosis reflex by the female was recorded. Sexual receptivity was quantified as the lordosis to mount (L/M) ratio (number of lordosis responses by the female divided by the number of mounts by the male). Sexual behavior was monitored continuously for 60 min, the data were organized into 11 observation intervals including the preinjection testing, and the L/M ratios for each of the intervals were computed.

For the IC studies, testing took place in the BAS CMA/120 containment system. After a female had been fitted to the harness and the internal cannulae had been inserted, she was placed into the observation chamber. Each female was allowed to adjust to the chamber and harness for 15 min. The male (previously adapted to the containment system and the infusion apparatus) was then placed with the female. The female's behavior was recorded for 10 mounts. Infusion was then initiated and behavior continued to be recorded for an additional 30–35 min. Data were divided into 5 min intervals prior to, and after the initiation of the infusion. The L/M ratio and the quality score for each lordosis response for each 5 min interval were computed. Lordosis quality was scored similar to that described by Hardy and DeBold (10), except that a lordosis failure was given a score of 1.0 and a lordosis response with minimal arching of the back was given a score of 2.0. A normal lordosis reflex was scored as 3.0, and an exaggerated reflex was scored as 4.0.

Histological Procedures

Females with bilateral IC implants were injected with Equithesin (5 mg/kg) and were perfused intracardially with 0.9% saline followed by 10% buffered formalin. The brain was excised and placed in 10% buffered formalin for a minimum of 24 h. The brain was blocked and sectioned (100–300 μm) on a Lancer vibratome. Tissue sections were stained with cresyl violet, and cannula locations were verified according to König and Klippel (12).

Statistical Methods

Data were compared by two-way (treatment by testing interval) repeated measures ANOVA with subjects as the random factor and testing interval as the repeated factor. For post hoc comparisons, the Dunnett's test was used. An alpha level of 0.05 was required for rejection of the null hypothesis. The statistical reference was Zar (28).

RESULTS

Following IP treatment, 8-OH-DPAT produced a rapid, dose-dependent inhibition of sexual behavior (Fig. 1). In this experiment, the precise times after treatment were not recorded. Therefore, the data were grouped into testing intervals of 5 mounts. Repeated measures ANOVA indicated a significant effect of the testing interval, $F(10,240) = 21.33$, $p = 0.0001$. Throughout testing, there was a dose-dependent reduction of sexual behavior, but since all doses of 8-OH-DPAT produced

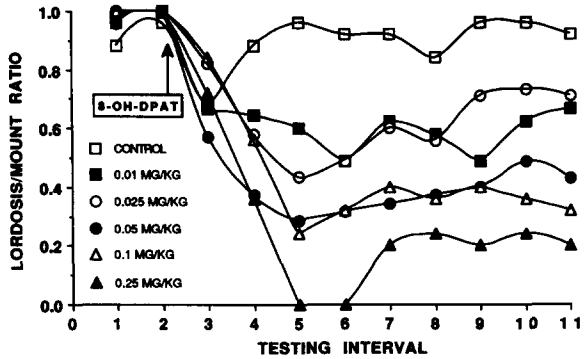

FIG. 1. Effect of 8-OH-DPAT on sexual behavior of proestrous rats. Intact proestrous rats were tested for sexual receptivity for 10 to 15 consecutive mounts (the first two intervals on the graph). The females were immediately injected IP with 8-OH-DPAT (0.01 to 0.25 mg/kg) or the saline vehicle and were retested for sexual behavior. Behavior was monitored for 60 min after 8-OH-DPAT. Data were grouped into intervals of 5 mounts. The figure shows the mean lordosis to mount (L/M) ratio for five to nine animals in each dose group. The SEM, typically less than 0.2, ranged from a low of 0.001 to a high of 0.245 and were omitted from the graph for easier viewing of the data. The figure indicates the L/M ratio during the two five-mount intervals prior to injection (1 and 2) and the nine five-mount intervals after injection (3 to 11).

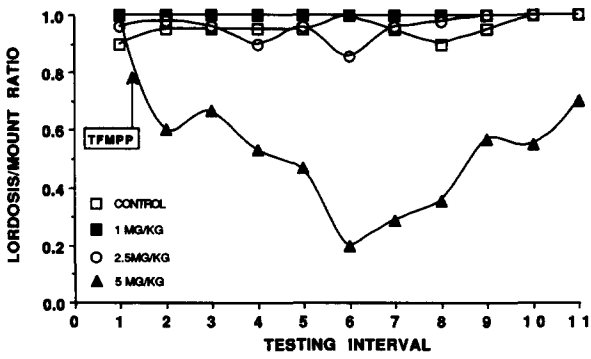

FIG. 2. Effects of TFMPP on sexual behavior of proestrous rats. Intact proestrous rats were tested for sexual receptivity and were then injected IP with TFMPP (1.0, 2.5 or 5.0 mg/kg). Behavior was monitored for 60 min after TFMPP and were grouped into equal temporal intervals throughout the testing period. The figure shows the mean lordosis to mount (L/M) ratio for 4 control rats and 6, 5, and 3 rats given 1.0, 2.5 and 5.0 mg/kg TFMPP respectively. SEM of the individual groups were ≤ 0.09.

some inhibition of lordosis behavior, there was no overall effect of dose. There was a significant dose by interval interaction, $F(50,240) = 2.24$, $p = 0.0001$, due to the accentuated dose response effect during the later testing intervals.

There was a tendency for higher doses of 8-OH-DPAT to produce inhibition earlier following treatment. This can be seen as a dose-dependent increase in the slope of the inhibition curve when the first 5 observation periods are examined. The higher doses of 8-OH-DPAT also produced a more prolonged suppression of sexual receptivity. By 30 to 60 min after injection (intervals 7 to 10), animals receiving 0.01 or 0.025 mg/kg 8-OH-DPAT were exhibiting L/M ratios between 0.6 and 0.8. In contrast, animals that received doses greater than or equal to 0.05 mg/kg showed L/M ratios lower than controls throughout the 60 min observation period (from interval 4 through interval 11, all $q \geq 2.44$, $p \leq 0.05$, Dunnett's test, $k = 5$).

The effects of 1.0 to 5.0 mg/kg of TFMPP on sexual behavior were examined prior to the use of this drug in combination with 8-OH-DPAT. As is evident from Fig. 2, neither 1.0 nor 2.5 mg/kg TFMPP had any effect on lordosis behavior, while 5.0 mg/kg TFMPP substantially reduced lordosis responding. Since the animals given 1.0 mg/kg TFMPP had no variation in their L/M ratios (L/M = 1.0 throughout the testing period), the statistical analysis was performed with this group excluded. Repeated measures ANOVA of the control, 2.5 mg/kg and 5.0 mg/kg groups showed a significant effect of treatment, $F(2,90) = 26.79$, $p = 0.0002$, testing interval, $F(10,90) = 2.25$, $p = 0.021$, and treatment by interval interaction, $F(20,90) = 2.71$, $p = 0.0007$. Each of these effects resulted from a transient suppression of the L/M ratio by 5.0 mg/kg TFMPP. No other group differed from the controls ($p > 0.05$).

Based on these results, a dose of 1.0 mg/kg TFMPP was chosen for study in combination with 0.1 mg/kg 8-OH-DPAT. As can be seen in Fig. 3, TFMPP failed to prevent the inhibitory effect of 8-OH-DPAT on lordosis behavior, but it did reduce the duration of the inhibition. As a result, the repeated measures ANOVA showed lordosis behavior to differ significantly over the time after treatment, $F(10,230) = 6.78$, $p = 0.0001$, and the treatment by testing interval was significant, $F(10,230) = 2.84$, $p = 0.0023$, but the main effect of treatment was not significant, $F(1,230) = 1.06$, $p > 0.05$. Animals given 8-OH-DPAT plus saline and those given 8-OH-DPAT plus TFMPP did not differ prior to interval 7, but at interval 7 and at every interval thereafter (except for interval 10), the L/M ratio of 8-OH-DPAT-plus TFMPP-treated animals was significantly higher than that of 8-OH-DPAT plus saline (Dunnett's test with $k = 2$, all $q \geq 2.21$, $p \leq 0.05$).

This apparent enhancement of recovery following TFMPP pretreatment was confirmed by multiple regression procedures of the intervals 1–5 and 6–11. Over the first 5 intervals of testing, the slopes for the two treatments were not different (respectively slopes for 8-OH-DPAT plus saline and for 8-OH-DPAT plus TFMPP were -7.6×10^{-2} and -7.9×10^{-2}, $p = 0.985$). In contrast, over the intervals of 6–10, the slopes were significantly different (respectively for 8-OH-DPAT plus saline and for 8-OH-DPAT plus TFMPP, slopes were 8.89×10^{-3} and 4.79×10^{-2}, $p \leq 0.0001$).

Figure 4 shows the effects of intracerebral application of 8-OH-DPAT into the ventromedial hypothalamus on lordosis behavior. There was a rapid and robust, dose-dependent decrease of lordosis behavior following 8-OH-DPAT treatment. Maximum inhibition of sexual behavior appeared to occur with the 200 ng bilateral infusions, so animals given 500 ng or 1000 ng 8-OH-DPAT were pooled for the analysis. Repeated measures ANOVA showed a significant effect of the dose, $F(4,77) = 8.4$, $p = 0.002$, and of the testing interval, $F(7,77) = 7.65$, $p = 0.0001$. The dose × testing interval was not significant. The effect of dose was evident in both the degree of inhibition and the latency to inhibition. Females infused with 50 ng 8-OH-DPAT showed evidence of declining lordosis behavior by 25 min, but at no time were these females significantly different from the controls (Dunnett's test with $k = 5$, $p > 0.05$). With 100 ng, a decreased L/M ratio occurred at 20 min, but animals given this dose were not significantly different from controls until 35 min. In contrast, females infused with 200 ng or higher amounts of 8-OH-DPAT showed a rapid onset of inhibition. L/M ratios were significantly different from controls by 15 min (for 200 ng) and by 10 min (for the highest dose group) and remained different from the controls throughout the testing interval (all comparisons

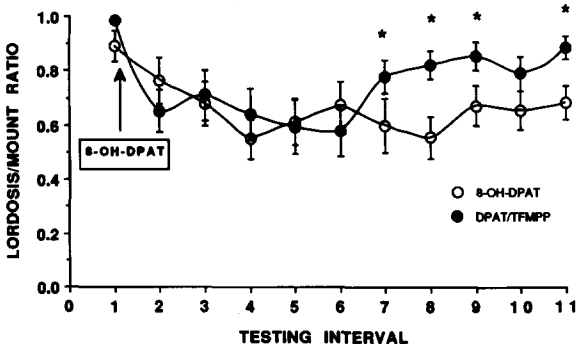

FIG. 3. Effects of pretreatment with TFMPP on the inhibition of lordosis behavior following 8-OH-DPAT. Intact proestrous rats were injected IP with 1 mg/kg TFMPP or saline. Thirty min later, the rats were pretested for sexual receptivity. After a minimum of 10 mounts by the male, the females were removed and injected IP with 0.1 mg/kg 8-OH-DPAT and behavior was monitored for 60 min as described for Fig. 2. The figure shows the mean ± SEM lordosis to mount (L/M) ratio for 11 females in each group. Asterisks indicate significant differences between groups within the same testing interval.

to control, $q \geq 2.51$, $p \leq 0.05$).

If a lordosis response did occur, its quality was also decreased by intrahypothalamic infusion of 8-OH-DPAT (Fig. 5). Repeated measures ANOVA showed a significant effect of the dose, $F(4,77) = 8.58$, $p = 0.002$, the testing interval, $F(7,77) = 15.52$, $p = 0.0001$, and the dose by interval interaction, $F(28,77) = 1.96$, $p = 0.033$. As for the L/M ratio, a significant decline in lordosis quality occurred earlier in the higher doses, but the quality of the lordosis behavior was generally reduced about 5 min prior to the reduction in the L/M ratio. Once lordosis quality was reduced, it remained suppressed during the remainder of the experiment. For the 100 ng dose, quality was first suppressed 20 min after initiation of the test. For the doses of 200 ng and higher, respectively, quality was first significantly suppressed at 10 min and at 5 min (all comparisons to control, Dunnett's with $k = 5$, $q \geq 2.51$, $p \leq 0.05$).

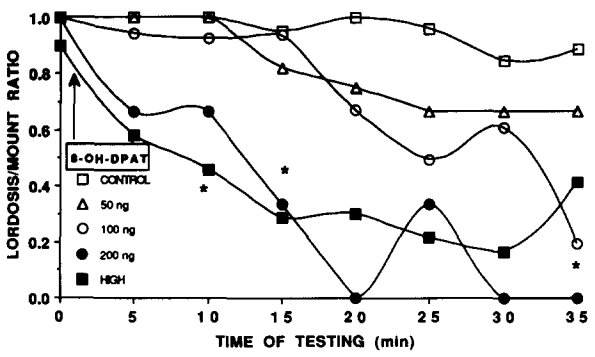

FIG. 4. Intracerebral effects of 8-OH-DPAT into the ventromedial hypothalamus on L/M ratios. The figure shows the mean L/M ratios for regularly cycling proestrous rats infused bilaterally into the ventromedial hypothalamus with saline or with 50 ng, 100 ng, 200 ng or a higher dose (500 or 1000 ng) of 8-OH-DPAT immediately following a 5 min pretest for sexual receptivity. Data were collected continuously for 35 min following infusion and the L/M ratio was computed for each 5 min interval. The figure shows the data for 4 saline-treated females and 3 females for each dose of 8-OH-DPAT. Asterisks indicate the first time at which groups differed from controls. After the asterisks, all other data for that group are significantly different from control. All animals represented in the figure had cannulae tips located within the ventromedial hypothalamus. The most dorsal location was the ventral tip of the dorsal ventral nucleus, and the most ventral location was the base of the ventromedial nucleus. The average SEM for the groups ranged from 0.029 to 0.168 and were omitted from the figure for ease of presentation.

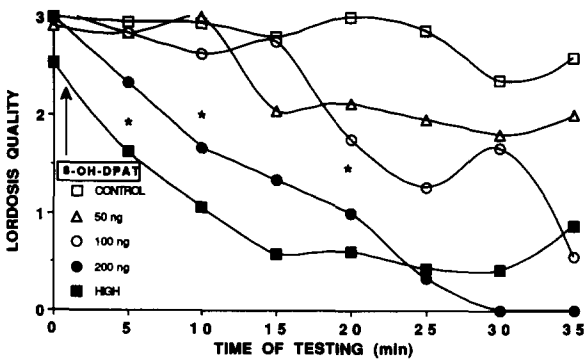

FIG. 5. Intracerebral effects of 8-OH-DPAT on lordosis quality. The figure shows the mean lordosis quality scores for the same animals indicated in Fig. 4. Regularly cycling proestrous rats were infused bilaterally with saline or with 50 ng, 100 ng, 200 ng or higher doses of 8-OH-DPAT immediately following a 5 min pretest for sexual receptivity. Data were collected continuously for 35 min after infusion and the lordosis quality score was computed for each 5 min interval. The figure shows the average quality score for the lordosis reflexes which did occur during the testing interval. Data are for 4 saline-treated females and 3 females for each dose of 8-OH-DPAT. The high dose (HIGH) includes one female treated bilaterally with 500 ng and two treated bilaterally with 1000 ng 8-OH-DPAT. Asterisks indicate the first time at which groups differed from controls. After the asterisks, all other data for that group are significantly different from control. The average SEM for the groups ranged from 0.101 to 0.545 and were excluded from the figure for ease of presentation.

Figure 6 shows the effect in two animals of 1000 ng of 8-OH-DPAT infused within the hypothalamus but outside the ventromedial hypothalamus. These two animals had cannulae located in the posterior hypothalamus. For these animals, the inhibition produced by 8-OH-DPAT was either transient (female 1653) or required a much longer time to develop (female 1713) than with the more medial infusions. Therefore, the rapid decrease in lordosis behavior following intrahypothalamic infusion of 8-OH-DPAT appeared to require placement of the cannulae within the ventromedial hypothalamus.

DISCUSSION

Previous studies with ovariectomized females have led to the suggestion that activation of 5-HT_{1A} receptors is incompatible with the expression of lordosis behavior. However, this is the first report in which sexual behavior of intact, regularly cycling rats has been studied following 8-OH-DPAT treatment. Since hormonal replacements given to ovariectomized rats do not replicate precisely the temporal pattern of hormonal events in the intact female, the inclusion of intact females in these observations is important. The results are in general agreement with the findings seen in hormonally primed ovariectomized rats (5,15), but intact females may have been more sensitive to the inhibitory effects of 8-OH-DPAT. The lowest dose (0.01 mg/kg) of 8-OH-DPAT administered systemically to intact females suppressed lordosis behavior, while this dose or an even higher dose (0.0625 mg/kg) were ineffective in ovariectomized rats (5,15). The control L/M ratio reported by Mendelson and Gorzalka (15) was relatively low (between 0.6 and 0.7), so it is possible that the higher L/M of our control intact females made the sup-

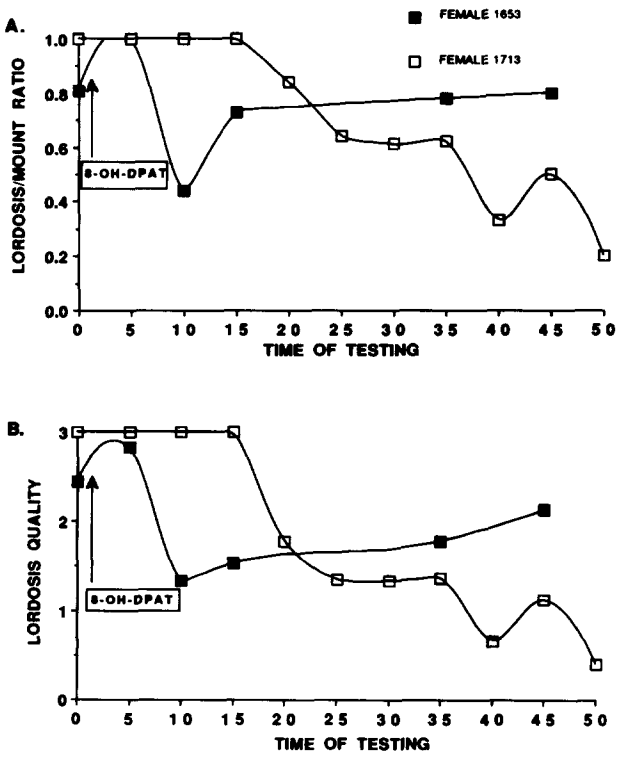

FIG. 6. Intracerebral effects of 8-OH-DPAT into the posterior hypothalamus. The figure shows the L/M (A) or lordosis quality score (B) of 2 female rats, infused bilaterally with 1000 ng 8-OH-DPAT into the posterior portion of the dorsal ventral nucleus [atlas levels 37 and 38 from König and Klippel, (12)]. 8-OH-DPAT was infused immediately after the pretest and the lordosis behavior of the females was monitored continuously for the duration indicated on the graph. The graph shows an extended testing period which spanned 40–50 min after infusion. The effects of 8-OH-DPAT in the more posterior hypothalamus produced either transient inhibition of lordosis behavior (female 1653) or inhibition that was relatively slow in developing (female 1751).

pression by low doses of 8-OH-DPAT easier to detect. However, control ovariectomized rats in the study by Fernandez-Guasti et al. (5) had L/M ratios as high as those in the current study, so this is not likely to be the only explanation for the increased sensitivity of the intact females. In addition to their effects on female sexual behavior, 5-HT_{1A} agonists have been shown to modulate a variety of CNS functions [e.g., temperature, anxiety, eating; (6, 8, 13)]. With a few exceptions (6), either males or ovariectomized females have been used to study the effects of 5-HT_{1A} agonists, so it is not known if this apparent increase in sensitivity extends to other behavioral effects of 5-HT_{1A} agonists.

Several investigators have suggested that 5-HT_{1A} and 5-HT_{1B}, or 5-HT_2, receptors interact in the control of lordosis behavior. Most 5-HT_{1B}-preferring agonists facilitate rather than inhibit sexual behavior of hormonally primed ovariectomized rats (16). Although TFMPP is not a selective 5-HT_{1B} agonist, it has a 3–4-fold greater potency at 5-HT_{1B} than at 5-HT_{1A} sites (20) and, in some cases, can antagonize the effects of 8-OH-DPAT (8). Therefore, it was anticipated that TFMPP would attenuate 8-OH-DPAT's reduction in lordosis behavior. Although the highest dose of TFMPP (5 mg/kg) actually decreased sexual behavior, it also produced symptoms of the 5-HT syndrome, primarily flattened posture, which has been associated with stimulation of postsynaptic 5-HT_{1A} sites (13). Therefore, it is unlikely that the inhibition following 5 mg/kg TFMPP reflects an exclusively 5-HT_{1B} effect. In fact, this dose of TFMPP was 500-fold greater than the effective 8-OH-DPAT dose for inhibition of lordosis behavior, while TFMPP has only a 3–4-fold preference for 5-HT_{1B} relative to 5-HT_{1A} sites. The decrease in sexual behavior after 5 mg/kg TFMPP may have resulted, therefore, from an effect of TFMPP on 5-HT_{1A} sites. The attenuated duration of 8-OH-DPAT-induced inhibition occurred at a dose of TFMPP which alone did not affect lordosis behavior, so the current results are consistent with the suggestion that activation of 5-HT_{1B} sites facilitates female sexual behavior.

Some investigators (2) have argued that lower doses of 8-OH-DPAT ($\leq$60 μg) administered systemically, preferentially activate somal/dendritic autoreceptors, while higher doses are required for postsynaptic activation. Attenuation of the effects of 8-OH-DPAT on hyperphagia (produced by relatively low doses of the 5-HT_{1A} agonist) following 5-HT depletion (3) are consistent with the suggestion that the hyperphagia results from activation of the somal/dendritic autoreceptors. In contrast, the 5-HT syndrome (which develops after higher doses of 8-OH-DPAT) is thought to require activation of postsynaptic 5-HT_{1A} sites (13). Lordosis behavior is inhibited at lower systemic doses of 8-OH-DPAT than are required to produce the serotonin-syndrome. It might be expected, therefore, that inhibition of sexual behavior involves somal/dendritic autoreceptors. However, the potent suppression of lordosis behavior following intrahypothalamic administration of 8-OH-DPAT suggests that it is activation of 5-HT_{1A} receptors in the terminal fields, rather than on the raphe cell bodies, that suppresses sexual receptivity. Since terminal autoreceptors are probably 5-HT_{1B} receptors (18,20), and not 5-HT_{1A} receptors, we may speculate that 8-OH-DPAT's inhibition of lordosis behavior involves postsynaptic sites. However, the present data cannot rule out a role for presynaptic 5-HT_{1A} receptors in the behavioral change. Moreover, it is not yet known if behavioral suppression would also have occurred following infusion of 8-OH-DPAT in the dorsal raphe.

Observation of females treated systemically with 8-OH-DPAT suggested that they resisted mating attempts by the male. This was also true following the intrahypothalamic infusions. Females given 200 ng 8-OH-DPAT bilaterally into the ventromedial hypothalamus were highly successful at avoiding the males' mounts. The female would run away from the male, roll over and engage in wrestling with the male, or rear on her hind legs and box with the male. Although this behavior was sometimes seen in saline-treated females, it was not as aggressive as in the 8-OH-DPAT-treated animals, and seldom prevented the male from mounting. As the dose of 8-OH-DPAT increased, females became more passive and were less successful at preventing mounts by the male.

Although the present results are consistent with earlier findings in which intrahypothalamic infusion of 5-HT inhibited lordosis behavior, this is the first report in which the intracerebral effects of 8-OH-DPAT on intact, female sexual behavior have been described. Furthermore, following both systemic and intrahypothalamic application of 8-OH-DPAT, suppression of lordosis behavior occurred at doses which did not produce the serotonin syndrome. Consequently, the suppression of sexual behavior may be the more sensitive index of the postsynaptic effects of 8-OH-DPAT. Finally, these studies target reproductively relevant, hypothalamic sites as a locus involved in the inhibition of sexual behavior by 8-OH-DPAT.

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