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Gender and Estrous Cycle Differences in the Response to the 5-HT_{1A} Agonist 8-OH-DPAT

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UPHOUSE, L., S. SALAMANCA AND M. CALDAROLA-PASTUSZKA. *Gender and estrous cycle differences in the response to the 5-HT_{1A} agonist 8-OH-DPAT.* PHARMACOL BIOCHEM BEHAV **40**(4) 901–906, 1991.—The effects of the 5-HT_{1A} agonist, 8-hydroxy-2-9(di-n-propylamino)tetralin (8-OH-DPAT) on eating behavior and on rectal temperature were examined in adult male rats and in diestrous, proestrous, and estrous female rats. The 5-HT_{1A} agonist produced evidence of hyperphagia at some dose (0.125, 0.25, 0.5 and 1.0 mg/kg) in all groups examined. However, hyperphagia was most evident in diestrous females and least evident in proestrous and estrous rats. These findings are interpreted as an estrous cycle modulation of somatodendritic 5-HT_{1A} autoreceptors. The hypothermic response to 8-OH-DPAT was present in all females and at all doses of 8-OH-DPAT (0.1, 0.25 and 0.5 mg/kg). These findings suggest that postsynaptic 5-HT_{1A} sites involved in 8-OH-DPAT-induced hypothermia do not vary during the estrous cycle. However, males showed less hypothermia following 8-OH-DPAT than did females. The gender difference was evidenced primarily as a slower onset of hypothermia in males treated with the lower doses of the drug.

Hyperphagia Hypothermia Serotonin Gonadal hormones Male and female rats Autoreceptors

SEROTONIN (5-HT) is well recognized as a hypothalamic neurotransmitter influencing male and female reproductive function, but its precise role in reproduction has remained elusive. Early pharmacological studies provided evidence for inhibition, facilitation and no effect following treatment with 5-HT (34), but the discovery of the multiple 5-HT receptor subtypes (35,36) has helped to clarify this apparent contradictory evidence. It now appears that activation of the 5-HT_{1A} subtype is inhibitory, and that activation of the 5-HT_2 or 5-HT_{1B} subtype is facilitatory to female lordosis behavior (1, 12, 30, 31). In contrast, activation of the 5-HT_{1A} site in male rats facilitates sexual behavior by reducing the ejaculatory threshold (2, 13, 31, 38). Studies with 5-HT_2 antagonists or the nonselective 5-HT_{1B} agonist, trifluromethylphenyl piperazine (TFMPP), suggest an inhibitory effect of the 5-HT_2 and 5-HT_{1B} site on male copulatory behavior (32,33).

The sex difference in behavioral responses to 5-HT drugs is not limited to reproductive behaviors. The "serotonin syndrome," consisting of a group of stereotyped behaviors including flattened posture, straub tail, forepaw treading, resting tremor, lateral head weaving, and hypersensitivity can be more readily elicited in female than in male rats (15). Kennett et al. (22) reported that male and female rats respond differently to a single 2 h period of restraint and to the antidepressant-like effects of the 5-HT_{1A} agonist, 8-hydroxy-2-9(di-n-propylamino)tetralin (8-OH-DPAT).

Sex differences in the response to 5-HT drugs might be expected since functional and anatomical differences in the 5-HT system are present between males and females (6, 7, 39, 40). However, female gonadal hormones modulate the 5-HT system (5, 10, 15, 19, 44) so it might also be anticipated that the female's response to 5-HT drugs would vary during the estrous cycle. In particular, it might be anticipated that endogenous activation of those receptor subtypes that inhibit or facilitate sexual behavior would vary in accordance with the gonadal hormonal regulation of the reproductive cycle. Work in our laboratory (43) has shown that injections of the 5-HT_{1A} agonist, 8-OH-DPAT, into the vicinity of the ventromedial nucleus of the hypothalamus (VMN) reduce lordosis behavior of the intact, proestrous rat. This observation provides evidence for the presence of functionally relevant 5-HT_{1A} receptors within the VMN, a brain region essential for the expression of female lordosis behavior (e.g., sexual receptivity) (37). If activation of the 5-HT_{1A} receptor is truly inhibitory to female lordosis behavior (which occurs on only one night of the estrous cycle), a decreased activation of this site during sexual receptivity would appear to be inevitable. A reduced activation of the postsynaptic 5-HT_{1A} receptor could occur either by decreasing the number and or sensitivity of postsynaptic 5-HT_{1A} sites or by decreasing the release of 5-HT from the presynaptic terminal. Estrous cycle modulation of the 5-HT_{1A} site is of particular interest, since this receptor subtype resides not only postsynaptic to 5-HT nerve terminals, but also functions on 5-HT cell bodies as a somatodendritic autoreceptor where its activation reduces firing of raphe neurons and release of 5-HT (41). Consequently, modulation of the 5-HT_{1A} receptor during the estrous cycle could occur at either or both of these sites.

In the following manuscript, we describe the effects of 8-OH-DPAT on hyperphagia and hypothermia in male rats and in female rats during the stages of diestrus, proestrus and estrus. These two behaviors were selected for study because both eating behavior and body temperature are influenced by gonadal hormones (3, 8, 28, 45). Furthermore, these behaviors have received careful study in male rats following treatment with 8-OH-DPAT (16, 17, 20, 27). Convincing arguments have been made that the hyperphagia induced by 8-OH-DPAT results from the drug's action at the somatodendritic autoreceptors of the raphe nucleus (11,20). In contrast, the hypothermia induced by 8-OH-

DPAT is thought to result from activation of postsynaptic 5-HT_{1A} sites (19,46). Thus estrous cycle modulation of the effects of 8-OH-DPAT on these two behaviors could provide evidence regarding the location of the 5-HT_{1A} site which is being modulated during the female reproductive cycle.

METHOD

Animals and Housing Conditions

Adults rats (CDF-344) were bred in our laboratory from stock obtained from Charles River Laboratories (Kingston, NY). Rats were weaned into polycarbonate shoebox cages at 25–30 days of age and were housed 3 or 4 per cage with like-sex littermates. The colony room was maintained at 75°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, females were monitored daily for vaginal cyclicity for at least 2 complete estrous cycles as previously described (42). Stage of the estrous cycle was determined by the vaginal smear on each day of the experiment and by the smear history during the preceding days. Vaginal smears with nucleated cells, or primarily nucleated with a few cornified cells but an absence of leucocytes, were judged as proestrous smears. Estrous females showed a fully cornified smear and had exhibited a proestrous smear 24 h earlier. Diestrous 1, diestrous 2, and diestrous 3 females were dated from their previous day of proestrus.

Measurement of Hyperphagia Induced by 8-OH-DPAT

Rats were 70–80 days of age at the initiation of the experiment. Average body weights (±S.D.) of the males and females respectively were 254±137 and 167±16 grams. One-half the males were age-matched and the remainder weight-matched to the females. Rats were housed in a 12-12 h light-dark cycle with lights on at 6:00 a.m. (CST). Rats were individually housed in metal hanging cages 24 h prior to initiation of the experiments. At noon (during the middle of the light cycle), on the first day of the study, rats were removed from the home cage and were weighed and injected (SC) with saline or with the 5-HT_{1A} agonist 8-OH-DPAT [8-hydroxy-2-9(di-n-propylamino)tetralin; Research Biochemical, Inc., Natick, MA; 0.1 to 1.0 mg/kg; 0.1 ml/100 gram rat]. For each dose and each stage of the cycle, rats were matched with control, saline-treated rats. After injection, the rat was immediately replaced into the home cage with premeasured quantity of food pellets (Teklad Premier). Four hours later, the food was removed and weighed and the quantity remaining was subtracted from the original food allotment. Food intake (in grams) was computed as the original food allotment minus the food remaining and was corrected for waste, collected on construction paper beneath the cage. Twenty-four hours later, the entire procedure was repeated. Females were in the stages of diestrus 2, proestrus or estrus on the first day of the study. These same females, respectively, were in diestrus 3, estrus, or diestrus 1 on the second day of the study. The average food intake for saline control males and for saline control females on each day of the estrous cycle was used as a measure of the expected food intake for that stage or sex. The eating behavior of 8-OH-DPAT-treated rats was evaluated as the ratio of this expected food intake.

Measurement of Hypothermia Induced by 8-OH-DPAT

Two independent experiments were performed. In the first experiment, male and female rats (70–80 days of age, respectively, average body weight±S.D. of 257±87 and 147±23 grams) were used. Females were in the stages of diestrus 2, proestrus or estrus. In the second experiment, females (80–90 days of age; average body weight±S.D. of 176±21) from all 5 days of the estrous cycle were used.

At weaning, rats were group-housed (4 per cage with like-sex littermates) in polycarbonate shoebox cages. On the day of the experiment, rats were removed from the home cage and basal rectal temperature was determined (Ret-2, Type T thermocouple; Sensortek, Inc.). Rats were immediately injected (SC) with saline or with 8-OH-DPAT (0.1 to 0.5 mg/kg; 0.1 ml/100 gram rat) and rectal temperature was again determined at 15, 30 and 60 min after injection. Saline controls were included for males and for females from each stage of the estrous cycle.

In the first study, the experiment was conducted during the middle of the light cycle as described for the study of hyperphagia. The second experiment was performed during the dark portion of the light cycle, 2–4 hours after lights off.

Statistical Methods

Since eating behavior varies during the female estrous cycle (3) and between males and females, it was necessary to control for this variation in assessing the effects of 8-OH-DPAT. Food intake following the treatment with 8-OH-DPAT was divided by the average food intake of the appropriate control group. Food intake of each rat was expressed as a ratio to control and was compared by two-way ANOVA with dose of the drug and stage (or sex) as main factors. When appropriate, individual means were compared by the Tukey test. The effects of 8-OH-DPAT on hypothermia were assessed by repeated measures ANOVA with treatment (8-OH-DPAT vs. saline), dose, and stage of the cycle (or sex) as main factors. Time after treatment was the repeated factor. Group differences were then compared by the Tukey test. The statistical reference was Zar (48), and in all comparisons, an alpha level of 0.05 was required for rejection of the null hypothesis.

RESULTS

Hyperphagia

Figure 1A shows the effects of the first 8-OH-DPAT injection on eating behavior. All groups showed evidence of hyperphagia at some dose of 8-OH-DPAT. There was a significant effect of both dose, $F(4,101)=3.76$, $p<0.05$, and stage of the cycle (or sex), $F(3,101)=2.85$, $p<0.05$. The interaction term was not significant. Across all doses of 8-OH-DPAT, there was least hyperphagia in the proestrous females and maximal hyperphagia in the diestrous females. These two groups differed significantly, Tukey $q(101,4)=3.87$, $p\leq 0.05$, but across all doses, no other pairwise comparisons were significantly different.

On the second day of treatment (Fig. 1B), stage of the estrous cycle was confirmed by the vaginal smear. Females that were proestrus on day 1 were now estrus. Estrous females were now diestrus 1 and diestrous 2 females were now in diestrus 3. As was true on the first day of treatment, there was a significant effect of dose, $F(4,100)=10.98$, $p=0.0001$, and stage of the cycle (sex), $F(3,100)=7.67$, $p=0.0001$. However, there was also a significant dose × stage (sex) interaction, $F(12,1000)=2.146$, $p=0.02$. Substantial hyperphagia was present in males at 0.125 mg/kg and in the diestrous 3 females by 0.25 mg/kg (Tukey, $p\leq 0.05$). Diestrous 1 females and estrous females showed little evidence of hyperphagia until the higher dose of 8-OH-DPAT. Across all doses, the estrous females showed significantly less hyperphagia than the diestrous 3 females, $q(101,4)=4.04$, $p<0.05$, Tukey. No other group comparisons were significant.

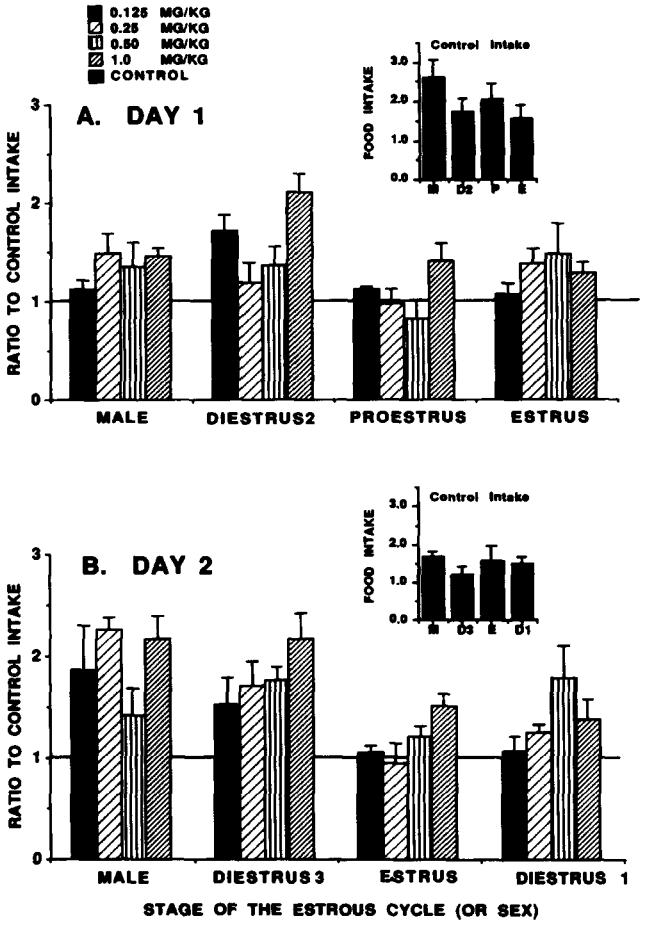

FIG. 1. Hyperphagia in male and female rats after treatment with 8-OH-DPAT. Male rats or diestrous, proestrous or estrous female rats were injected SC with 8-OH-DPAT (0.125 to 1.0 mg/kg). Control rats received the saline vehicle. Food intake was measured 4 h after treatment with 8-OH-DPAT or saline which occurred on each of 2 consecutive days (A and B). A shows the effects of 8-OH-DPAT on the first day of treatment. The figure indicates the mean ± S.E. of the ratio between food intake of the 8-OH-DPAT-treated rats and control rats of the same sex or stage of the estrous cycle. The solid line indicates the control (or expected) ratio in the absence of 8-OH-DPAT. The S.E. for the control ratio was 0.096. The inset figure shows the mean ± S.E. food intake (in grams) for saline-treated male (M), diestrous 2 (D2), proestrous (P) and estrous (E) females. N's for the controls, respectively, were 9, 10, 12 and 11. For each 8-OH-DPAT treatment, 5–6 rats were used. B shows the effects of 8-OH-DPAT on the second day of treatment. The solid line indicates the control (or expected) ratio in the absence of 8-OH-DPAT for rats treated for the second day with saline. The S.E. for the control ratio was 0.079. The inset figure shows the mean ± S.E. food intake (in grams) for saline-treated male (M), diestrous 3 (D3), estrous (E) and diestrous 1 (D1) females. N's for the controls, respectively, were 9, 10, 12 and 11. In each 8-OH-DPAT condition, 5–6 rats were used.

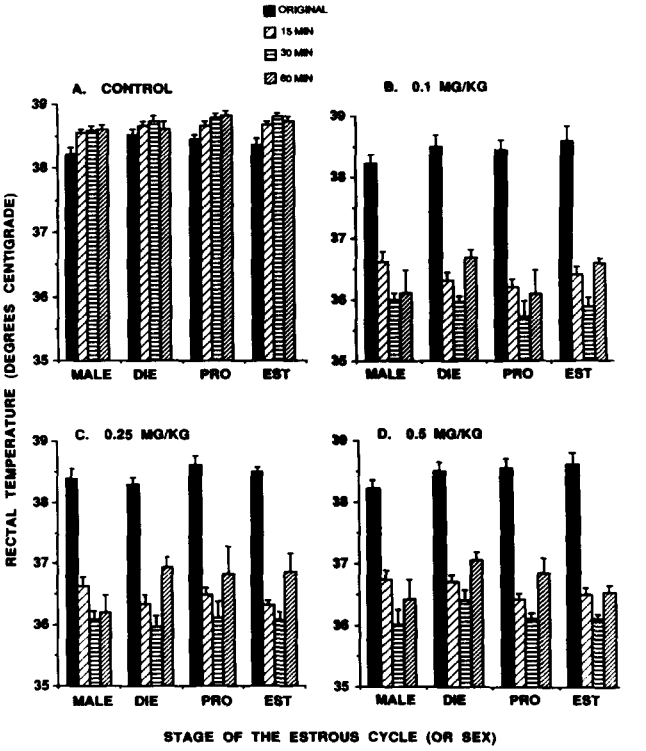

FIG. 2. Rectal temperature in male and female rats after treatment with 8-OH-DPAT during the light portion of the light/dark cycle. Figure 2 shows the rectal temperature of saline-treated (A) and rats treated with 0.1 (B), 0.25 (C), or 0.5 mg/kg (D) 8-OH-DPAT before injection and 15, 30 and 60 min following injection. Females were in diestrus 2 (DIE), proestrus (PRO) or estrus (EST) on the day of treatment. The figure shows the mean ± S.E. rectal temperature for 5 animals in each group for each dose of 8-OH-DPAT or saline.

Hypothermia

Figure 2 shows the hypothermic response to 8-OH-DPAT during the light portion of the light-dark cycle. In contrast to the estrous cycle differences in 8-OH-DPAT-induced hyperphagia, the hypothermic response did not vary during the estrous cycle. All animals evidenced hypothermia following treatment with 8-OH-DPAT [ANOVA, saline vs. 8-OH-DPAT, $F(1,96) = 1368.51$, $p \leq 0.0001$]. Across all groups, saline-treated rats showed a slight increase in rectal temperature (Fig. 2A) following the injection. These time-dependent changes in rectal temperature produced a significant effect of the repeated measures variable, time, $F(3,288) = 275$, $p \leq 0.0001$, as well as a significant treatment × time interaction, $F(3,288) = 48$, $p \leq 0.0001$. The dose × time interaction, $F(6,288) = 2.131$, $p \leq 0.05$, and the treatment × stage (sex) × time interaction, $F(9,288) = 3.51$, $p \leq 0.05$) were also significant. The 3-way interaction primarily reflected the slower response of the males, relative to all groups of females, to the 0.1 mg/kg dose of 8-OH-DPAT [Tukey, all $q(288,4) \geq 3.633$, $p \leq 0.05$ (Fig. 3)]. Males also had significantly lower rectal temperature at the beginning of the experiments, all $q(288,4) \geq 3.633$, all $p \leq 0.05$.

Figure 4 shows the hypothermic effects of a representative dose (0.25 mg/kg) of 8-OH-DPAT during all 5 days of the estrous cycle during the dark portion of the light-dark cycle. Similar patterns were present for the 0.1 mg/kg and the 0.5 mg/kg doses (data not shown). In agreement with results obtained during the light, the hypothermic response did not vary during the estrous cycle, $F(4,108) = 2.243$, $p = 0.07$. Significant differences were present between saline and 8-OH-DPAT, $F(1,108) = 580.65$, $p = 0.0001$, and among the doses, $F(2,108) = 38.09$, $p < 0.05$. No

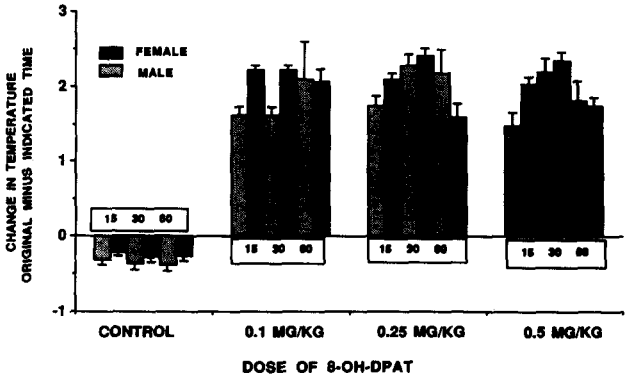

FIG. 3. Change in rectal temperature in males and in female rats after 8-OH-DPAT. This figure shows the mean ± S.E. change in rectal temperature of male and female rats (shown by stage in Fig. 2) 15, 30 and 60 min after treatment with 8-OH-DPAT (SC 0.1, 0.25 or 0.5 mg/kg). The figure represents the results from 5 male and 15 female rats in each dose condition.

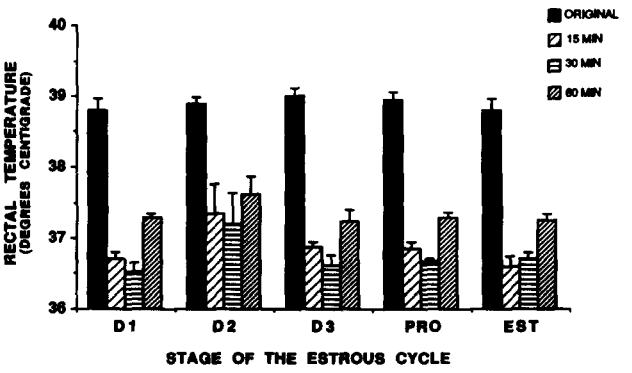

FIG. 4. Rectal temperature in female rats after treatment with 8-OH-DPAT during the dark portion of the light-dark cycle. This figure shows the rectal temperature of saline-treated rats and rats treated with 0.25 mg/kg 8-OH-DPAT. Temperatures before injection and 15, 30 and 60 min following injection are shown. Females were in diestrus 1 (D1), diestrus 2 (D2), diestrus 3 (D3), proestrus (PRO) or estrus (EST) on the day of injection. The figure shows the mean ± S.E. rectal temperature for 5 animals in each group for each dose of 8-OH-DPAT or saline.

interaction term, in which the main factor of stage appeared, was significant (all $p \geq 0.30$).

DISCUSSION

In the present studies, we have examined two behaviors, hyperphagia and hypothermia, invoked by treatment with the 5-HT_{1A} agonist, 8-OH-DPAT. Gender differences were present for both behaviors, while variation during the estrous cycle was present only for hyperphagia. Gender differences in peripheral metabolism of several neurally active compounds have been reported (21,47) so that sex differences in the response to 8-OH-DPAT could result from differential clearance of the drug. However, this is unlikely to be the explanation for the present findings because males showed less hypothermia than females, but were slightly more sensitive than estrous or proestrous females to the hyperphagic effects of the drug. Since the presynaptic somatodendritic sites have been implicated in the hyperphagia induced by 5-HT_{1A} agonists (4, 11, 20), sex differences in the presynaptic 5-HT_{1A} autoreceptor may account for the greater sensitivity of males than proestrous or estrous females to 8-OH-DPAT-induced hyperphagia. The reduced sensitivity of males to 8-OH-DPAT-induced hypothermia suggests that males and females may also differ in postsynaptic 5-HT_{1A} activation. Although the neural location responsible for 8-OH-DPAT's reduction in temperature is not known, in the rat, a postsynaptic 5-HT_{1A} location has been suggested (46).

The inverse, relative sensitivity of the males and the females to hyperphagia and hypothermia supports prior arguments that the location of the 5-HT_{1A} site mediating the effects of 8-OH-DPAT on these two behaviors is different. However, the doses of 8-OH-DPAT used in these experiments probably led to activation of 5-HT_{1A} sites in terminal fields and on 5-HT neurons. Thus the gender and cycle differences ultimately reflect the net result of multiple sites of 8-OH-DPAT action. Nevertheless, the data are consistent with other observations. For example, females are reported to have more active 5-HT systems than males. Consequently, we might expect there to be less autoinhibition at raphe neurons in the female. Thus females should exhibit less evidence of a behavior (e.g., hyperphagia) which requires autoreceptor activation. At terminal fields, females would be expected to have higher levels of endogenous 5-HT to sum with the exogenously administered 5-HT_{1A} agonist. Thus we might anticipate that females would show greater evidence of drug-elicited behaviors (e.g., hypothermia, 5-HT syndrome) that require activation of the postsynaptic sites. Unfortunately, gender differences in the response to 8-OH-DPAT have not been thoroughly evaluated for hypothalamic nuclei likely to be responsible for eating behavior or hypothermia. Haleem et al. (18) reported greater 5-HT synthesis in the hippocampus of females relative to males, but the decrease in 5-HT synthesis by 8-OH-DPAT (presumably due to somatodendritic effects of 8-OH-DPAT) was also more robust in females than in males. Unfortunately, the stage of the estrous cycle was not reported.

Variation during the estrous cycle in the hyperphagia, but not the hypothermia, produced by 8-OH-DPAT, also suggests that the precise location of the 5-HT_{1A} site responsible for the two behavioral responses is different and that the autoreceptor but not the postsynaptic site, is regulated by the estrous cycle. Alternatively, since both 5-HT_{1A} and 5-HT_2 receptors are involved in the regulation of body temperature in the rat (17), the absence of an estrous cycle effect in 8-OH-DPAT-mediated hypothermia may reflect a parallel modulation of both 5-HT_{1A} and 5-HT_2 receptors during the female reproductive cycle.

The higher doses of 8-OH-DPAT needed to induce hyperphagia in proestrous and in estrous rats is consistent with Lakoski's (26) observation that 8-OH-DPAT's application to the dorsal raphe neurons was less effective in decreasing raphe firing in estrogen-primed than in nonprimed ovariectomized rats. The lower sensitivity of proestrous rats to 8-OH-DPAT-induced hyperphagia is also in agreement with Fernandez-Guasti and Picazo's (14) report that the anxiolytic effects of 5-HT_{1A} compounds were smaller in proestrous than in metestrous female rats. These findings agree with our observation of an estrous cycle modulation of 5-HT_{1A} mediated hyperphagia, with proestrous and estrous rats generally less sensitive than females in other portions of the cycle. However, in Fernandez-Guasti and Picazo's study, proestrous females and males were roughly equal in their response to the 5-HT_{1A} agonists, while in the present study, males were less likely to show changes in temperature and more likely to exhibit hyperphagia following 8-OH-DPAT.

The present studies were also designed to address a second question regarding 5-HT_{1A} receptors and hyperphagia. According to Kennett et al. (24), a single treatment with 8-OH-DPAT

reduced the hyperphagia induced by a second treatment 24 hours later. In the present studies, on the second day of treatment, there was no evidence for an attenuation of the hyperphagia elicited by 8-OH-DPAT. In fact, the hyperphagic response on the second day was slightly greater than on day 1. Thus these findings disagree with Kennett's assumption that a single 8-OH-DPAT treatment produces a rapid downregulation of somatodendritic 5-HT_{1A} autoreceptors and a consequent reduction in 8-OH-DPAT-induced hyperphagia. The present findings do agree, however, with Larsson et al.'s (27) observation that 8-OH-DPAT's ability to reduce 5-HT release was not attenuated by prior 8-OH-DPAT treatment. The reason for the discrepancy between our findings and those of Kennett et al. (24) is not clear. In our studies, as in the study by Kennett et al., the absolute magnitude of food intake following 8-OH-DPAT treatment was smaller on day 2 than on day 1. However, in our studies, the food intake of saline-treated rats was also consistently lower on day 1 so that there was a reduced baseline on day 2 from which the hyperphagic effects of 8-OH-DPAT were assessed.

In summary, the present studies have demonstrated gender and estrous cycle differences in the response to the 5-HT_{1A} agonist, 8-OH-DPAT. If the 8-OH-DPAT-induced hyperphagia stems from an effect of 8-OH-DPAT on somatodendritic autoreceptors of the raphe neuron, the present results suggest a reduced sensitivity of these receptors during proestrus and estrus relative to males or to diestrous females. The failure of the hypothermic response to be modulated by the estrous cycle is in agreement with previous conclusions that behavioral responses mediated by postsynaptic 5-HT receptors do not vary during the female's reproductive cycle, although gender differences do exist (15). Recent studies suggest that the 5-HT_{1A} agonists may be effective anxiolytic compounds (9, 23, 24) and the serotonin autoreceptor has been implicated as a possible site of action. Thus the present studies add further evidence for the interesting possibility that the ability of gonadal hormones to influence anxiety include their modulation of presynaptic 5-HT_{1A} autoreceptors.

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