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BRIEF COMMUNICATION

Estradiol Modulation of the Hyperphagia Induced by the 5-HT_{1A} Agonist, 8-OH-DPAT

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SALAMANCA, S. AND L. UPHOUSE. *Estradiol modulation of the hyperphagia induced by the 5-HT_{1A} agonist, 8-OH-DPAT.* PHARMACOL BIOCHEM BEHAV **43**(3) 953–955, 1992.—Ovariectomized rats were primed with sesame oil or estradiol benzoate followed 48 h later by either sesame oil or progesterone. Four hours later, rats were treated with either saline or 0.25 mg/kg 8-hydroxy-2-9(di-*n*-propylamino)tetralin (8-OH-DPAT). Rats were allowed to eat for 4 h after this final treatment. Animals in all hormonal conditions showed hyperphagia following 8-OH-DPAT. However, the hyperphagia was significantly attenuated by pretreatment with estradiol benzoate. There was no effect of progesterone on the hyperphagic response. These results suggest that previous findings of an estrous cycle modulation of the hyperphagic response to 8-OH-DPAT arise from the modulatory effects of estradiol, and not progesterone, during the female reproductive cycle.

Female rats Progesterone Serotonin autoreceptors

GENDER differences in the response to serotonergic drugs are well known. While some of these differences probably result from developmental differences in the pattern of serotonergic innervation (8,9), others appear to derive from the modulatory influences of gonadal hormones (1–4). Unfortunately, the stage of the female's reproductive cycle is often ignored when male/female differences are compared. Recently, we described gender differences in the hyperphagic and hypothermic responses to the 5-hydroxytryptamine$_{1A}$ (5-HT_{1A}) agonist, 8-hydroxy-2-9(di-*n*-propylamino)tetralin (8-OH-DPAT) (10). Estrous cycle modulation was observed for the hyperphagia, but not the hypothermia, induced by 8-OH-DPAT. In particular, proestrous and estrous rats showed less hyperphagia following treatment with 8-OH-DPAT than did either diestrous females or males. The estrous cycle modulation of 8-OH-DPAT-induced hyperphagia was particularly interesting because: a) Hyperphagia following 8-OH-DPAT treatment is thought to be mediated by the activation of somatodendritic 5-HT_{1A} autoreceptors (5,6,11); and b) estrogen is reported to reduce the sensitivity of the 5-HT_{1A} autoreceptors to 8-OH-DPAT (7). However, the female estrous cycle is characterized by changes in progesterone as well as estrogen. The following experiment was designed to differentiate the contribution of these two gonadal hormones to the reduced sensitivity of the proestrous and estrous rat to 8-OH-DPAT-induced hyperphagia.

METHOD

Female rats (CDF-344) were bred in our laboratory from stock originally purchased from Charles River Laboratories (Kingston, NY). Rats were weaned into polycarbonate shoebox cages at 25–30 days of age and were housed three or four per cage with like-sex littermates. The colony room was maintained at 72°F and 55% relative humidity on a 12 L : 12 D cycle, with lights on at 7:00 a.m. (CST). Food and water were available ad lib. Rats were ovariectomized at 60–80 days of age. Two weeks later, rats were individually housed in suspended metal caging and hormonal pretreatments were initiated.

Ovariectomized rats received SC injections of either sesame oil or estradiol benzoate (25 μg/animal; Fisher Scientific, Houston, TX). Forty-eight hours later, rats received SC injections of either sesame oil or progesterone (500 μg/animal; Fisher Scientific). This injection scheme produced four groups, differing in the nature of their hormonal priming: a)

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oil-oil, b) oil-progesterone, c) estradiol benzoate-oil, and d) estradiol benzoate-progesterone. Estradiol benzoate and progesterone were administered SC, respectively, in a volume of 0.5 or 1.0 ml/kg. Volume of the sesame oil vehicle injection was either 0.5 or 1.0 ml/kg as appropriate.

Four hours after the second injection, rats were removed from their home cage and weighed and injected SC with saline or the 5-HT_{1A} agonist 8-OH-DPAT (Research Biochemical, Inc., Natick, MA; 0.25 mg/kg; 1 ml/kg). For the four treatments (oil-oil, oil-progesterone, estradiol benzoate-oil, and estradiol benzoate-progesterone), respectively, eight, eight, seven, and nine rats received saline; eight, eight, eight, and eight rats received 8-OH-DPAT. The mean ± SD body weight was 183.7 ± 12.3 and did not differ among the eight treatment conditions. After injection, the rat was immediately replaced into the home cage with a 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.

Data were evaluated by three-way analysis of variance (ANOVA) (estradiol benzoate vs. oil; progesterone vs. oil; and 8-OH-DPAT vs. saline) as the main factors. An α level of 0.05 was required for rejection of the null hypothesis and the statistical reference was Zar (12).

RESULTS AND DISCUSSION

Figure 1 shows the food intake of ovariectomized rats following injection with either saline or 0.25 mg/kg 8-OH-DPAT. In agreement with previous findings, this dose of 8-OH-DPAT produced hyperphagia in female rats (10) [main effect for saline vs. 8-OH-DPAT, $F(1, 56) = 26.4$, $p \leq 0.0001$]. However, this hyperphagia was significantly attenuated in animals that had received estradiol priming during the first hormonal treatment [main effect of estradiol vs. oil, $F(1, 56) = 6.7$, $p \leq 0.012$]. There was no effect of the second hormonal treatment [i.e., progesterone vs. sesame oil, $F(1, 56) = 0.23$, $p > 0.05$]. Because some hyperphagia was present in all animals, none of the interaction terms were significant (all $p \geq 0.05$). However, it is clear from the figure that the effects of 8-OH-DPAT were less robust in the estradiol + oil (EO) and estradiol + progesterone (EP) conditions. Such impressions could be confirmed by posthoc comparisons of the individual means. Tukey comparisons between saline and 8-OH-DPAT treatments for the four groups (oil-oil, oil-progesterone, estradiol benzoate-oil, and estradiol benzoate-progesterone), respectively, were: $q(56, 8) = 4.45, 5.24, 1.57,$

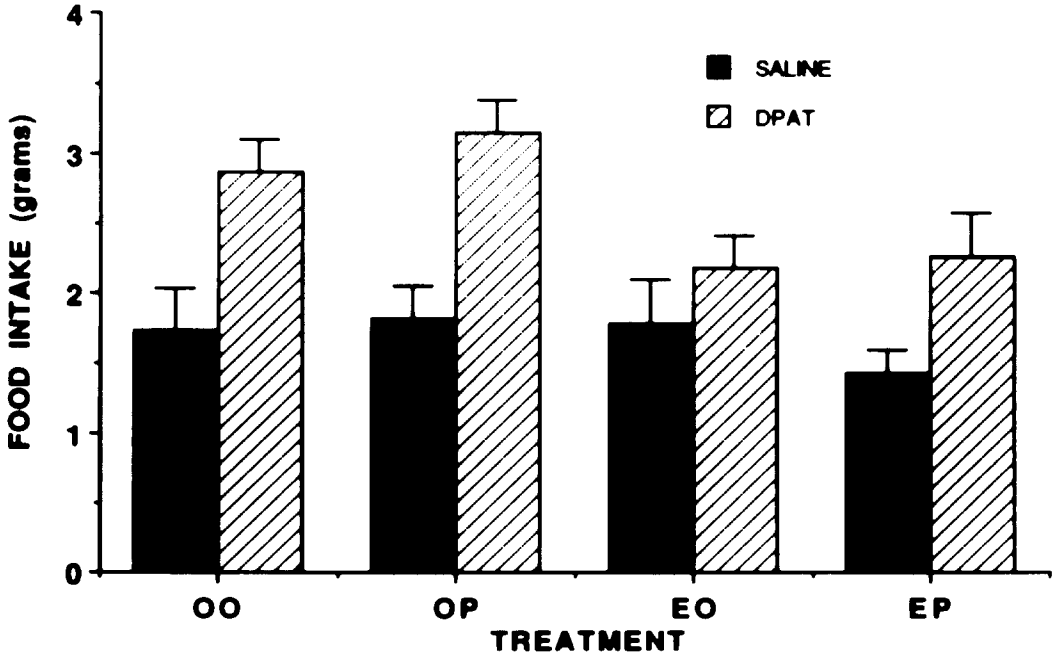

FIG. 1. Hyperphagia in hormone-primed ovariectomized rats after treatment with 8-OH-DPAT: Mean ± SE of food intake in ovariectomized rats following treatment with 8-OH-DPAT or saline. Ovariectomized rats were injected SC with either sesame oil or estradiol benzoate (25 μg). Forty-eight hours later, rats received either sesame oil or progesterone (500 μg) SC. Four hours later, rats were given a premeasured quantity of food pellets. Rats in each treatment condition were injected SC with either saline or 8-OH-DPAT (0.25 mg/kg) and returned to their home cage for 4 h. Food intake over the 4-h period was determined. Mean ± SE food intake (in grams) for females given oil on the first injection and oil on the second injection (OO), oil plus progesterone (OP), estradiol benzoate plus oil (EO), and estradiol benzoate plus progesterone (EP) are shown. For saline controls, the *ns*, respectively, are 8, 8, 7, and 9; for 8-OH-DPAT-treated females, the *ns*, respectively, are 8, 8, 8, and 8. Estradiol, but not progesterone, attenuated the hyperphagia produced by 8-OH-DPAT.

and 3.30. Only in the oil–progesterone and oil–oil groups did the saline and 8-OH-DPAT animals differ significantly, $q(56, 8) \geq 4.4, p \leq 0.05$.

Ovariectomized rats were primed with estradiol benzoate or estradiol benzoate plus progesterone to simulate the changes in gonadal hormones that occur during the female reproductive cycle and especially on the day of proestrus. In previous reports, proestrous and estrous females (relative to diestrous females) were found to show a reduced hyperphagia in response to 8-OH-DPAT. The present experiment confirms this earlier observation in that females that had experienced 52 h of estradiol priming showed an attenuated hyperphagia after treatment with 0.25 mg/kg 8-OH-DPAT. Progesterone did not influence the sensitivity of ovariectomized rats to 8-OH-DPAT.

Thus, these findings suggest that the reduced sensitivity of proestrous and estrous rats results from estrous cycle changes in estradiol. If, as Wilkinson and Dourish suggested (11), 8-OH-DPAT-induced hyperphagia depends upon agonist activation of the dorsal raphe 5-HT_{1A} autoreceptor, the present results suggest that estradiol, but not progesterone, is capable of modulating this receptor site.

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