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Pharmacology, Biochemistry and Behavior 71 (2002) 701–707

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Estrous cycle and food availability affect feeding induced by amygdala 5-HT receptor blockade

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Received 28 June 2001; received in revised form 30 August 2001; accepted 6 September 2001

Abstract

We have recently reported that bilateral infusions of the 5-HT receptor antagonist metergoline (MET) into the posterior basolateral amygdala (pBLA) elicit feeding in female rats tested at mid-light cycle. The present study was performed to determine whether (1) testing at two different phases of the estrous cycle, and/or (2) the palatability of the food might modify this effect. Subjects were 18 adult females with bilateral pBLA cannulae. Following familiarization with Froot Loops cereal, a within-subjects design tested all animals for 1- and 2-h food intake under 2 Drug (0.3 nmol MET vs. Vehicle), 2 Estrous Cycle (diestrus vs. estrus) and 2 Food (lab chow vs. Froot Loops) conditions. Rats weighed more at diestrus than at proestrus ($P<.05$) or estrus ($P<.005$). Multivariate analyses of variance (MANOVAs) revealed a preference for Froot Loops over lab chow ($P<.0001$). MET increased feeding regardless of food type ($P<.0001$). Rats ate more Froot Loops ($P<.01$), but not lab chow, at diestrus vs. estrus. A three-way interaction ($P<.05$) showed rats ate more during the first hour in estrus than in diestrus to lab chow but not Froot Loops. These data suggest pBLA MET differentially affects feeding over the estrous cycle depending on the palatability of food available.

Keywords: Feeding; Estrous cycle; Serotonin; Palatability; Metergoline; Basolateral amygdala; Estrus; Diestrus

1. Introduction

Stimulation of brain serotonin 1A (5-HT1A) autoreceptors elicits feeding in freely feeding prefed rats (Bendotti and Samanin, 1987; Hutson et al., 1988). This behavior is probably mediated at one or more forebrain sites by decreases in 5-HT levels (Bosker et al., 1994). Recent studies from our laboratory have demonstrated that feeding following administration of the 5-HT1A agonist, (±)-8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), directly into the dorsal raphe nucleus can be attenuated by bilateral electrolytic lesions of the posterodorsal amygdaloid area (Coscina et al., 2000). Smaller lesions centered on the posterior basolateral amygdala (pBLA) completely blocked the feeding effects of systemic 8-OH-DPAT (Parker and Coscina, 2001). More direct evidence of a 5-HT-related feeding effect was shown by eliciting reliable food intake in prefed female rats by bilateral administration of the broad acting 5-HT antagonist, metergoline (MET), into the pBLA (Parker et al., 2001a).

Energy balance varies across the ovarian cycle of female mammals (Kennedy, 1969; Johnson et al., 1994). Gonadal hormones influence body weight by altering feeding as well as metabolism (see Wade, 1972 for review). Food intake covaries with estrogen levels, being maximal at diestrus and minimal at estrus (Wade and Gray, 1979; Fantino and Brinnel, 1986). It has been suggested that hormonal controls over food intake may act in part by modulating appetite, and in particular, taste reactivity (Wade and Zucker, 1969). 5-HT-related feeding also appears to be modulated by the estrous cycle. Rats in diestrus have been reported to be more likely than rats in estrus to show increased feeding of standard lab chow following systemic 8-OH-DPAT (Uphouse et al., 1991). This effect was probably due to the actions of estrogen (Salamanca and Uphouse, 1992). There is an overlap of brain areas associated with estrogen and those associated with control of feeding and body weight, including subnuclei of the amygdala. Estrogen is capable of changing the

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0091-3057/02/$ – see front matter
PII: S0091-3057(01)00668-2

density of 5-HT receptors in several brain regions including the amygdala (Biegon and McEwen, 1982).

Other research suggests that 5-HT is capable of influencing neuronal activity within the basolateral amygdala by modulating both GABAergic (Koyama et al., 1999; Rainnie, 1999) and glutamatergic neurotransmission (Cheng et al., 1998). Amygdalo-fugal projections originating local to our pBLA infusions that innervate structures involved in feeding include in particular a ventromedial hypothalamic innervation from the posterior basomedial nucleus (Petrovich et al., 1996). Another major innervation projects to the nucleus accumbens from both the posterior basomedial nucleus (Petrovich et al., 1996) and the basolateral amygdala (McDonald, 1991). The amygdaloid projection to the accumbens is associated with reward-related stimuli (Cador et al., 1989)—conveying what Louilot describes as "affective perception" (Louilot and Besson, 2000). Although these previous investigations focused primarily on dopamine (DA), 5-HT manipulations can strongly influence DA levels at both sites (Cumming et al., 1997; Romaniuk et al., 2001).

Based on the foregoing information, we predicted that the magnitude of feeding elicited by infusing MET into the pBLA might change across different phases of the estrous cycle. In addition, we were interested to see whether manipulating the palatability of foods available might influence the ability of pBLA MET to elicit feeding. To address both of these issues, the present study was performed to determine whether (1) testing at two different phases of the ovarian cycle and/or (2) the palatability of the food offered might modulate feeding induced by pBLA 5-HT receptor blockade.

2. Methods

2.1. Animals

Twenty female Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, IN) were housed singly in plastic shoebox cages with sawdust bedding and overhead steel tops that also served as holders for water bottles and food pellets (LabDiet, PMI Nutrition, Brentwood, MO). Cages were located in a temperature-controlled (21–23 °C) colony illuminated 12 h daily (0600–1800). Average (mean ± S.E.M.) animal weight at surgery was 268 ± 4.5 g. Throughout these studies, rats had ad-libitum access to food and water. Daily measurements were made of body weight. All procedures were approved by the Wayne State University Animal Investigation Committee as complying with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

After 1 week of habituation to housing conditions, daily vaginal lavages were performed on each animal between 0830 and 0930 h with approximately 1 ml of warmed distilled water. Samples collected were inspected independently by two observers the same morning using light microscopy. The stage of ovarian cycling was characterized as described previously (Freeman, 1994; Parker et al., 2001b). Feeding tests occurred on days corresponding to a morning lavage cytology indicating estrus (preponderance of cornified cells in the lavage samples) or diestrus (mostly much smaller leukocytes).

2.2. Surgery

Rats were injected intraperitoneally with 1.85 ml/kg of 0.54 mg/ml atropine sulfate (Radix Laboratories, Eauclaire, WI) 30 min before being anaesthetized with 43 mg/kg ip sodium pentobarbital (Butler, Columbus, OH). Buprenorphine (0.1 mg/kg, BUPRENEX, Reckitt and Colman, Hull, UK) was administered subcutaneously and each rat positioned in a Kopf small-animal stereotaxic frame with the incisor bar set horizontal to interaural line. Single guide cannulae (C313G, Plastics One, Roanoke, VA) were lowered bilaterally to bregma −2.1, lateral ± 4.5, skull surface −3.4, terminating 5 mm above the sites targeted for microinjection. Each preparation was secured by the adherence of dental cement (Stoelting, Wood Dale, IL) to the cannula assembly and stainless steel mounting screws (Plastics One) embedded in the skull plates. The area surrounding the implants was treated with bacitracin zinc ointment (Fougera, Melville, NY) and sutured closed. Sutures were removed 4–7 days after surgery. Two animals were lost due to anaesthetic overdose.

2.3. Drugs

MET (Sigma, St. Louis, MO, mol wt 403.5) was dissolved in 5% tartaric acid (Fisher, Pittsburgh, PA) and adjusted to pH 6.5 using dropwise addition of NaOH (Fisher). Vehicle infusions (VEH) were of similarly pH-adjusted 5% tartaric acid.

2.4. Habituation

Prior to surgery, all rats were transferred to hanging wire-mesh cages used for feeding tests and given 1-h access to Froot Loops cereal on a daily basis. Froot Loops have 3.9 kcal/g (87.5% carbohydrate; 3.1% protein, 3.1% fat by weight) while standard lab chow used has 3.4 kcal/g (56% carbohydrate; 23% protein; 4.5% fat by weight). Water was freely available during both habituation and testing but not measured. This procedure was repeated until overall mean intakes of Froot Loops were seen to asymptote. This same procedure was resumed 4 days following surgery. In order to accustom animals to the testing cages and the regimen of food exchanges used during drug trials, a minimum of four mock injection tests were also performed. Feeding tests began once individual body weights had recovered to at least presurgery levels and the weight of food consumed in mock tests had stabilized. All animals achieved both criteria by 10 days postsurgery.

2.5. Intra-pBLA MET feeding tests

Rats were transferred to single wire-mesh testing cages for 3-h sessions between 1300 and 1600 h. Water was available ad libitum during tests. After an initial hour of access to fresh lab chow, each rat was removed and microinjected bilaterally with VEH or 0.3 nmol MET per hemisphere (0.3 + 0.3 = 0.6 nmol total infusion) in 0.5-μl volumes over 2 min. This dose of MET had been previously determined (Parker et al., 2001a) to be the lowest capable of eliciting feeding from a dose range spanning four orders of magnitude. Infusions were performed using stainless steel injection cannulae (C313I, Plastics One) that were cut so as to extend 5 mm below the guide cannula to deliver the infusate to the pBLA. The cannulae were connected by polyethylene tubing to 5-μl Hamilton syringes mounted in an infusion pump (model "22," Harvard Apparatus, Holliston, MA). One hour postinjection, all food was removed from the cage for weighing and fresh food given for the second hour of feeding. Tests across animals were counterbalanced using a repeated measures design with 2–3 days between tests until each animal had been tested once in estrus and diestrus with VEH as well as MET for consumption of lab chow versus Froot Loops. All food intake was corrected for spillage.

2.6. Histological analysis

Rats were euthanized using 120 mg/kg sodium pentobarbital ip, then their brains removed and stored in 10% formalin. Under light microscopy, an independent examiner localized the injection sites based on tissue damage visible on 40-μm sections taken from a selection of brains.

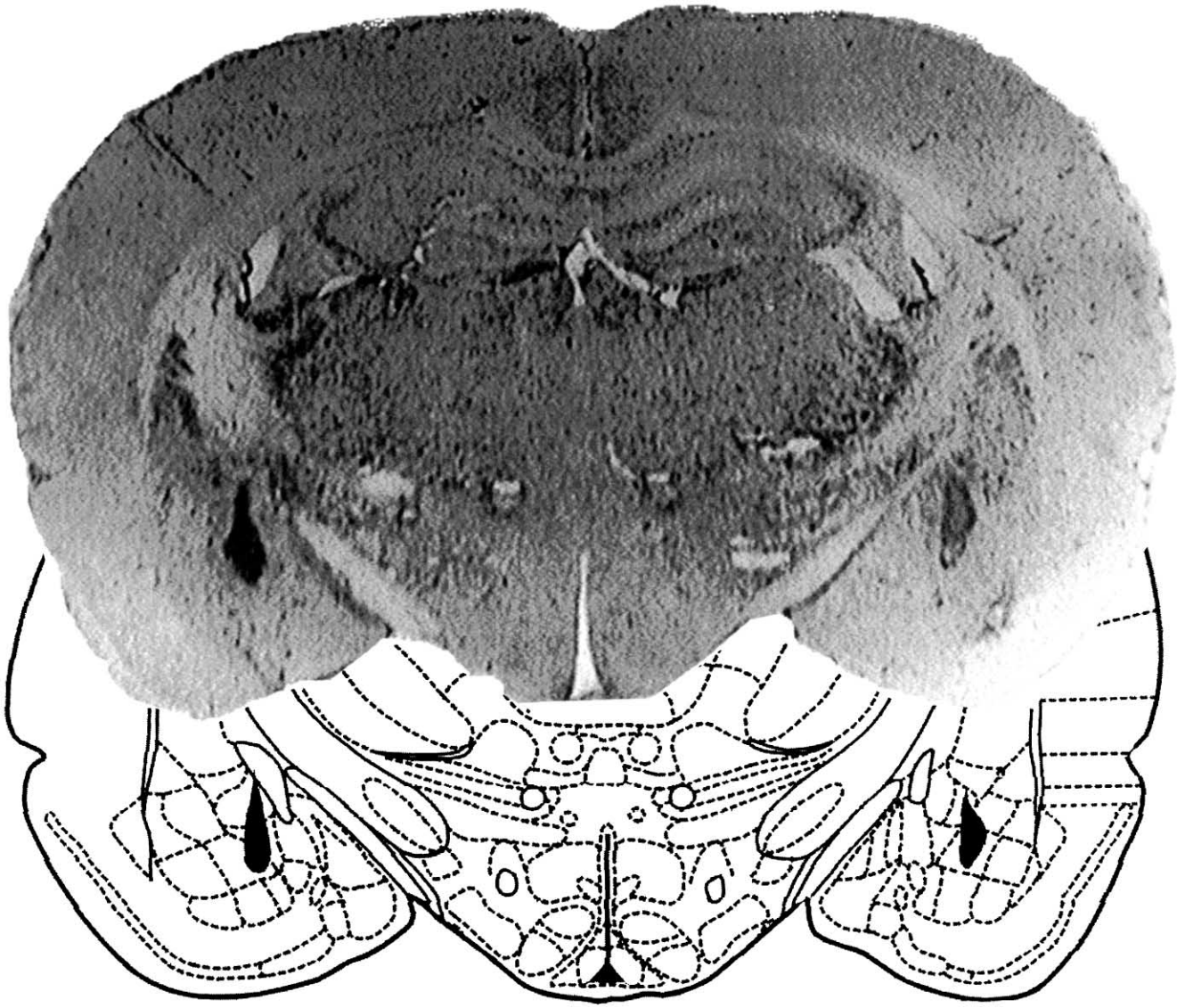

Fig. 1. A photomicrograph showing representative bilateral injection cannulae placements in the pBLA and a schematic depiction at bregma −3.14 mm (Paxinos and Watson, 1998).

2.7. Statistical analyses

Both the body weight and the feeding data were analyzed using multivariate analyses of variance (MANOVAs) followed by Tukey post hoc tests where appropriate. One 1-way MANOVA was performed on the body weight data with one within variable, estrous phase (four levels: diestrus, proestrus, estrus and metestrus). One 4-way MANOVA was performed with three within variables; estrous phase (two levels: diestrus vs. estrus), food (two levels: lab chow vs. Froot Loops) and drug (two levels: VEH vs. MET), and one between variable, hour (two levels: hour 1 vs. 2). The feeding data were reanalyzed after separating the lab chow and Froot Loop results into two separate MANOVAs to clarify the results of significant interactions found in the 4-way MANOVA. All statistical analyses were performed using STATISTICA '98 Edition (StatSoft, Tulsa, OK).

3. Results

3.1. Histology

The presence of tissue damage indicated that the injection cannulae used delivered the infusate within the posterior amygdala (Fig. 1) and primarily the basolateral division of this nucleus. These placements show good agreement with our other investigations using the same surgery (Parker et al., 2001a; Coscina and Parker, 2001).

3.2. Body weight analysis

Body weights on the days associated with the four different phases of the estrous cycle were averaged across the number of ovarian cycles taken to complete the feeding tests. These data are presented in Fig. 2. The median number of cycles required for an individual rat to complete all conditions of the feeding tests was four, with a maximum of eight. The day associated with each phase of the ovarian cycle had a significant effect on body weight, $F(3,180)=4.94$, $P<.005$. Weight at diestrus was significantly higher than at both proestrus ($P<.05$) and estrus ($P<.005$).

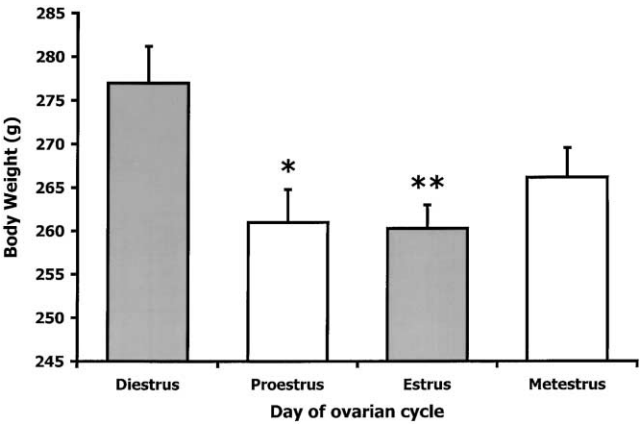

Fig. 2. Body weight associated with the four phases of the ovarian cycle (mean ± S.E.M.). Data were collected and included over the four to eight complete ovarian cycles necessary to complete MET feeding tests on each animal. MET feeding tests only occurred at diestrus and estrus (shaded bars). Body weight was higher at diestrus than at proestrus ($*P<.05$) and at estrus ($**P<.005$).

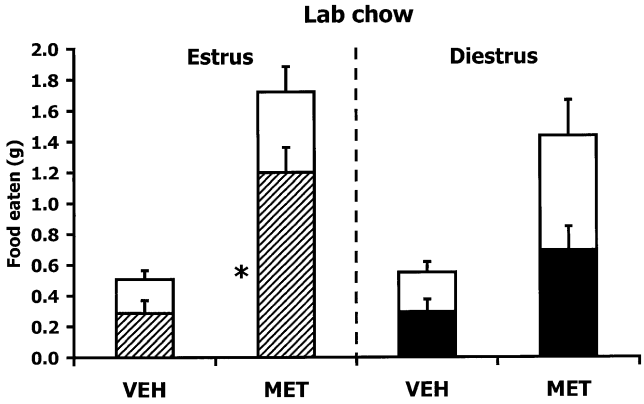

Fig. 3. Mean weight (grams) of lab chow eaten during the first and second hours (filled and open stacked bars, respectively) following bilateral intra-pBLA infusion of MET (0.3 nmol either side) or VEH in female rats during estrus (figure left) or diestrus (figure right). A three-way interaction ($*P<.05$) showed that first-hour MET-induced feeding was higher during estrus than diestrus.

3.3. Intra-pBLA MET lab chow feeding tests

Due to cannula blockages or displacement of implants, the median number of data points contributed by each rat was six. Figs. 3 and 4 show, respectively, lab chow and Froot Loops eaten over 2 h following bilateral intra-pBLA injections. A highly significant preference for Froot Loops relative to lab chow was revealed by the four-way MANOVA, $F(1,100)=261.71$, $P<.0001$. The large disparity in the amount eaten of the two food types prompted

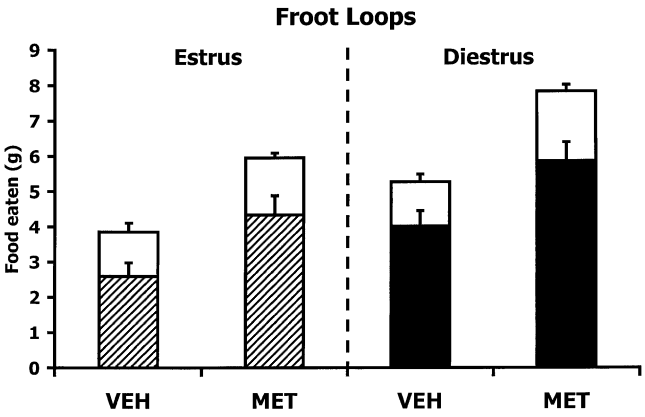

Fig. 4. Mean weight (grams) of Froot Loops eaten during the first and second hours (filled and open stacked bars, respectively) following bilateral intra-pBLA infusion of MET (0.3 nmol either side) or VEH in female rats during estrus (figure left) or diestrus (figure right).

us to reanalyze these data sets in two separate three-way MANOVAs.

Lab chow consumption was increased by MET, $F(1,52) = 27.18$, $P < .0001$. Most of the feeding occurred during the first hour of testing, $F(1,52) = 6.95$, $P < .02$. Rats did not show a main effect of estrous phase ($P = .55$) but there was a significant interaction of Estrous Phase × Hour, $F(1,52) = 7.62$, $P < .01$, such that the first hour of estrus feeding was higher than the second, as well as being higher than both hours of diestrus. That this drug effect was substantially over after the first hour was also suggested by the Drug × Hour interaction nearing significance, $F(1,52) = 3.54$, $P = .06$. Finally, the three-way interaction of Estrous Phase × Drug × Hour, $F(1,52) = 6.50$, $P < .02$, shows that consumption of lab chow was slightly yet selectively increased over the first hour during estrus.

3.4. Intra-pBLA MET palatable feeding tests

Froot Loop consumption (see Fig. 4) showed strong main effects of MET, $F(1,48) = 17.28$, $P < .0001$, and hour, $F(1,48) = 114.44$, $P < .0001$. However, unlike lab chow consumption, Froot Loop intake was higher during diestrus than during estrus, $F(1,48) = 8.66$, $P < .005$. The interaction of Estrous Phase × Hour, $F(1,48) = 6.75$, $P < .05$, suggests this was accounted for entirely by an increase in Froot Loop feeding in diestrus over the first hour. Similarly, the Drug × Hour interaction, $F(1,48) = 6.42$, $P < .05$, indicated that the MET-induced feeding increase was largely limited to the first hour. In contrast to lab chow consumption, none of the interactions involving estrous phase and drug were significant: Estrous Phase × Drug ($P = .68$), Estrous Phase × Drug × Hour ($P = .81$).

4. Discussion

As reported previously (Parker et al., 2001a), infusions into the pBLA of the nonspecific 5-HT antagonist MET elicits feeding in prefed female rats tested at mid-light cycle. The data reported here suggest this effect is differentially modulated by the phase of the estrous cycle and the palatability of the food available.

As expected, rats showed a marked preference for Froot Loops as compared to standard lab chow. The high proportion of carbohydrate in Froot Loops (~87.5%) makes this food extremely palatable as indicated by the high levels of intake seen during these short-term feeding tests. Lab chow has a similar caloric content but a lower relative carbohydrate content (~56%) and contains no refined sugar (McGregor and Lee, 1995). Expressed as absolute changes in weight of foods consumed, MET increased intake of Froot Loops significantly more than it increased lab chow intake, $F(1,100) = 4.90$, $P < .05$. This was so despite the fact that consumption of Froot Loops was much higher than lab chow regardless of manipulations. However, when expressed as percentage intake increases over VEH, the MET effects were stronger for lab chow consumption (estrus 340%, diestrus 261%) than for Froot Loops (estrus 154%, diestrus 149%). Taken together, these data demonstrate that pBLA MET was effective in driving quantitatively smaller, but relatively greater, intake of this less preferred food. Rats generally eat more during diestrus than in estrus (Wade and Gray 1979; Fantino and Brinnel, 1986). This fact was reflected here by an increase in both the body weight and in the Froot Loops feeding tests on the days associated with diestrus. In contrast, test intakes of lab chow showed no significant effect of estrous phase. This probably occurred because animals were tested during mid-light cycle after having eaten fresh lab chow for an hour prior to injection. Although test intakes of Froot Loops were greatly increased in diestrus, estrous phase had no effect on the MET-induced feeding effect. However, being in estrus selectively increased lab chow intake over the first hour following MET infusion. Hence, antagonism at one or more 5-HT receptors appears capable of selectively increasing feeding on the day associated with estrus cytology. This offers the tantalizing possibility that a circuit including pBLA 5-HT may normally mediate the cyclic feeding suppression associated with increased estrogen. These analyses confirm that the consumption of lab chow and Froot Loops are qualitatively as well as quantitatively different.

It is difficult to explain the differential increases in short-term feeding elicited by pBLA MET during estrus but not diestrus as a function of food type. Several explanations seem possible. One is that rats in estrus could be eating to correct a metabolic fuel need. Lab chow, which served as our animals' regular diet, was neither novel nor highly palatable. It served to provide them with their daily nutritional requirements and to maintain whole-body energy balance. However, the ability of pBLA MET to slightly but significantly increase chow intake more during estrus than diestrus seems counterintuitive if its purpose were to correct metabolic differences we have recently reported occur during these two hormonal phases (Parker et al., 2001b). Rats in estrus show lower respiratory quotients (RQs), implying they have less carbohydrate available for metabolic needs. Since Froot Loops contain more carbohydrate than lab chow, it seems logical that eating to correct that deficiency would be achieved more efficiently by consuming Froot Loops. However, the infrequent availability of Froot Loops prior to testing may have led rats to learn that lab chow was the appropriate food to eat to serve their normal metabolic needs. Other explanations relate to the strong feeding effect elicited by Froot Loops. Tests at mid-light cycle revealed very little intake of lab chow while Froot Loops consumption was an order of magnitude higher. The strength of this quantitative difference suggests such intake reflects an exaggerated, nonnutritionally motivated response to a palatable foodstuff (see Berridge, 1996 for a comprehensive review on food reward). pBLA 5-HT receptor blockade may have enhanced

the ability of available environmental stimuli to recruit the animal's attention to eat under less than maximal conditions. Since Froot Loops were already highly salient and elicited near-maximal feeding under control conditions, pBLA MET during estrus may have had a limited capacity to augment that response.

Evidence suggests that 5-HT is capable of influencing neuronal activity within the basolateral amygdala by modulating both GABAergic (Rainnie, 1999) neurotransmission via 5-HT1A (Koyama et al., 1999) and/or 5-HT2 receptors (Rainnie, 1999) as well as glutamatergic neurotransmission (Cheng et al., 1998) via presynaptic 5-HT1A receptors. Uphouse et al. (1991) have suggested that rats in diestrus more readily demonstrate 8-OH-DPAT feeding to standard lab chow. Therefore, we predicted that our MET-induced feeding effects might also be potentiated during diestrus. This clearly was not the case.

5-HT release in the forebrain is diminished during estrus (Gundlah et al., 1998). Interestingly, estradiol is capable of increasing amygdala 5-HT transporter binding (McQueen et al., 1997) while decreasing 5-HT1A mRNA and binding (Osterlund and Hurd, 1998; Osterlund et al., 2000). However, estrogen restores to intact levels the decrease in 5-HT2A mRNA and receptor binding associated with ovariectomy (Cyr et al., 2000) and can, by itself, increase 5-HT2A receptor mRNA in intact animals (Sumner and Fink, 1997). Since MET acts at 5-HT1, 5-HT2 and 5-HT7 receptors, it is possible that the 5-HT2A receptor is a candidate for mediating the MET feeding effects reported here.

Our data demonstrate that intake of either standard lab chow or the more palatable Froot Loops is increased acutely following blockade of 5-HT receptors with MET in the pBLA. This powerful effect may represent a generalized enhancement of feeding, regardless of food type similar to that seen after systemic treatments with 8-OH-DPAT (Fletcher et al., 1991), which also impede brain 5-HT neurotransmission. Of broader interest, rats presented with Froot Loops showed more eating during diestrus regardless of pBLA drug treatment. This could reflect a behavioral attempt to replenish carbohydrates at a time in the ovarian cycle when this fuel is utilized more to support whole-body metabolism (Parker et al., 2001b). In contrast, intake of lab chow seemed generally unaffected by estrous phase, but did show a small selective increase in the first hour after pBLA MET during estrus. Therefore, feeding induced by 5-HT receptor blockade in this portion of the amygdala modifies some component of ingestive behavior that is dependent on phase of estrous cycle. These data extend our recent work (Coscina et al., 2000; Parker and Coscina, 2001; Parker et al., 2001a) focusing on characterizing extrahypothalamic controls of 5-HT-related mechanisms modulating increased feeding in females. Current work is focusing on which 5-HT receptor subtypes mediate the MET-induced feeding effects reported here (Coscina and Parker, 2001).

Acknowledgments

We thank Ms. Jennifer Hobday for her help in data collection. This research was supported by funds from the College of Science, Wayne State University. C.B. was supported by an NRSA award from NIDA. Portions of this work were presented at the annual meetings of the International Behavioral Neuroscience Society (March 2001) and the Society for the Study of Ingestive Behavior (June 2001).

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