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Effects of Systemic 8-OH-DPAT on the Feeding Induced by Hypothalamic NE Infusion

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DE ROOY, E. C. H. AND D. V. COSCINA. *Effects of systemic 8-OH-DPAT on the feeding induced by hypothalamic NE infusion.* PHARMACOL BIOCHEM BEHAV **36**(4) 937–943, 1990.—Past research suggests that activating brain serotonin (5-hydroxytryptamine or 5-HT) systems can inhibit feeding induced by activating brain norepinephrine (NE) systems. To explore this interaction more fully, we tested the capacity of the endogenous 5-HT release inhibitor, 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), to enhance feeding stimulated by infusing NE into the medial hypothalamus. All experiments were conducted using ad lib-fed adult male rats with indwelling cannulae aimed at the paraventricular nucleus (PVN). In the first study, proven PVN-NE responders were tested for 40-min food intake after receiving 20 nanomoles (nmol) l-NE or saline in the PVN following subcutaneous (SC) pretreatment with 250 μg/kg 8-OH-DPAT or saline. Both drugs produced equivalent, reliable increments in feeding compared to PVN-saline. However, no additivity or synergy was seen when they were combined. Short-term water intake was unaffected by these treatments as was subsequent food or water intake over the next 22 hr. In a second study, additional proven PVN-NE responders were tested under two comparable conditions when 1) the 8-OH-DPAT dose was left at 250 μg/kg but the NE dose was lowered to 10 nmol, and 2) the 8-OH-DPAT dose was lowered to 120 μg/kg and the NE dose was increased to 40 nmol. In the first case, no reliable feeding was seen in response to either agent alone or combined. In the second case, NE alone enhanced feeding but 8-OH-DPAT did not. The combination of both produced the same enhanced feeding as seen with NE alone. These findings suggest that it is not possible to enhance the acute food intake elicited by PVN-NE stimulation with systemic 8-OH-DPAT as a second feeding stimulus. Additional work will be needed to confirm the more general implication of this finding, which is that impeding brain 5-HT neurotransmission may not enhance food intake initiated by other processes.

Norepinephrine Feeding Paraventricular nucleus Serotonin 8-OH-DPAT Rat Intracerebral

ONE of the most powerful and well-studied means of eliciting feeding in satiated rats is by injecting norepinephrine (NE) into the medial hypothalamus. A particularly sensitive site for producing this effect is the paraventricular nucleus (PVN) (37,38). A series of recent studies has shown that this feeding response can be attenuated by a variety of direct or indirect serotonin (5-hydroxytryptamine or 5-HT) agonists injected peripherally or directly into the PVN (20, 42, 65). These findings, along with a variety of others [see (12, 30, 39, 61) for reviews, as well as (35,54) for recent related evidence], suggest that NE and 5-HT interact in an antagonistic fashion in their control over feeding.

In an attempt to more fully characterize this apparent interaction, we wondered if pharmacological treatments known to impede 5-HT neurotransmission might enhance feeding induced by infusing NE into the PVN. If such an effect could be demonstrated, it would have at least two implications. The first is that previous evidence of this interaction through the use of 5-HT agonists (20, 42, 65) could not be ascribed to nonspecific suppression of NE-induced feeding. The second is that the in vivo systems which mediate these pharmacological interactions might normally operate in a bidirectional mode with regard to their influences over feeding. The latter possibility is of fundamental importance if we are to ultimately understand the natural processes which contribute to hunger and satiety. Accordingly, we have undertaken several different studies to test this possibility, the first of which is reported here.

In this series, we measured the feeding response of satiated rats to PVN-NE infusion following pretreatment with 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT). This prototypic $5HT_{1A}$ agonist is known to elicit feeding following systemic administration (3, 14, 17–19, 23, 33) and has been suggested to do so by inhibiting endogenous 5-HT neurotransmission (3,33). If the

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latter is true, and endogenous 5-HT serves to inhibit NE-induced feeding elicited from the PVN, then systemic 8-OH-DPAT might be expected to enhance this ingestive response.

EXPERIMENT 1

Pilot studies demonstrated that 20 nanomoles (nmol) of l-NE injected into the PVN or 250 μg/kg of 8-OH-DPAT injected subcutaneously (SC) would individually produce reliable feeding in satiated rats. Thus, Experiment 1 tested these doses in a 2×2 design. These pilot studies also revealed that rats receiving 8-OH-DPAT consistently defecated 4–8 loose stools within 30 min of injection. The latter information served as a nominal indicator that this compound had successfully been administered.

METHOD

Subjects and General Housing Conditions

Twenty-three male Sprague-Dawley rats (Charles River, Montreal, Quebec; initial weights = 250–300 g) were used. Animals were housed in separate stainless-steel cages in a temperature- (22 ± 2°C) and humidity- (40–50% relative) controlled colony room illuminated 12 hr daily beginning at 0800 hr. All rats had ad lib access to Purina Lab Chow (4% fat by weight) on cage floors as well as tap water throughout these studies.

Surgery

After 10 days of habituation to the colony, all rats were anesthetized with sodium pentobarbital (Nembutal; 50 mg/kg), and stereotaxically implanted with unilateral 26-gauge outer guide cannulae (Plastic Products, Roanoke, VA) aimed 1.0 mm dorsal to the PVN. With heads flat between lambda and bregma skull sutures, the coordinates were: 7.2 mm anterior to interaural line; 0.4 mm lateral to midline; 7.0 mm below dura. Protective dummy cannulae were fitted inside these guide cannulae at the end of surgery and at all times when rats were not being tested.

Drugs

The drugs used were l-NE bitartrate (Arteronol, Sigma Chemical Co., St. Louis, MO) and 8-OH-DPAT hydrobromide (Research Biochemicals Inc., Wayland, MA). Both drugs were dissolved in 0.9% saline immediately prior to use. NE was dissolved by agitation using a Vortex mixer; 8-OH-DPAT was added to warm saline (40°C) and gently stirred. 8-OH-DPAT was administered SC in a volume of 1 ml/kg. Vehicle (Veh) for both drugs was saline.

Test Procedures

During a one-week postoperative recovery period rats were weighed, handled and mock injected twice to habituate them to the test procedures. For initial screenings as well as testing, animals were infused with a volume of 0.5 μl via a 33-gauge injector that projected 1 mm beyond the tip of the implanted cannula. The infusion itself took about 10 sec, with the injector being left in place for another 30 sec to permit diffusion. Rats were then returned to their cages in which fresh food pellets were placed for 40-min tests of intake. A single NE (20 nmol) vs. Veh screening was conducted for each subject separated by two days using a counterbalanced design across subjects. Rats whose NE feeding responses were at least two standard deviations above the mean Veh response were retained for subsequent testing.

For the actual experiment, a randomized design was used across subjects in which 20 NE responders were each subjected once to all four test conditions: 1) SC saline + PVN-saline (Veh/Veh), which served as the control condition; 2) SC saline + PVN-NE (Veh/NE); 3) SC 8-OH-DPAT + PVN-saline (DPAT/Veh); and 4) SC 8-OH-DPAT + PVN-NE (DPAT/NE), the condition of primary experimental interest. The dosages used were 250 μg/kg of 8-OH-DPAT and 20 nmol of NE. For each combination of treatments the SC injection preceded the PVN injection by 45 min. This was necessary to permit the testing of multiple animals per day as well as to maximize the possibility of both agents acting simultaneously. To ensure that rats were not eating in response to the first treatment by the time the second was given, rats were deprived of food between injections. This brief restriction was unlikely to have affected the test responses since pilot work revealed no differences between the amounts eaten during the last 45 min of a 2-hr feeding test vs. the entire 2-hr test following 250 μg/kg SC 8-OH-DPAT alone.

In addition to food intake, water intake was also recorded during these tests. Furthermore, food and water intakes were measured for the remainder of the 24 hr which followed each test (approximately 22 hr). All screenings and testings were done between 1300 and 1600 hr.

Histology

At the end of these tests, rats were retained for use in another study to be reported elsewhere, after which they were sacrificed by decapitation and their brains removed for dissection. The hypothalamus was stored in 10% formalin for three weeks, then frozen, sectioned at 40 microns and stained with cresyl violet. Injector tip sites were verified by light microscopy according to the atlas of Paxinos and Watson (51).

Statistical Analysis

All intake and weight data were analysed by independent two-way analyses of variance (ANOVAs) with corrections for unequal ns or by selected independent *t*-tests to clarify individual group responses. All *p* levels reported represent two-tailed distributions.

RESULTS

All rats remained healthy throughout the experiment. However, due to the loss of one cannula implant plus occasional injector blockages on individual test days, data collected ranged from 15 to 20 subjects per condition.

The results of all four drug tests are summarized in the lower frame of Fig. 1. A two-way ANOVA revealed significantly greater 40 min feeding responses to NE as a main effect, $F(1,67) = 15.77$, $p<0.0001$, as well as to 8-OH-DPAT as a main effect, $F(1,67) = 5.17$, $p = 0.026$. In addition, the DPAT/NE interaction was also significant, $F(1,67) = 4.77$, $p = 0.032$. However, individual *t*-tests revealed no significant differences among the feeding responses of the three drug groups (see Fig. 1, lower frame). Contrasting to this, 40-min water intakes were not significantly altered (see Fig. 1, upper frame). Furthermore, 22-hr food and water intakes were not reliably altered by any drug condition (data not shown).

Assessment of all injection sites was compromised because rats had not been perfused and many hypothalami sustained freeze-fracture during tissue processing. However, in material from seven animals in which clear assessments were possible, all placements were in the appropriate anterior/posterior and medial/lateral planes. While there was some variability in the dorsal/ventral plane, the cannula tips terminated in or near the PVN. Such variability was

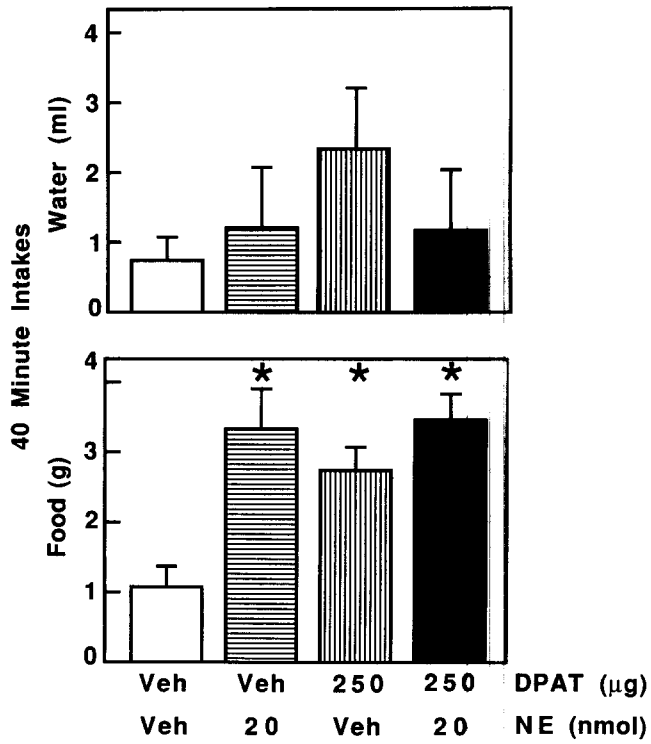

FIG. 1. Forty-minute food intakes (lower panel) and water intakes (upper panel) of rats pretreated SC with vehicle (Veh) vs. 250 μg/kg 8-OH-DPAT (DPAT) followed 45 min later with PVN infusion of Veh vs. 20 nmol l-NE. Values graphed represent mean ± s.e.m. responses. Group sizes (n) are: Veh/Veh (20); Veh/NE (17); DPAT/Veh (15); DPAT/NE (19). Asterisks indicate responses significantly higher ($p<0.01$) than Veh/Veh controls.

considered acceptable since it has been demonstrated in this laboratory (50) and others [e.g., (22)] that exact positioning within the PVN is not critical in order to obtain reliable NE feeding responses and because we independently confirmed the efficacy of these injection sites in preliminary NE screenings.

DISCUSSION

Enhancing brain 5-HT activity is generally acknowledged to inhibit feeding (5, 6, 43, 61). In addition, it has recently been suggested to be a potent suppressor of the short-term feeding response elicited by injecting NE into the PVN (20, 42, 65). Therefore, it seemed possible that a drug treatment which acutely impeded endogenous 5-HT release might reduce potential endogenous 5-HT inhibitory effects, resulting in further feeding enhancement following a noradrenergic stimulus. 8-OH-DPAT is a 5-HT_{1A} agonist which decreases raphe firing (4,14), impedes 5-HT release (27), and, in the dose range used here, elicits feeding in sated rats [see (18) for review] perhaps by decreasing 5-HT metabolism (3,33). For these reasons, we predicted that 8-OH-DPAT would enhance feeding in response to PVN-NE injection.

In the design used here, intrahypothalamic injection of NE, either alone or in combination with SC 8-OH-DPAT, elicited significantly more short-term feeding than did saline without changing short-term water intake or either ingestive response over the remaining 24-hr period. These observations confirm the well-known capacity of NE in the PVN to produce feeding in satiated rats (37,38). In addition, we confirmed that systemic 8-OH-DPAT could elicit significant feeding in its own right. However, the primary focus of this study was to test the possible synergistic enhancement of feeding by coadministering both agents. While the results of the ANOVA confirmed a reliable interaction between the two, this apparently occurred because the differences between NE vs. non-NE treatments exceeded that of 8-OH-DPAT vs. non-8-OH-DPAT treatments. Further inspection of the data suggests that this was largely due to the low responding by Veh/Veh rats compared to all other groups. Individual *t*-tests confirmed that there were no statistical differences in short-term feeding responses across the three different drug conditions. Therefore, these findings imply that the inhibition of endogenous 5-HT release evoked by 8-OH-DPAT does not synergize with exogenous NE infusion in the PVN to enhance food intake.

EXPERIMENT 2

In considering why the first study may have failed to provide any evidence of feeding synergy, at least two pharmacological issues presented themselves. The first was that the use of 20 nmol NE as a feeding stimulus might have produced near maximal (ceiling) effects under our experimental conditions, against which further feeding increments might not be seen. Alternatively, it is possible that the dose of 8-OH-DPAT chosen produced mild motoric effects that interfered with the capacity to show enhanced feeding. Although we saw no evidence of this from our informal observations, Dourish and coworkers (18) have previously reported that stereotypies can occur beginning at the 250 μg/kg dosage used. Therefore, to address these possibilities, two additional experiments were performed. In the first study, the test dosage of NE was lowered while retaining the same dosage of 8-OH-DPAT. In the second study, the test dosage of 8-OH-DPAT was lowered while the dosage of NE was returned to a strong feeding activational level.

METHOD

Twenty-eight new rats were implanted, screened and generally tested as described in Experiment 1. All 28 were found to be NE responders. As in Experiment 1, a 2×2 design was employed. However, unlike Experiment 1, animals were exposed to only one of the four possible drug conditions (n=7 each by random assignment) and tested only once. Also, since no differences in short-term water intake nor 22-hr feeding or drinking were seen in Experiment 1, these variables were not recorded during these studies.

In the first test, the dose of SC 8-OH-DPAT was left at 250 μg/kg, but the dose of PVN-NE was lowered from 20 nmol to 10 nmol. At the completion of this study, all rats remained viable. After two days rest, they were reassigned to one of four new groups (n=7 each) with equal experience to the drug classes used in the first test. A small pilot study run on separate normal animals determined that 120 μg/kg of SC 8-OH-DPAT could produce small (1.0–1.5 g) but significant feeding increases over those elicited by saline. Therefore, this dosage was chosen for the second test. With regard to the PVN-NE dosage used, 40 nmol was chosen as pilot studies revealed less robust feeding effects at 20 nmol in these rats than that seen in the animals used in Experiment 1.

At the end of both tests, rats were retained for use in another study to be reported elsewhere which ultimately required neurochemical assays of their hypothalami. Therefore, no histological

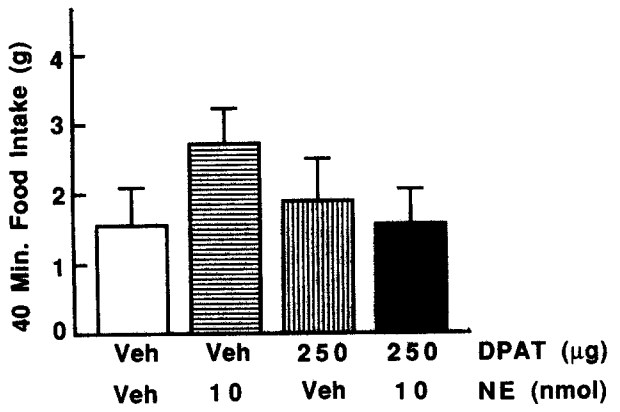

FIG. 2. Forty-minute food intakes in response to 250 μg/kg 8-OH-DPAT and/or 10 nmol NE. Treatment conditions and group abbreviations are the same as described in Fig. 1. Group sizes were 7 for each condition.

data are available to confirm the locus of implantation sites. All feeding data were collected and analyzed in the same fashion as described in Experiment 1.

RESULTS

The results of the first test are summarized in Fig. 2. A two-way ANOVA revealed no significant main effects for either drug treatment nor any interaction between them.

The results of the second test are summarized in Fig. 3. A two-way ANOVA revealed a significant main effect of NE- over non-NE-treated rats, $F(1,24)=25.96$, $p<0.0001$. However, 8-OH-DPAT did not produce significant feeding compared to the non-8-OH-DPAT-treated groups. Inspection of the graph shows that feeding in response to both drugs was apparently due to the NE component since the means of Veh/NE and DPAT/NE were essentially the same.

DISCUSSION

In the first of these two tests, neither the use of 10 nmol NE nor 250 μg/kg 8-OH-DPAT alone elicited reliable feeding. This was unexpected in both cases. While the mean NE response during testing was 1.0 g higher than Veh (see Fig. 2), this was not sufficient to attain statistical significance. Perhaps the manipulation of rats required during the systemic drug pretreatment which preceded PVN injections was responsible for this variable effect. Another contributing factor may have been the relatively small numbers of rats tested, making the minimal planned feeding effects more difficult to detect. In support of that possibility, 8-OH-DPAT alone also did not elicit reliable feeding, even though the mean response was statistically indistinguishable from that seen in the larger number of rats tested in Experiment 1 (compare data in Fig. 1, lower frame, with that in Fig. 2). However, all animals defecated shortly after SC administration, suggesting that the drug had been successfully administered. In addition, baseline food intake (i.e., Veh/Veh group) appeared somewhat higher compared to the responses seen in Experiment 1. Regardless of the reasons why neither agent alone was effective, the primary aim of this study was not necessarily invalidated as its purpose was to determine if submaximal NE stimulation would reveal any feeding enhancement elicited by concurrent 8-OH-DPAT. Since there was clearly room for enhanced feeding to be evoked when both drugs were given, the lack of any reliable feeding increment again mitigates against the hypothesis that suppressing 5-HT function might enhance NE-induced feeding.

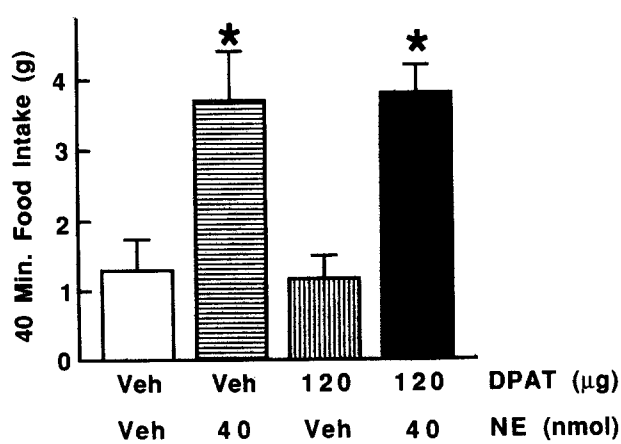

FIG. 3. Forty-minute food intakes in response to 120 μg/kg 8-OH-DPAT and/or 40 nmol l-NE. Treatment conditions and group abbreviations are the same as described in Fig. 1. Group sizes were 7 for each condition. Asterisks indicate responses significantly higher ($p<0.01$) than Veh/Veh controls.

In the second test, 40 nmol NE elicited strong, significant feeding as expected. However, the lower dose of 8-OH-DPAT did not, even though rats again showed the characteristic defecation pattern. Since rats receiving both drugs ate the same amount as those receiving NE alone, these data again argue against the likelihood that the failure to observe synergy in Experiment 1 could be ascribed to nonspecific effects of the higher 8-OH-DPAT dose originally used. The fact that the lower dose of this 5-HT_{1A} agonist was ineffective alone might again be related to the use of a small sample size and/or the added manipulations of animals associated with the dual-injection paradigm.

GENERAL DISCUSSION

A large amount of research has shown that treatments which enhance brain postsynaptic 5-HT activity can impede feeding under a variety of conditions. One such feeding condition is that stimulated by infusing NE into the medial hypothalamus of satiated rats (20, 42, 65). Separate research has shown that both monoamines are tonically released within this brain site in freely moving, unrestrained animals and that hunger enhances such release (36, 46, 59, 60). Recent work suggests that the relative amount of NE released appears to exceed that of 5-HT when feeding is stimulated (46). Collectively, these findings imply that the state of hunger and/or the act of feeding may be due to an imbalance between medial hypothalamic NE and 5-HT metabolism in which a relative abundance of NE is released. This possibility formed the conceptual basis for the current studies wherein the combined use of systemic 8-OH-DPAT along with PVN-NE infusion was conceived of as one means of functionally exaggerating this NE to 5-HT ratio.

Taken at face value, our results do not support the notion that impeding brain 5-HT function may enhance feeding elicited by medial hypothalamic infusion of NE. However, it would be erroneous to dismiss this possibility based solely on the experiments reported here. Such a conclusion can only be merited if the test conditions truly evoked the brain monoaminergic pattern desired in a selective fashion. In assessing additional literature on this subject, it may be that those conditions were not met. A fundamental design problem may have been the use of 8-OH-DPAT via the systemic route of administration. A more direct test

of our hypothesis would have been to acutely impede brain 5-HT function at the site of the NE injection. Unfortunately, pilot work revealed that PVN infusion of 8-OH-DPAT was ineffective in modifying feeding, a result which has been reported by others (32). This observation is in keeping with the now generally held conclusion that this 5-HT_{1A} agonist operates primarily on somatodendritic 5-HT receptors within the midbrain raphe complex rather than directly at terminal sites (29, 45, 63). Given that fact, as well as previous documentation that 8-OH-DPAT could reliably elicit feeding after SC injection [see (18)], we decided to employ this route for practical reasons. However, other research has shown that this procedure alters a variety of other processes, some of which might be incompatible with or disruptive to observing an enhanced NE feeding response. Specifically, in the dose and time range used here, 8-OH-DPAT has been shown to modify body temperature (1, 28, 31, 49, 67), cardiovascular (16, 44, 53, 58), respiratory (24), pancreatic (9,10), and adrenal (2, 23, 34, 49, 52) responses. From behavioral perspectives other than feeding, 8-OH-DPAT is known to modify such diverse processes as sleep-waking cycles (15), sexual behavior (55), salt thirst (11) and immobility to forced swim stress (7,8). While it is unclear which, if any, of these effects might have mitigated against a synergistic action with PVN-NE-induced feeding, the broad range of 8-OH-DPAT's functional consequences clearly brings into question the capacity of this route to elicit the specific effects desired.

Perhaps related to the issue of route of drug administration route is the added fact that 8-OH-DPAT may exert effects on receptor sites or neurotransmitter systems other than those characterized as 5-HT_{1A}. Two particularly salient examples come to mind: the α_2 adrenergic system and the dopaminergic (DA) system. With regard to the first, recent work from both receptor binding assays (13), as well as behavioral studies (66), indicates that 8-OH-DPAT may possess some α_2 antagonistic activity. This is potentially important since the NE feeding response has been strongly implicated as operating via agonistic activity at this receptor site (25, 40, 41, 64). Examination of our data does not suggest that a pure α_2 antagonism could explain our results since the magnitude of feeding elicited by 20 (Fig. 1, lower frame) or 40 (Fig. 3) nmol NE was unaffected by 8-OH-DPAT. However, it seems possible that a mixed 5-HT_{1A} agonism in conjunction with some α_2 antagonism might have produced a more complex change in brain neurochemical profile than planned. In addition to this possibility, the feeding elicited by 8-OH-DPAT has been suggested to have a strong DA agonistic component (19, 21, 48). Since changes in the metabolism of this neurotransmitter within the medial hypothalamus have also been implicated in the initiation or maintenance of feeding (46, 56, 57), the systemic route of administering 8-OH-DPAT may have also elicited changes along this axis that were unplanned for yet functionally significant.

Based on these additional considerations, it seems premature to discard the possibility that impeding brain 5-HT metabolism might synergize with a stimulus like PVN-NE infusion to further enhance food intake. Additional tests are needed in which more rigorous control is exercised over the site of action and the specificity of the pharmacological agent used in order to more properly probe this question. As part of that endeavor, we have already collected data showing that chronic depletion of brain 5-HT by intracisternal 5,7-dihydroxytryptamine treatment can enhance PVN-NE feeding responses (unpublished observations). To determine the generality of that finding, it is desirable to determine if more acute treatments which suppress 5-HT function might also amplify NE-induced feeding. Perhaps infusion of a 5-HT antagonist along with NE into the PVN might provide one means of testing that possibility.

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