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Feeding Behavior Induced by Central Norepinephrine Injection is Attenuated by Discrete Lesions in the Hypothalamic Paraventricular Nucleus[1]

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LEIBOWITZ, S. F., N. J. HAMMER AND K. CHANG. *Feeding behavior induced by central norepinephrine injection is attenuated by discrete lesions in the hypothalamic paraventricular nucleus.* PHARMACOL BIOCHEM BEHAV **19**(6) 945–950, 1983.—Extensive brain-cannula mapping studies in the rat have demonstrated that the hypothalamic paraventricular nuclues (PVN) is the most sensitive brain site for eliciting eating behavior with central norepinephrine (NE) injection. The present experiments examined the impact of lesions aimed at the PVN on this NE-elicited eating response. In rats with NE injection cannulas aimed at the lateral ventricle, bilateral lesions of the PVN significantly attenuated, by 60 to 70%, the eating effect induced by NE, at doses ranging from 20 to 160 nmoles. PVN lesions which extended ventrally to damage tissue lying within the periventricular region were more effective in abolishing the NE response than were lesions that remained confined to the dorsal aspects of the PVN. Large lesions located just dorsal to the PVN had no impact on the NE response. This evidence supports the primary role of the PVN in mediating the eating behavior elicited by central noradrenergic activation.

Feeding behavior Norepinephrine Hypothalamus Paraventricular nucleus

CENTRAL injection of norepinephrine (NE) into the hypothalamus of brain-cannulated animals has been shown to stimulate feeding behavior in several different species [7,12]. This stimulatory phenomenon, which has been most extensively investigated in the rat, is found to occur in food-satiated animals, which exhibit a vigorous eating response after NE injection, and also in hungry animals, which show an enhancement of their baseline feeding response after NE. To determine the nature of the brain receptors mediating this phenomenon, several investigators have interacted with NE a variety of receptor antagonists, and have obtained a selective blockade of NE-stimulated eating with locally administered α-adrenergic antagonists [5, 11, 16].

The brain site of NE's action has also been explored, and the evidence suggests that the medial hypothalamus, at the level of the anterior hypothalamic nucleus, is the most effective site for potentiating eating [6, 13, 20]. An extensive mapping study of 35 different brain areas, in over 500 rats, has demonstrated that essentially all sites outside the hypothalamus, as well as in the lateral portion of the hypothalamus, are relatively or totally unresponsive to NE [13]. In the medial hypothalamus, the paraventricular nucleus (PVN) was clearly distinguished as the most effective site for initiating feeding behavior with noradrenergic activation in the satiated animal. Sites greater than 0.5 mm rostral, caudal, dorsal, ventral, or lateral to this nucleus, including the ventromedial and dorsomedial nuclei, yielded significantly smaller effects. The threshold dose for eliciting eating with NE injection was remarkably low within the PVN, between 1.0 and 4.2 ng, and this effective dose became significantly higher as the injection site moved up to 0.7 mm lateral to the PVN [11,14].

In addition to eliciting feeding in satiated rats, NE has also been found to potentiate the ongoing feeding response of mildly hungry rats [13]. Anatomical analyses of this phenomenon showed the PVN, once again, to be most responsive; however, a smaller but reliable potentiation of eating was also found to occur along the periventricular hypothalamus adjacent to the third ventricle, both rostral and caudal to the PVN. In the lateral hypothalamus, in contrast, NE actually produced the opposite effect, namely, a suppression of feeding behavior.

This evidence has provided the basis for the present study, which was designed to test the dependence of the NE-induced feeding response on the integrity of the PVN. In these experiments, electrolytic lesions were aimed at the PVN, and their impact on eating induced by lateral ventricular injection of NE was tested. The results clearly indicate that discrete damage to the PVN is effective in attenuating or abolishing the robust eating response induced by NE injec-

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tion. These results were presented in preliminary form at the Annual Meeting of the Society for Neuroscience in 1979 [15].

METHOD

Subjects

A total of 41 male albino Sprague-Dawley rats (350–400 g) were used. They were housed individually and maintained and tested, in their home cages, on Purina lab chow pellets and tap water. They were kept on a 12:12 light-dark cycle with lights on at 6:00 a.m.

Surgery

As described previously [10], each rat was stereotaxically implanted under pentobarbital anesthesia with a chronic unilateral cannula aimed at the left lateral ventricle and bilateral stainless steel electrodes (size 00 insect pins) aimed at the PVN. With the upper incisor bar raised 3.5 mm above interaural line, the coordinates for the ventricular cannula were: 0.7 mm anterior to Bregma, 1.3 mm lateral to midline, and 5.0 mm ventral to skull surface. The coordinates for the bilateral PVN electrodes (insulated with Epoxylite and bared to a 0.5 mm concial tip) were: 0.5 mm posterior to Bregma, 0.4 mm lateral to midline, and 8.5 mm below skull surface. After placement of the cannula and electrodes, dental cement was used to permanently attach these implants to the skull. At the appropriate time, lesions were made (with the rats under light ether anesthesia) using a 1 mA direct anodal current, for a duration of 15 sec, and a rectal cathode. Sham-operated rats received identical treatment, except that no current was passed through the lesion electrode.

General Test Procedure

The rats were given 2 weeks of postoperative recovery before testing started. During this period, they were frequently handled and mock-injected, in order to adapt them to the test procedure. The drug tests were conducted in the morning every 2 or 3 days. During a 60-min pretest period, the rats were given fresh food and water, to insure maximal satiation, and were handled and mock-injected at least twice during this period. These satiating procedures were essential for maintaining low baseline eating, particularly after lesion when some of the rats were prone to exhibit overeating. At the end of this satiation period, the rats received lateral ventricular injections of the drug vehicle (5.0 μl of sterile physiological saline) and then were immediately given measured lab chow pellets. (Fresh water was available for the test, but water intake was not measured.) The food was removed 60 min later, at which point the drug test began. The rats received injections of *l*-norepinephrine-*d*-bitartrate (NE) dissolved in saline. Immediately after NE injection, the animals were given fresh pellets, and then the final measurement was taken 60 min later.

Before initiation of the actual experiment, all rats were given 2–3 screening tests to determine their responsiveness to ventricular injection of NE (40 nmoles). Those that responded consistently to NE and exhibited a food intake of at least 1.5 g (compared with a 0.3 saline score) were used in these experiments. As a result of this screening, 12 (29%) of the animals were eliminated from the experiment.

Subsequent to these screening procedures, all rats received 5 additional tests with 40 nmoles of NE prior to lesion, to obtain a precise evaluation of their pre-lesion baseline score. After lesion or sham operation, each rat received a total of 12 tests with 4 doses of NE (20, 40, 80, and 160 nmoles), presented according to a Latin square sequence. During the course of these NE tests, the rats' body weights were also recorded every 3 to 4 days, both before and after lesion. Statistical evaluations of the results were based on two-tailed *t*-tests for dependent or independent means.

Histology

To determine the precise placement of the drug injection cannulas and the hypothalamic lesions, the rats at the termination of the experiment were sacrificed under pentobarbital anesthesia and perfused with saline and a 10% buffered Formalin solution. Their brains were removed from the skull, and frozen sections of 50 μ were cut and then stained with cresyl violet. The location of the cannula tips and lesions was determined according to the atlas of König and Klippel [9]. In all sham-operated and lesioned rats, the tips of the cannulas appeared to be located within the ventricle at the level of the anterior commissure, approximately 1 mm rostral to the PVN.

RESULTS

Photomicrographs of frontal brain sections, showing the hypothalamic lesions, are presented in Fig. 1. The behavioral results obtained with ventricular injections of NE can be seen in Table 1 and Fig. 2. The outcome of this study clearly indicates that the integrity of the PVN is needed to produce a reliable NE eating response. Of the 20 rats lesioned, 10 had lesions which destroyed the entire PVN. Figure 1 (a–d) illustrates four of these bilateral PVN lesions. All of them were clearly focused on the PVN and, with one exception (Fig. 1d), produced little or no damage to the dorsomedial, ventromedial and anterior hypothalamic nuclei. Depending on the total size of the lesion, variable damage occurred to tissue lying ventral to the PVN. That is, in addition, to having total damage to the PVN, 5 of the PVN lesion animals sustained some damage to the periventricular area immediately ventral to the PVN (Fig. 1c, d and "PVN + periventricular" group in Table 1). This contrasts with the other 5 animals which had more circumscribed lesions that remained essentially confined to the PVN itself (Fig. 1a, b and "PVN only" group in Table 1). In addition to these 10 PVN lesion rats, there were animals (N=4) in this experiment which received only partial damage to the PVN, either unilateral (Fig. 1e) or involving just the dorsal aspect of the PVN ("Partial PVN" group in Table 1). A final set of animals (N=6) sustained lesions immediately dorsal to the PVN, with minimal damage occurring to the nucleus itself (Fig. 1f and "Dorsal to PVN" group in Table 1). This lesion was generally quite large, extending well into the thalamus.

Prior to lesion, each of these groups of animals exhibited a reliable and stable eating response (2.5–2.9 g) to ventricular injection of NE at 40 nmoles, as compared with the saline baseline scores of 0.1–0.4 g (Table 1). The post-lesion NE scores (Fig. 2 and Table 1) reveal a profound attenuation of NE-induced eating with bilateral lesions in the PVN. The sham-operated rats exhibited a dose-related eating effect after ventricular injection of NE at doses of 20–160 nmoles. A reliable eating response (at $p<0.01$) was obtained at all dose levels. In contrast to these sham animals, the bilateral PVN lesion rats failed to respond reliably to NE at doses of 20–80 nmoles, although at 160 nmoles, a small but significant effect on food intake (1.6 g, $p<0.05$) was observed. This score remains 59% ($p<0.01$) below that exhibited by the

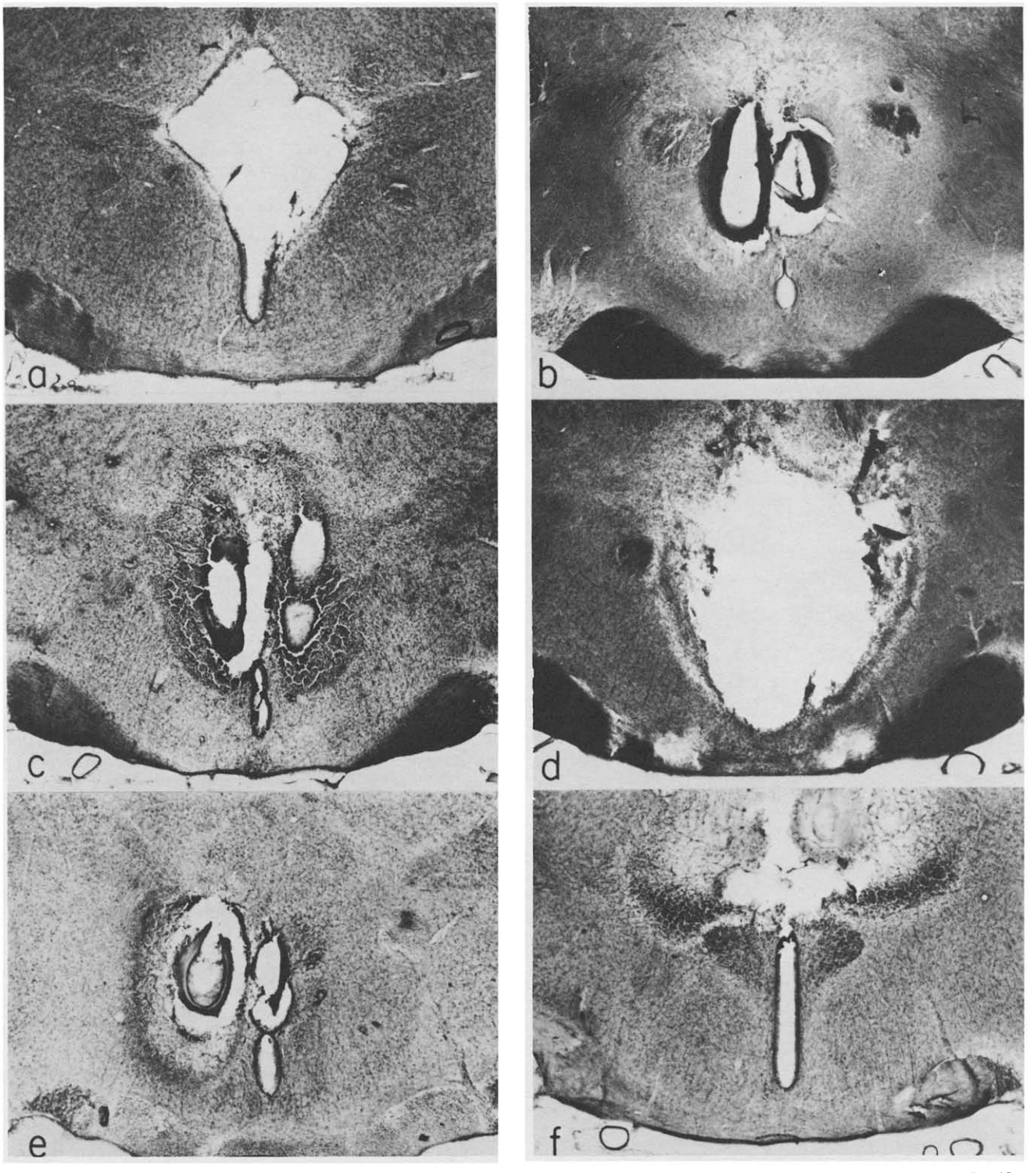

FIG. 1. Photomicrographs of frontal, cresyl-violet stained sections of the rat brain showing representative electrolytic lesions in the area of the paraventricular nucleus (PVN). All rats had injection cannulas aimed at the lateral ventricles, approximately 1 mm rostral to the PVN. 1 a, b: moderate size, bilateral PVN lesions with minimal damage to the periventricular region ventral to the nucleus. 1 c, d: large bilateral PVN lesions with additional damage extending into the ventral periventricular area. 1 e: partial (unilateral) PVN lesion. 1 f: large lesion dorsal to PVN.

TABLE 1

THE IMPACT OF LESIONS IN THE VICINITY OF THE PARAVENTRICULAR NUCLEUS (PVN) ON EATING (IN GRAMS) INDUCED BY NOREPINEPHRINE INJECTION INTO THE LATERAL VENTRICLE (20–160 nmoles)

		Pre-Lesion	Post-Lesion			
Lesion	N	40	20	40	80	160
Sham	9	2.9 ± 0.5§	1.7 ± 0.3†	2.8 ± 0.3§	3.3 ± 0.6§	3.9 ± 0.8§
Bilateral PVN	10	2.9 ± 0.3§	0.6 ± 0.2	0.9 ± 0.6	1.0 ± 0.5	1.6 ± 0.5*
PVN only	5	2.8 ± 0.4§	0.8 ± 0.3	1.1 ± 0.5	1.4 ± 0.4*	2.0 ± 0.4†
PVN + Periventricular	5	2.9 ± 0.3§	0.4 ± 0.1	0.7 ± 0.3	0.6 ± 0.3	1.2 ± 0.7
Partial PVN	4	2.5 ± 0.3§	0.7 ± 0.2	1.6 ± 0.5*	1.6 ± 0.3*	2.5 ± 0.5†
Dorsal to PVN	6	2.7 ± 0.6§	1.5 ± 0.5*	2.6 ± 0.5†	2.7 ± 0.5†	3.6 ± 0.8§

Given are means ± SEM for norepinephrine-induced food intake scores. All scores were statistically compared, via *t*-tests for dependent means, with the saline baseline scores (0.1–0.4 g) for each group. *$p<0.05$; †$p<0.01$; §$p<0.001$.

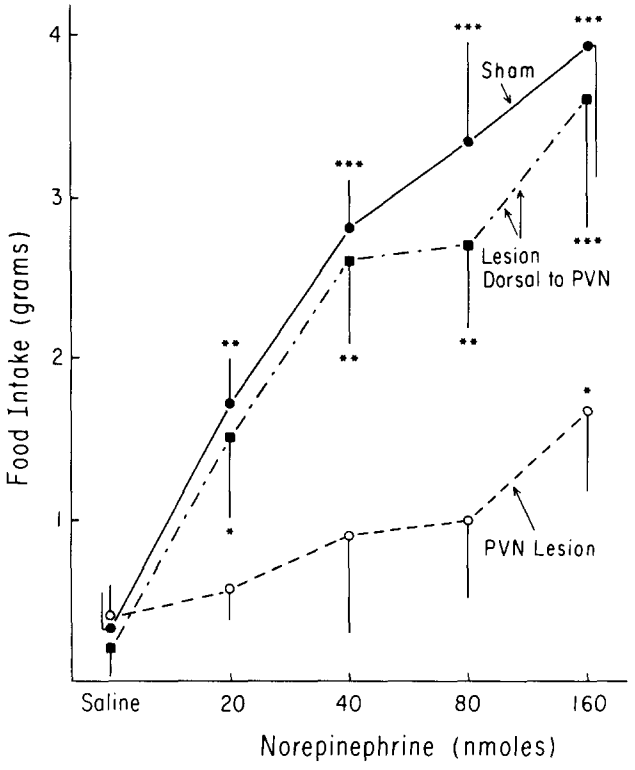

FIG. 2. Impact of electrolytic PVN lesions on the eating response induced by lateral ventricular injections of norepinephrine (NE, 20–160 nmoles). Bilateral PVN lesions essentially abolished the NE response, except at the highest dose (160 nmoles) which elicited a small but reliable eating response ($p<0.05$) in the lesion rats. Electrolytic lesions dorsal to the PVN had no effect on the NE dose response. Statistical comparisons between NE and saline baseline scores were significant at: *$p<0.05$; **$p<0.01$, and ***$p<0.001$.

sham animals at this high dose. The PVN lesion rats that sustained periventricular damage immediately ventral to the PVN appeared to show a greater loss of NE responsiveness than the animals with more restricted PVN lesions (Table 1). The "PVN + periventricular" lesion rats (Fig. 1c, d) failed to respond reliably to any dose of NE, in contrast to the "PVN only" rats (Fig. 1a, b), which exhibited small but reliable eating scores at 80 and 160 nmoles. By comparing these rats' scores with those of the sham animals, one can see that the PVN + periventricular lesion essentially abolished NE's action, whereas the more restricted PVN lesion significantly attenuated it by approximately 60%.

Rats with only partial damage to the PVN (Fig. 1e) showed a smaller but significant attenuation of their NE responsiveness at all dose levels (Table 1). They ate reliably to the 3 highest doses when compared with their saline baseline, and were attenuated by approximately 40% ($p<0.05$) when compared with the sham rats' NE scores. The large lesions that fell just dorsal to the PVN (Fig. 1f) appeared to have no impact on NE responsiveness (Table 1 and Fig. 2). These rats exhibited a reliable response to all NE doses and responded in an essentially identical fashion to the sham animals.

The body weight measurements taken from the animals used in these experiments demonstrated the pre-lesion body weight gain for all groups was in the range of 1–3 g/day. After lesion, some animals from each group exhibited a transient decrease in body weight during the first 2 to 3 days after lesion, but subsequent to this period, all rats rapidly regained their pre-lesion body weight and showed normal post-lesion weight gain throughout the drug testing period. Only the bilateral PVN lesion rats exhibited a significant change in body weight, namely, an increase from 1.8 g/day pre-lesion to 5.4 g/day post-lesion ($p<0.01$). In a recent study on non-cannulated animals, PVN lesions have been reported to cause hyperphagia and obesity in both male and female rats [18]. The present finding in cannulated animals is consistent with this report, although the magnitude of the effect in the present rats appears to be somewhat smaller than the 7.8 g/day body weight gain observed in the non-cannulated lesion animals of the other study.

DISCUSSION

This study establishes that the integrity of the hypothalamic PVN is essential for a normal feeding response to be elicited by central NE injection in satiated rats. It also suggests that periventricular tissue immediately ventral to the PVN may play a role in mediating this response. This finding is consistent with the results of cannula mapping studies which have examined the brain's receptivity to NE injection [13]. These studies have demonstrated that the medial aspect of the PVN, which is a predominantly parvocellular region [17], is most sensitive to NE's actions. In addition, however, the evidence indicated that, although NE-receptive sites may be most concentrated within the PVN itself, NE sensitivity can be detected along a more extended area within the hypothalamic periventricular zone, at the level of, as well as somewhat rostral and caudal to, the PVN [13]. In the present study, lesions which destroyed the PVN as well as the ventral periventricular area essentially abolished NE-induced eating at all dose levels. In contrast, lesions confined to the PVN abolished the NE eating response at the two lowest doses (20 and 40 nmoles) but left intact a small eating response (60% attenuated) at the two highest doses of NE (80 and 160 nmoles).

To determine the anatomical specificity of these PVN lesion effects and the exact limits of NE-receptive tissue, it will be necessary to examine a variety of other lesions which extend caudal and rostral to the PVN. Although the dorsomedial nucleus does not appear to be very receptive to direct NE injection [13], there is evidence to indicate that catecholamine innervation to this nucleus may be involved in the control of feeding behavior [28], as well as in mediating the eating response induced by 2-deoxy-D-glucose [2], a compound suggested to act through hypothalamic noradrenergic neurons [4, 16, 21–23]. Although the dorsomedial nucleus has not yet been examined in studies combining lesions with central NE injections, two other hypothalamic areas, namely, the lateral and ventromedial areas, have been investigated in this manner. Large lesions placed in the lateral hypothalamus have been found to leave intact the eating effect induced by lateral ventricular injection of NE [3]. This evidence is consistent with the finding that the lateral hypothalamus is relatively insensitive to local NE administration and thus, presumably, has relatively few noradrenergic sites for stimulating feeding [13]. This study also suggests that the efferent fibers which mediate the NE effect do not course through the lateral or far-lateral hypothalamus at the level of the ventromedial nucleus, where the lesions of this study were located. Knife cuts just lateral to the PVN, which would damage fibers passing between the lateral and medial hypothalamus, have also been found to leave intact the NE response [1].

The other study which tested hypothalamic lesion effects on NE-induced eating was conducted by Herberg and Franklin [8], who established that lesions in the ventromedial hypothalamus (VMH) were effective in attenuating the eating response induced by perifornical injection of NE. In this study, some of the VMH lesions increased daily food intake and consequently body weight gain; however, no relation between this effect and the attenuation of NE eating was observed. Further, not all VMH lesions were effective in antagonizing NE's action and, in some cases, an apparent disruption of the NE eating was actually due to an increase in the saline baseline control score rather than to a decrease in the NE score. Although PVN lesions also cause overeating and obesity [18] and present study), the saline baseline of the PVN lesion animals of this study remained unchanged, perhaps because of the particular procedures that were employed to fully satiate the animals prior to testing. Thus, further experiments will need to be done to determine whether the VMH is essential for NE-elicited eating. In light of the fact that the VMH is considerably less responsive to direct NE injection compared with the PVN [13], it would appear that the VMH does not contain a very high concentration of the α-noradrenergic receptors mediating the eating.

Instead of causing direct damage to these receptors, it is possible that the VMH lesion may disrupt NE feeding either by disturbing the animals' hormonal balance and/or by destroying specific fibers of passage, perhaps efferents which directly mediate NE feeding or fibers which descend to the autonomic nuclei of the lower brainstem and thereby modulate feeding. Evidence is accumulating to suggest that the PVN may be an important integrator of neuroendocrine and autonomic processes, and recent anatomical studies have defined the neural substrates for these functions, including long ascending and descending fibers linking the PVN to the medullary dorsal vagal complex, and shorter fibers coursing ventrally to the medial eminence and hypophysis [27]. It has been demonstrated that eating elicited by PVN NE injection is blocked by adrenalectomy and restored specifically by administration of corticosterone [17]. In addition to this study suggesting a permissive role for glucocorticoids in noradrenergic control of feeding behavior, there is evidence indicating that the NE eating response requires an intact vagus nerve, apparently dependent upon neural efferents to the pancreas that affect insulin release [15,25]. These studies, therefore, establish a link between the PVN noradrenergic system and neuroendocrine-autonomic function, and thereby lead us to propose that VMH lesion effects on NE feeding may be indirect, through damage of crucial projection systems rather than of NE receptor sites for feeding.

The present lesion results, showing an attenuation or blockade of NE eating after PVN lesions, are consistent with the brain-cannula mapping studies [13] which show the PVN to be the most responsive brain site to direct NE injection. These two studies support the existence of PVN noradrenergic receptors which modulate or control spontaneous eating behavior in the normal rat. This proposal is consistent with the study of Martin and Myers [19] which demonstrated that, during a rat's spontaneous eating bout, an increase in the efflux of ^{14}C-labeled NE occurs specifically in the periventricular region at the level of the PVN and ventromedial nucleus. It also agrees with the finding that chronic injection of NE into the PVN is effective in producing overeating and increased body weight gain [24]. With the recent finding that PVN lesions also cause hyperphagia and obesity [18], this evidence leads to the suggestion that the PVN has a normally inhibitory effect, either direct or indirect, on feeding behavior, and that NE acts to enhance food intake by inhibiting a PVN-controlled satiety function. Although there is a variety of additional evidence to support this concept [18], further studies will be needed to define the specific efferent projections which mediate this process [1].

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