Evoked release of $[14C]$norepinephrine from the rat hypothalamus during feeding

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The injection of norepinephrine (NE) into the brain can elicit dose-dependent feeding in the rat or monkey (4, 13, 20, 29) whether this monoamine is given at a discrete diencephalic locus (5, 32) or into the cerebral ventricles (29). When applied in a similar fashion, dopamine (DA) may also evoke feeding, but the total amount of food consumed is less than that following the application of NE and the latency of the response ordinarily is much longer (5, 14, 29). However, when dopaminergic neurons in the brain are destroyed by 6-hydroxydopamine (6-OHDA) in the rat, the aphagia is even more marked than that resulting simply from the depletion of norepinephrine stores alone (34, 39).

Although the part that the endogenous catecholamines play in feeding behavior remains to be clarified, Click et al. (11) reported that 48 h of food deprivation dramatically reduces the content of hypothalamic norepinephrine in the rat. In addition, Friedman et al. (10) concluded that the synthesis of both dopamine and norepinephrine is involved in the regulation of food intake. Clearly, if these monoamines mediate normal consummatory behavior, one crucial issue is whether either amine is actually released from hypothalamic neurons during the act of eating.

In previous experiments carried out in this laboratory, Myers (20) found that a pharmacologically potent humoral factor is released from the diencephalon of the fasted monkey. Moreover, a catecholamine-like substance was found to be liberated from several sites in the diencephalon of a primate fasted similarly (38). In the present investigation, sites in the brain at which an injection of NE induces the rat to feed were labeled with a microinjection of $[14C]$NE. Then the hypothalamus and other structures in the brainstem were perfused with an artificial cerebrospinal fluid (CSF) while the rat was in the act of feeding or while the animal pressed a lever to obtain food pellets. Curves reflecting the washout of radioactivity were derived (26) as the rat consumed food so that the characteristics of NE release could be determined. In addition, representative effluents collected from different sites of perfusion were analyzed by thin-layer chromatography (TLC) to obtain the ratio of NE to its metabolites.

METHODS

Each of 33 male albino rats of the Sprague-Dawley strain, weighing between 300 and 500 g, was housed individually and maintained on a 12-h dark, 12-h light cycle. Water was available ad libitum to 27 animals, but food was offered only for a 4 h interval each day to ensure that the rat ingested food when it was presented. The remaining six rats were trained in a Skinner box to obtain a 45-mg Noyes pellet by depressing a lever on a FR-6 schedule of reinforcement (that is, each rat was rewarded with a pellet on every sixth lever press). Each of these animals was placed in the operant chamber for 2 h of its 4-h feeding period. Rates of lever pressing were monitored on a cumulative recorder and the total number of lever presses per session was recorded on a digital counter. All animals were maintained at 85% of their body weight on either feeding regimen, but supplemental food was always provided if the rat failed to maintain 85% of its predeprivation weight.

Surgery. Using methods described previously (21), we implanted stainless steel guide tubes cut from 20-gauge thin-wall tubing in the brain of each rat after 35 mg/kg sodium pentobarbital had been given intraperitoneally. One of three sets of stereotaxic coordinates were used: 1) lateral cerebral ventricle, AP +5.4, L +1.7, H +4.0; 2) third cerebral ventricle, AP +5.4, L 0.0, H -1.5; and 3) anterior hypothalamus, AP +6.2, L +0.8, H -1.5. In 19 animals, two guide tubes were positioned bilaterally...
so that the tips rested 1 mm above the intended site of injection and perfusion; in the other rats, one guide tube was similarly implanted. So as to avoid the problem associated with glial inclusion, only at the moment of intraventricular injection or perfusion was a cannula actually inserted into the ventricular space.

The midline coordinate was derived by visualizing the superior sagittal sinus which was exposed after the overlying calvaria was removed by a dental bur. Each guide cannula, fitted with an indwelling stylet, was held in place by cranioplast cement packed around the cannula and three stainless steel anchor screws. Postoperatively, each rat was permitted at least 5 days to recover before it was used in an experiment.

Microinjection procedure. On the day of an experiment, the home cage containing the rat was brought from the colony to the test room. Except where noted during each injection or perfusion, the rat remained entirely unrestrained in its home cage. Radioactive dl-[methylene-\textsuperscript{14}C]norepinephrine bitartrate with a specific activity ranging from 47 to 56 mCi/mmol (Amersham/Searle) or crystalline [\textsuperscript{3}H]inulin with a specific activity of 140 mCi/mmol was used. After it had been lyophilized under nitrogen, the catecholamine was resuspended in an artificial CSF (22) freshly prepared in the following millimolar concentrations: Na\textsuperscript{+}, 127.65; K\textsuperscript{+}, 2.55; Ca\textsuperscript{++}, 1.26; Mg\textsuperscript{++}, 0.93; and Cl\textsuperscript{-}, 134.58. To retard degradation of the amine, 0.2 mg/ml of ascorbic acid was added to the stock solution to bring the pH of the solution to 3.6. Expressed as the free base, the concentration of NE in the stock solution was 1.7 \mu g/\mu l per 0.5 \mu Ci. A stock solution of [\textsuperscript{3}H]inulin was prepared with a concentration of 70 \mu g/\mu l per 0.5 \mu Ci.

A 23-gauge stainless steel injector needle was connected to a microfilter syringe by a length of PE-50 tubing. Before an injection was made, a volume of 1 \mu l was extruded and transferred carefully to a counting vial containing 10 ml of the scintillation cocktail. Then the tip of the injector needle was wiped with a sponge, inserted into the guide shaft to a depth 1 mm beyond the tip, and the injection was made. When given intraventricularly, 0.5–5.0 \mu Ci of NE (1.7–17 \mu g) were allowed to flow in by gravity over a 30- to 60-s interval in a volume of 2–10 \mu l; however, when the nuclide was applied to a tissue site, the solution was concentrated so that 0.5–2.0 \mu l of the solution containing 0.5–2.0 \mu Ci of NE was injected over 30–60 s. In both cases, the needle was wiped in place for 45 s after the injection to permit dispersion of the solution (21).

Push-pull perfusion. Prior to an experiment, the artificial CSF solution was passed through a 0.22 \mu m Swinnex Millipore filter. Concentric push-pull cannulas, similar to those used previously (23), were connected via polyethylene tubing to calibrated 1-ml syringes mounted on an infusion-withdrawal pump (Harvard Apparatus Co., model 935). The PE-50 tubing fastened to the 23-gauge pull cannula marked in 25-\mu l volumes by pieces of tape so that the exact rate of the perfusion could be constantly monitored by the movement of a minute air bubble in the line. The 20-gauge push cannula was connected to the push syringe via PE-20 tubing. A plastic bag containing crushed ice was placed on the pull syringe to help retard the degradation of the substances in the effluent. In addition, 0.2 mg/ml of ascorbic acid was added to the solution on the pull side of the system. The rate of perfusion was 20 or 23 \mu l/min and each perfusion ordinarily lasted for 5 min. Evidence obtained from dye studies shows that the extent of the area of tissue from which released [\textsuperscript{14}C]NE would be captured in the perfusate is a sphere of approximately 1 mm (23).

At the end of each perfusion the effluent was expelled rapidly into a calibrated centrifuge tube kept in an ice bath. A 50-\mu l aliquot of the chilled effluent was then pipetted into a scintillation vial containing 10 ml of PCS (Amersham/Searle) and the activity was counted in a Packard model 3320 Tri-Carb liquid scintillation spectrometer. The remaining perfusate was placed immediately under a stream of nitrogen and dried to its constituent salts. If the count rate of the 50-\mu l aliquot was greater than 500 cpm, the lyophilized sample was stored at −10°C for subsequent chemical analysis.

The first perfusion was performed 30 min after the injection of the labeled substance and successive perfusions were carried out at 30-min intervals for up to 13 h. If an occlusion occurred in the push-pull system or if the perfusate became discolored, the experiment was terminated immediately. The count rate (cpm) of each sample was corrected for quenching either by the method of internal or external standardization. Five microliters of [\textsuperscript{3}H]toluene with a specific activity of 3 \times 10\textsuperscript{6} dpm/ml (New England Nuclear) were used as the internal standard, whereas the radium 226 source of the spectrometer was used as the external standard. All samples were counted for 10 min and corrected to disintegrations per minute.

Thin-layer chromatography. The lyophilized effluent was prepared for thin-layer chromatography by resuspending the thin-layer chromatogram. Abbreviations are: NE, norepinephrine; NMN, norepinephrine; DHMA, dihydroxymandelic acid; and DHPG, dihydroxyphenylglycol.

### TABLE 1. Levels of [\textsuperscript{14}C]norepinephrine and its metabolites following cerebral injection of [\textsuperscript{14}C]NE

<table>
<thead>
<tr>
<th>Sample of Effluent</th>
<th>NE</th>
<th>NMN</th>
<th>MHPG</th>
<th>VMA</th>
<th>DHMA + DHPG</th>
<th>Trailing</th>
<th>Origin</th>
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<tbody>
<tr>
<td>0</td>
<td>15±2</td>
<td>14±5</td>
<td>23±6</td>
<td>31±3</td>
<td>27±8</td>
<td>24±8</td>
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<tr>
<td>60</td>
<td>9±5</td>
<td>8±5</td>
<td>10±2</td>
<td>7±3</td>
<td>3±1</td>
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<td>150</td>
<td>12±5</td>
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<td>7±3</td>
<td>3±1</td>
<td>8±2</td>
<td>14±5</td>
<td>15±7</td>
</tr>
<tr>
<td>180</td>
<td>13±5</td>
<td>13±5</td>
<td>7±3</td>
<td>3±1</td>
<td>8±2</td>
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<td>7±3</td>
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<td>8±2</td>
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<td>15±7</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SE of activity detected after cerebral injection of [\textsuperscript{14}C]NE. Each percentage figure was determined from the indicated number of samples. * Values below sample numbers represent interval after intracerebral injection of [\textsuperscript{14}C]NE. min.
it in 25 or 50 μl of 0.01 N HCl containing 1 mg/ml of unlabeled NE. If the rate of decay in a 5.0-μl aliquot of the suspension was higher than 500 dpm, a 5 μl-sample was applied at a point 1.5 cm from the bottom and left side of the chromatogram, but if the decay rate was less than 500 dpm, then 10-μl samples were applied.

Unlabeled reference standards were dissolved in 0.01 N HCl in a concentration of 1 mg/ml. The following standards, obtained from Sigma Chemical Co., were dried under a stream of nitrogen as they were applied to each plate with a 1-μl Drummond Microcaps disposable capillary pipette: 1) norepinephrine (l-arterenol hydrochloride); 2) dl-nor-metanephrine hydrochloride (NMN); 3) N-b-(3-methoxy-4-hydroxyphenylglycol) piperazine salt (MHPG); 4) dl-3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid, VMA); 5) 3,4-dihydroxyphenylglycol (DHPG); and 6) dl-dihydroxymandelic acid (DHMA). To determine \( R^d \) values, each standard was run alone in the two-dimensional chromatography system described by Fleming and Clark (9) in which 20 cm x 20 cm glass-backed TLC plates precoated with Avicel microcrystalline cellulose powder, 80 μm, without fluorescent indicator are utilized (Merek, Darmstadt). After the separation and identification of spots on the developed chromatogram, each of the dense areas was scraped off and placed in a counting vial containing 0.5 ml of water. After the water was swirled to elute the radioactivity, 10 ml of the fluor were added, the samples were counted for 10 min in the spectrometer, and the counts were corrected to disintegrations per minute.

**Free feeding.** To measure the release of [14C]NE as the fastest animal was eating or drinking, food or water was presented to the rat within two to three perfusions following the peak of radioactivity in successive push-pull effluents. To quantify the amount of food taken, a predetermined amount of Noyes pellets or Lab-Blox chow was placed in the food well 5 min before the perfusion was begun. Following this perfusion, additional perfusions were carried out with no food available. As a control for the specificity of release, a similar paradigm was used in these experiments to determine whether [14C]catecholamine activity in the effluent would change in the fluid-deprived rat while it was drinking.

**Lever pressing.** The same procedure was followed except that the animal was removed from its home cage and placed in the operant chamber after the peak in radioactivity had been reached. After the animal had worked for the food pellets for 5 min, the push-pull cannula assembly was reinserted and the perfusions continued. At the end of this perfusion, the rat was either removed from the operant chamber or permitted to continue eating up to and through the next perfusion. Water was not used as a reinforcer.

**Inulin control.** As a control for the specificity of release of intracellular rather than extracellular radioactivity, the washout of radioactive [3H]inulin was also observed under identical experimental conditions. Again, the same procedures were followed except that [3H]inulin rather than the labeled catecholamine was injected.

**Histology.** At the end of the experiments, each rat was anesthetized with an overdose of sodium pentobarbital given intraperitoneally. Then 0.9% saline followed by 10% buffered neutral Formalin was perfused retrograde through the thoracic aorta after the heart had been clamped. After fixation, the brain was sectioned at 100 μm on a Lipshaw freezing microtome and stained with hematoxylin according to the method of Wolf (37). The focus of each perfusion site was verified following standard anatomical procedures.

**RESULTS**

Although an increase in the release of [14C]NE in the effluent occurred in many experiments while the rat fed ad libitum, this change was found to be dependent on the anatomical site of perfusion. Moreover, the differential concentration of the metabolites of NE shown in Table 1 remained relatively stable during the course of the successive perfusions carried out at 30-min intervals following the injection of the labeled catecholamine. Of the 880 push-pull samples collected, 47 were analyzed by thin-layer chromatography since their specific activity exceeded 500 cpm per 50 μl effluent. A representative chromatogram is presented in Fig. 1. An average of 41% of the total amount of radioactivity applied to the chromatogram was recovered. From this residual, the percent activity attributable to NE and its metabolites was then calculated after the radioactivity in each spot had been counted in the spectrometer.

**Anterior hypothalamus.** The release of labeled NE occurred during feeding at four of the seven sites in the rostral part of the hypothalamus as depicted in Fig. 2. Each triangle denotes a site at which an increased output of [14C]NE occurred during feeding, whereas the circles indicate no change in [14C]NE release. The eight hypothalamic sites, represented by squares, from which the control [14C]NE washout curves were derived are also presented in Fig. 2. The perfusion loci shown in coronal plane AP 5.5 were considered histologically to be at the caudalmost extent of the anterior hypothalamic area.

The enhanced output of [14C]NE observed in the per-
Although the samples obtained from the feeding animals displayed a slower rate of $[^{14}C]$NE decline than the controls, the differences between them at each point were not statistically significant when individual $t$ tests were run.

Dorso- and ventromedial hypothalamus. At six of seven hypothalamic sites adjacent to the third ventricle, the release of $[^{14}C]$NE was detected in the perfusate collected while the rat was feeding. An anatomical mapping of these sites is presented in Fig. 4. Each solid triangle denotes a site at which the output of $[^{14}C]$NE increased during feeding, whereas the solid circles indicate sites at which the output of $[^{14}C]$NE was maintained constant. Sites indicated in lower portion of figure by filled squares (■) are sites at which no change in release occurred. Sites indicated by open squares (□) are sites at which control perfusions were carried out in fasted rats in absence of feeding.
the squares represent the loci at which control perfusions were carried out.

The mean proportional efflux of [14C]NE for the feeding and the control rats within medial hypothalamic sites is presented in Fig. 5. During the perfusion carried out while the animals fed, indicated by the zero point (abscissa), the mean proportional [14C]NE efflux increased significantly \( (t = 1.88, P < .05, df = 18) \) (36).

Although the most substantial elevation in [14C]NE efflux was found at loci in or contiguous to the ventromedial hypothalamus, consistent increases in the release of the catecholamine were also found at perfusion sites located somewhat more dorsally. Two representative experiments illustrating this anatomical differentiation are shown in Fig. 6. As a ventromedial site at coronal plane AP 4.6 was perfused (left panel), the augmented release was evoked at the same time that the animal consumed 2.35 g of food. In this case, the radioactivity recovered in 50 μl of push-pull effluent collected during feeding increased from a level of 88 to 388 dpm. In the other experiment shown in Fig. 6 (right panel), the animal was permitted to feed during three of four consecutive perfusions beginning at the zero point (abscissa), i.e., perfusions 0, 1, and 3. An increase in the release of radioactivity did not occur until the second perfusion after the rat had begun to feed. Only a small release of [14C]NE occurred during perfusion 3.

Lateral ventricle. With but one exception, there was no change in [14C]NE release during feeding when six sites in the lateral ventricle were perfused. In this single experiment, however, the tips of the push-pull cannulas, as denoted by the triangle in Fig. 7, impinged upon the body of the fornix, which has been implicated in the feeding system (24).

Figure 8 presents the curves of radioactivity obtained for the control rats and those fed at the zero interval. Although Fig. 8 shows that the proportional effluxes did not decline as rapidly in the groups given food, the differences were not significant.

Lever pressing and [14C]NE release. A substantial increase in the efflux of radioactivity was observed at two anterior hypothalamic sites in experiments in which [14C]NE washout curves were derived as the animal depressed a lever to obtain food. Representative cumulative records are presented in Fig. 9 (top panel) of the lever-pressing rates of one animal (AHA-2) during two experiments. The perfusion intervals (0, 1, 2, 3) are denoted by the horizontal bars. As in other experiments, the push-pull perfusion of the rat's hypothalamus failed to affect the animal's rate of responding for food pellets. Reflected in the [14C]NE washout curves obtained while the animal was feeding is the fact that the efflux of [14C]NE was related to the rate of lever pressing. Figure 9 (bottom) reveals that the release of [14C]NE in experiment A (left panel) increased at the zero-perfusion interval when the rate of responding for food was the highest. Similarly, in experiment B, the enhanced efflux...
of $[^{14}C]$NE occurred at perfusions 0 and 1 (Fig. 9, bottom, right panel) during the period when the rat was responding for food. Then the radioactivity efflux declined to a level below 500 dpm during perfusions 2 and 3, which corresponded to the low rate of lever pressing.

Table 2 presents the level of radioactivity detected in an aliquot of the perfusate collected before (Pre) and during the first lever-pressing session in each experiment; the proportional measure of $[^{14}C]$NE efflux was computed from these two values. Table 2 shows that the three perfusates having the greatest $[^{14}C]$NE activity were also those that were obtained when the rat emitted the largest number of lever presses for food pellets. This table also illustrates the

![Figure 7](image7.png)

**Fig. 7.** Sites in or adjacent to lateral ventricle perfused after $[^{14}C]$NE had been injected intraventricularly. Triangle (▲) indicates site at which efflux of NE increased during feeding. Circles (●) indicate no change in $^{14}C$ efflux. Sites at which control curves were obtained in absence of feeding are shown in lower sections by filled squares (■).

![Figure 8](image8.png)

**Fig. 8.** Mean ± SE proportional efflux of $[^{14}C]$NE at sites in or adjacent to lateral ventricle in rats which fed during perfusion 0 as indicated by black bar (▲) and in nonfeeding control rats. Curves are based on 6 control experiments and 6 feeding experiments.

![Figure 9](image9.png)

**Fig. 9.** *Top:* cumulative records of lever pressing in 2 separate experiments (A and B) for a representative rat (AHA-2). Push-pull perfusions 0–3 were performed during intervals indicated by bar (▲). Each vertical excursion of pen indicates 500 lever presses. Records marked A and B correspond to a 2-h interval of lever pressing. Bottom: $[^{14}C]$NE washout curves for animal AHA-2, expressed in dpm, during same experiments shown at top. Site of the push-pull perfusion is shown in inset. Rat lever pressed intermittently (see *Top*) during period of time denoted by bar (▲). Perfusion were carried out at 0.5-h intervals.

**Table 2.** $[^{14}C]$NE radioactivity detected in a 50-μl aliquot of push-pull effluent

<table>
<thead>
<tr>
<th>Animal</th>
<th>Pre</th>
<th>During</th>
<th>DPM</th>
<th>Lever Responses and No. of Pellets</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA-1</td>
<td>790</td>
<td>1,518</td>
<td>1.92</td>
<td>132 (22)</td>
</tr>
<tr>
<td>AHA-2</td>
<td>9,089</td>
<td>7,763</td>
<td>1.39</td>
<td>132 (22)</td>
</tr>
<tr>
<td>AHA-1</td>
<td>183</td>
<td>79</td>
<td>.43</td>
<td>78 (13)</td>
</tr>
<tr>
<td>AHA-2</td>
<td>1,107</td>
<td>1,746</td>
<td>1.37</td>
<td>102 (17)</td>
</tr>
<tr>
<td>AHA-1</td>
<td>181</td>
<td>191</td>
<td>1.05</td>
<td>72 (12)</td>
</tr>
<tr>
<td>AHA-2</td>
<td>2,112</td>
<td>1,057</td>
<td>.50</td>
<td>36 (6)</td>
</tr>
</tbody>
</table>

Effluent was collected immediately before (Pre) and during first period of lever pressing for food on an FR-6 schedule of reinforcement. The proportion comparing these perfusates and the number of lever presses emitted during each perfusion are also presented.

The general reproducibility of the results of $[^{14}C]$NE efflux obtained when the same site is perfused in the same animal.

Three perfusates collected during lever pressing were analyzed for their content of NE and its metabolites.
the radioactivity scraped from the chromatogram, 32% was found in the NE spot, as indicated in Table 3. This value did not differ significantly from the percent of NE detected in the effluents collected at a corresponding interval following injections of $[^14]C$NE in the food-deprived rats ($t = .32$, df = 6, NS). The mean relative amounts of $[^14]C$NE and its metabolites shown in Table 3 were very similar to the profile of metabolites presented in Table 1 for the 47 perfusates collected during the ad libitum food intake experiments.

In the four control experiments with inulin, the average efflux of $[^3]H$inulin from the same hypothalamic site was not significantly different during lever pressing from that of the normal control washout curve. The mean proportional efflux of $[^3]H$inulin during the lever-pressing-feeding interval was 0.58 ± 0.26, as compared to a mean proportional $[^14]C$NE efflux of 1.17 ± 0.29 also obtained during intervals in which the rats were pressing the lever.

Histological sections are presented in Fig. 10, which shows two representative sites of perfusion: (A), in the anterior hypothalamus at the tip of the anterior commissure; and (B), on midline just below the dorsal aspect of the third ventricle.

**DISCUSSION**

These experiments provide physiological evidence that endogenous NE may actually be released from nerve terminals in the hypothalamus as an animal consumes food. However, the precise role of this catecholamine in hunger or satiety is still uncertain. Further, the afferent or efferent mechanism which triggers the observed release of NE from circumscribed sites is equally unclear. The fact that we failed to observe any significant release of NE in the lateral ventricle, or of $[^3]H$inulin at any site, strengthens the view that the alteration in the activity of NE occurs specifically at sites in the ventromedial and anterior hypothalamus during feeding. These results, therefore, could be interpreted in terms of the theories that implicate these two anatomical areas in ingestive behavior in rodent as well as in primate species (10, 11, 20, 31, 38).

One theory is that adrenergic receptors in the ventromedial hypothalamus are inhibited by the local release of NE (17). This would decrease the inhibitory outflow of impulses to the lateral hypothalamus which, in turn, would permit a hunger system in the lateral hypothalamus (30) to predominate. In accord with this idea, iontophoretically applied NE is known to attenuate the firing rate of a single neuron (3). The release of $[^14]C$NE in effluent collected during feeding from the ventromedial hypothalamus and other tissue adjacent to the third ventricle could reflect the initial step in this dual inhibitory process, i.e., the suppression of ventromedial inhibitory cells by the postsynaptic action of locally released NE.

The extirpation of the caudal part of the ventromedial hypothalamus abolishes the feeding response elicited earlier by the application of NE to the anterior hypothalamus (15). The anterior sites that are rendered insensitive to NE following this lesion are homologous to those thought to be most sensitive to exogenously applied NE (4, 8).

Herberg and Franklin (15) hypothesized that suppression of neuronal activity in the ventromedial hypothalamus occurs following the injection of NE into the anterior preoptic area, and that this inhibition is probably mediated by impulses transmitted along the hypothalamicopetal pathway of Chi (6) which projects to the posterior portion of the ventromedial hypothalamus via the amygdala and the postcommissural stria terminalis. Since the connections of the stria terminalis within the hypothalamus are so widespread (7), it is possible that feeding induced by NE injected at other hypothalamic sites may indeed be mediated via this diffuse pathway through an inhibitory mechanism to the ventromedial hypothalamus. In this connection, electrical stimulation of the ventromedial hypothalamus

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**TABLE 3. Relative amounts of $[^14]C$NE and its metabolites that were detected in three push-pull perfusates collected from rat as it emitted lever-pressing response**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Origin</th>
<th>Trial</th>
<th>Radioactivity (percent ± SE)</th>
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<tbody>
<tr>
<td>NE</td>
<td></td>
<td></td>
<td>32 ± 3</td>
</tr>
<tr>
<td>VMA</td>
<td></td>
<td></td>
<td>17 ± 4</td>
</tr>
<tr>
<td>5-MT</td>
<td></td>
<td></td>
<td>10 ± 4</td>
</tr>
<tr>
<td>MHPG</td>
<td></td>
<td></td>
<td>11 ± 4</td>
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<td>3,4-DHPG</td>
<td></td>
<td></td>
<td>2 ± 2</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td>17 ± 5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>6 ± 4</td>
</tr>
</tbody>
</table>

Values given are percent ± SE. Abbreviations are the same as in Table 1.
can enhance or suppress the single-unit activity recorded from cells in the lateral hypothalamus (35).

Overeating and obesity may occur following lesions either by 6-hydroxydopamine injections or by electrolytic means of the ascending ventral noradrenergic nerve bundle (1) which originates in the ventrolateral tegmentum of the mesencephalon (2). The lesions that are most effective in inducing obesity are located at the rostral tip of the ventromedial hypothalamus where noradrenergic fibers from the ascending noradrenergic bundle are densely packed (12). Thus, NE would seem to be involved in neural systems modulating satiety as well as feeding.

The excitatory-inhibitory nature of NE is exemplified in two ways. First, NE applied iontophoretically to the perifornical hypothalamic region causes both the inhibition and the excitation of nerve cells (16). Second, the depletion of catecholamines in the lateral hypothalamus by the direct injection of 6-OHDA causes severe and prolonged deficits in normal food intake of the rat (27, 33), but the similar depletion of NE from the ventral ascending bundle produces overeating (1). Therefore, NE may subserve an excitatory system in the lateral hypothalamus for food-seeking behavior, which functions simultaneously with an NE system which projects to the ventromedial hypothalamus and which inhibits the impulses underlying satiety.

A substantial release of [14C]NE from the anterior hypothalamus occurred while the rat was pressing the lever to obtain food which was similar to the efflux observed from the medial hypothalamus during ad libitum food intake. Whether this increased release of NE in the anterior region reflects additional neural activity necessary for the lever response, or an aspect of motivation-to-respond induced by the task, or the motor counterpart of the activity is not known. In this connection, NE injected into the rat’s cerebral ventricle does elicit the motivated response (lever pressing) to obtain food pellets (25), whereas the micro-injection of 6-OHDA into the lateral hypothalamus causes a motivational deficit in the same lever-pressing task for food getting (18).

Finally, we have observed that dopamine release from the hypothalamus is augmented during feeding, during the drinking of water, and during lever pressing for food (19). Thus DA may not only serve as a substrate for the metabolism of NE in the nerve ending, but also may possess an effect of its own in terms of motor control of ingestive behavior (34). Thus the catecholamines could constitute two humoral elements in the complex neuronal code (24) involving the monitoring of nutrients: the stimulus to feed, the signaling of satiation, and the effferent components underlying the act of feeding itself.

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