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Amphetamine-Induced Anorexia: Analysis With Hypothalamic Lesions and Knife Cuts

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McCABE, J T , D BITRAN AND S F LEIBOWITZ *Amphetamine-induced anorexia Analysis with hypothalamic lesions and knife cuts* PHARMACOL BIOCHEM BEHAV 24(4) 1047–1056, 1986 —The present study examined the hypotheses that the midlateral perifornical region of the hypothalamus (PFH), at the level of the ventromedial nucleus, plays a crucial role in amphetamine (AMPH)-induced anorexia and that mediating fibers ascending to this brain region follow a midlateral course through the caudal hypothalamus Electrolytic lesions that destroyed the PFH region attenuated the feeding suppression induced by intraperitoneal administration of AMPH Lesions placed anterior, dorsal, or medial to this region, in contrast, did not decrease AMPH's effect The medially-placed paraventricular nucleus lesion, in fact, enhanced drug response Midlateral coronal wire-knife cuts in the caudal hypothalamus also attenuated AMPH anorexia The crucial midlateral caudal hypothalamic cut also disrupted anorexia induced by direct injection of AMPH into the PFH area The results obtained from the lesion data support the hypothesis that the PFH region is essential to AMPH's suppressive effect upon feeding, and the KC data suggest that crucial catecholamine fibers mediating this drug response ascend specifically through the midlateral portion of the hypothalamus

Amphetamine Feeding Perifornical hypothalamus Amphetamine anorexia and knife cuts Catecholamines

RESEARCH conducted to date has provided some evidence that the well-known anorectic effect of amphetamine (AMPH) is mediated, at least in part, by hypothalamic catecholaminergic mechanisms Booth [7] first demonstrated that hypothalamic injections of AMPH suppress feeding. Leibowitz has utilized the central injection technique to more precisely determine the anatomical site where central injection of AMPH most effectively inhibits feeding in hungry rats [34,38] Direct injection to the perifornical lateral hypothalamus (PFH), specifically at the level of the ventromedial nucleus, induced the greatest anorectic response. Injections to many other hypothalamic sites, as well as extra-hypothalamic sites, were relatively ineffective Additionally, central injections of catecholamine antagonists to the PFH area were found to reliably block anorexia induced by perifornical AMPH injections, as well as by peripherally injected AMPH [35,38]

Consistent with the hypothesis that AMPH acts through hypothalamic mechanisms are the findings of hypothalamic lesion studies These studies have demonstrated that lesions in the lateral hypothalamus (LH), which damage the medial forebrain bundle, attenuate or abolish the anorectic effect of peripherally administered AMPH [6, 12, 23, 50]. In some cases, LH lesioned cats and rats have actually been found to increase their feeding in response to AMPH injection [56,60]. In contrast to the effect of LH lesions, animals sustaining damage to other hypothalamic regions, including the ventromedial hypothalamic area or anterior hypothalamus, are reported to have an enhanced anorectic response to AMPH [14, 20, 46, 48, 55].

In the present study, a more detailed analysis of the impact of hypothalamic manipulations on AMPH's anorectic action was conducted. Of particular interest was the midlateral PFH area, which as compared with the lateral and far-lateral hypothalamic areas was found to be maximally sensitive to AMPH's anorexigenic effect [34] We therefore focused our lesions on this area, which left intact the lateral portion of the medial forebrain bundle, and contrasted the effects of these lesions with those of lesions to the paraventricular nucleus (PVN), a medial area that mediates an opposite effect on feeding, namely, alpha-adrenergic stimulation of food intake [36,42] In addition, coronal wire-knife

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cuts (KCs), which produce greater damage to fibers while sparing local cell bodies, were used to examine potential projection routes taken by axons mediating AMPH anorexia Cuts through the medial and midlateral hypothalamus, at the caudal hypothalamic level, were investigated In these studies, feeding suppression was induced by intraperitoneal as well as PFH injections of AMPH. For comparison, fenfluramine (FENF), an anorectic drug which appears to act through the release of serotonin [24], was also studied

The results of these experiments, presented in preliminary form at the 10th annual meeting of the Society for Neuroscience [43], provide evidence to suggest that AMPH anorexia is mediated, at least in part, by the perifornical region of the hypothalamus Lesions or KCs specifically in this area, as opposed to in more medial, dorsal, and anterolateral hypothalamic sites, abolished anorexia induced by peripheral and central AMPH administration In contrast, none of these lesions or KCs affected anorexia produced by peripherally injected FENF

EXPERIMENT 1

In the first experiment, dose-response studies were undertaken with intraperitoneal AMPH and FENF injections These tests were conducted in order to determine the optimal dose for the planned lesion experiments, i e , a dose that produces a stable but only partial feeding suppression under the specific conditions of our experimental paradigm

METHOD

Subjects

Male, Sprague-Dawley rats (350 g Charles River) were individually housed in wire-mesh cages, and maintained on a 12 12 hr light (0700 hr) dark (1900 hr) cycle Except on test days (every other day), animals always had access to a sweetened milk-mash diet (25 g powdered Purina rat chow 25 g granulated sugar 20 g Carnation brand evaporated milk), and water was available ad lib Tests were conducted in the midafternoon (14 00–16·00 hr)

Test Procedure

Animals in the AMPH dose-response study (n=5) received intraperitoneal injections of normal saline (1 ml/kg) or 0.25, 0 50, 1 0, or 2.0 mg/kg/ml of d-amphetamine sulfate (Smith, Kline, and French) dissolved in saline Animals in the FENF dose response study (n=8) received intraperitoneal injections of saline (1 ml/kg) or 0.22, 0 66, 2.0, 6 0, or 12 0 mg/kg/ml of fenfluramine hydrochloride (A. H Robins) dissolved in saline. Each dose level was randomly administered to every animal 2 or 3 times, and at least 3 different dosages, in different animals, were tested on any single day On each test day, rats were food-deprived for 4 hr prior to drug injection The animals were then injected with drug or saline, and 15 min later were given a pre-weighed dish of fresh mash Consumption was measured by weighing each rat's mash dish 60 min after injection Spillage of food was negligible

RESULTS AND DISCUSSION

Figure 1 presents the mean feeding responses (±SEM) after peripheral injection of several dosages of AMPH Analysis of variance indicated a significant suppressive effect of AMPH on feeding behavior, $F(4,16)=33.83, p<0.001$

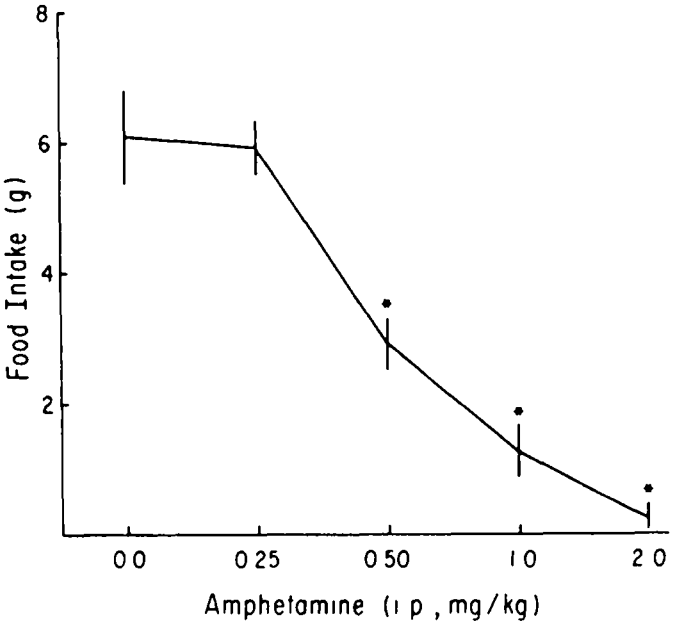

FIG 1 Dose-response study of feeding responses (grams±SEM) during 60 min after intraperitoneal (IP) injection of saline or d-amphetamine sulfate in 4-hr food deprived rats (n=5) Dunnett's t-statistic (*$p<0.01$) indicated that the 0 5–2 0 mg/kg dosages produced significant decreases in mash intake compared to saline injection

A Dunnett's t-statistic demonstrated that animals ate less food, compared to saline, after injection of every AMPH dose ($p<0.01$), except 0 25 mg/kg, $t(5,16)= -0.31, -4.99; -7.50, -9.06$, for 0.25, 0 50, 1 0, and 2.0 mg/kg, respectively At 0.5 mg/kg, AMPH produced approximately a 50% suppression of food intake

Figure 2 presents food intake responses after peripheral administration of FENF as a function of dose Analysis of variance indicated a significant change in amount consumed at different dosages, $F(6,42)=11.17, p<0.01$, and Dunnett's t-statistic indicated that food intake after the 2 0, 6.0, and 12 0 mg/kg dosages were significantly less than after saline, $t(6,35)= -3.68, -2.70, -4.18$, respectively, all $p<0.05$ The amount of food intake after administration of 0 22 and 0.66 mg/kg failed to differ significantly from saline baseline intake, $t(6,35)=0.96, -1.50$, both $p>0.10$

The dose responses to AMPH and FENF generally show that increasing dose levels significantly decrease the amount consumed by mildly food-deprived rats It is not clear why no greater feeding suppressive effect was observed with the 6.0 and 12.0 mg/kg doses of FENF, as compared with the 2 0 mg/kg dose. This may be due to the development of tolerance to this drug's anorectic action, which occurs rapidly, but not completely, at higher dosages [26, 40, 49] From these tests, it becomes clear that the optimal drug doses to be used in the lesion experiments are 0 5 mg/kg for AMPH and 2 0 mg/kg for FENF These are relatively low doses which produce a partial feeding suppression with minimal side effects

EXPERIMENT 2

In this experiment, animals sustained electrolytic lesions to the PFH area or to the PVN, to determine whether these

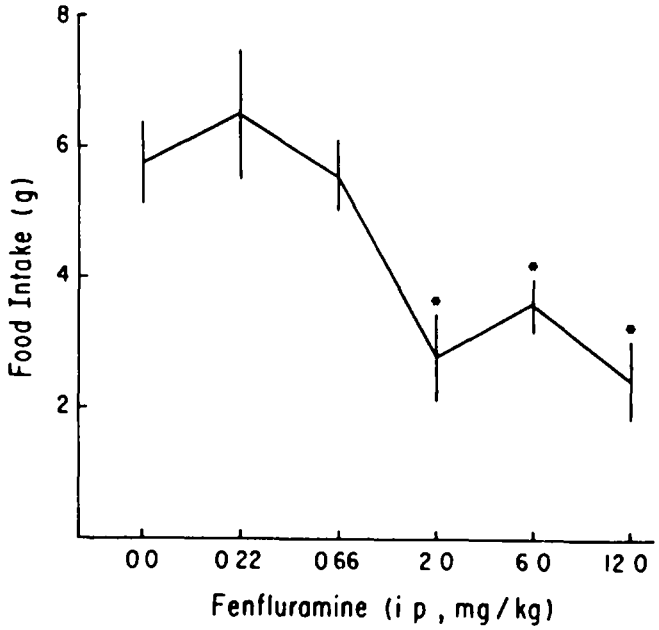

FIG 2 Dose-response study of feeding responses (grams ± SEM) during 60 min after intraperitoneal (IP) injection of saline or fenfluramine hydrochloride (FENF) in 4-hr food deprived rats Dunnett's t-statistic (*$p<0$ 05) showed intraperitoneal injection of 2 0–12 0 mg/kg of FENF significantly decreased food intake (60 min post-injection) below levels seen following injection of saline

hypothalamic sites are essential to the anorectic effects of peripherally administered AMPH and FENF.

METHOD

Subjects

A total of 28 rats received PFH lesions, 14 received PVN lesions, and 10 sustained sham surgery During the first three weeks after surgery, daily food intake was measured in some of these animals to ascertain the degree of lesion-induced debilitation These results are summarized elsewhere [42]. In brief, animals showing daily food intake of less than 20 g (compared with intake level of approximately 30 g/day for sham rats) were not used in this experiment. A sweetened milk-mash diet and water were available ad lib, except for 4 hr on testing days when the food was removed.

Surgery

Bilateral PVN and PFH lesions were made in different animals by passing a 1 mA anodal current for 12–15 seconds through a stainless steel insect pin (size 00) that was coated with epoxylite except for 0.5 mm at the tip Before surgery, each rat was anesthetized with 60 mg/kg (approximately 20 mg in 0.4 cc saline) sodium pentobarbital (Nembutal. Abbott Labs.) For both lesions, the nosebar was set 3.1 mm above interaural line, and the depth placement was determined with respect to skull surface For PVN lesions, the electrode carrier was tilted 4° in the lateral direction, and the electrode tip was placed in the PVN region using coordinates: 0 7 mm rostral to bregma suture/0.8 mm LAT/−8 7 mm DV. For PFH lesions, a straight carrier was used, and the electrode tip was placed into the PFH region with coordinates −0 6 mm behind bregma suture/1.2 mm LAT/8.8–9 2 mm DV. Sham animals received similar treatment except that the electrode was lowered to within 3 mm dorsal of the lesion sites, and no current was passed through the electrode.

Behavioral Testing

These animals were initially tested with other drugs during the first three to five weeks postsurgery [42]. Because of time constraints, single dose levels of AMPH and FENF were therefore selected for the present experiment where AMPH and FENF decreased food intake by a moderate 50% On each test day, animals were food-deprived for 4 hours. They were then administered saline (1 cc/kg), AMPH (0.5 mg/kg), or FENF (2.0 mg/kg) intraperitoneally, with saline injection always given in counterbalanced order with the drug Fifteen min after drug injection, animals received a preweighed dish of mash, and consumption was measured 60 min later. Every animal received 2–3 tests each with saline, AMPH, and FENF. After completion of these tests, the rats were transcardially perfused with 10% buffered formalin and their brains were placed in a 30% sucrose-buffered solution. Frozen 50 μ sections were cut and stained with cresyl violet for histological analysis

Data Analysis

To provide a complete picture of the baseline scores and drug effects observed in each set of animals, average group feeding responses to both saline and drug, and their statistical analyses, are given in the figures. In some cases, tests of homogeneity of variance indicated that an analysis of variance, using raw scores, involved pooling heterogeneous error variances. To circumvent this variance as well as simplify the data, the raw food intake scores were converted to percent inhibition of feeding scores (drug minus saline scores, divided by saline scores). These data were then used to compare the lesion and knife cut groups with the sham groups, using an analysis of variance. In cases where sample size was particularly small, these groups were not included in statistical comparisons, although within-group t-tests were performed to assess their drug response.

RESULTS AND DISCUSSION

A total of 10 of the original 28 rats that underwent PFH lesion surgery sustained bilateral on-target PFH lesions. These lesions were located in the midlateral hypothalamus and damaged the fornix itself and surrounding tissue (Figs. 3a and 4) In terms of their anterior-posterior extent, on-target lesions were centered at the level of the ventromedial nucleus (VMN) and extended as far anterior as the level of the PVN, and at times as far caudal as the caudal extent of the posterior hypothalamus. Often the lesions damaged the ventrolateral border of the dorsomedial nucleus (DMN) and dorsolateral border of the ventromedial nucleus, and extended into the medial half of the medial forebrain bundle and zona incerta, but not further lateral. As can be seen in Fig. 1, this lesion often dilated the third ventricle. Animals with bilateral PFH lesions were hypophagic immediately after surgery [42], but it appears that lesion-induced ventricular dilation does not cause decreased food intake since a similar effect after ventromedial hypothalamic lesions can produce overeating [58] Some additional animals sustained "unilateral PFH" lesions (n=9), with little or no damage apparent on the contralateral side or, in two cases, a small contralateral lesion in the area of the VMN Six animals sustained bilateral lesions that missed the PFH region

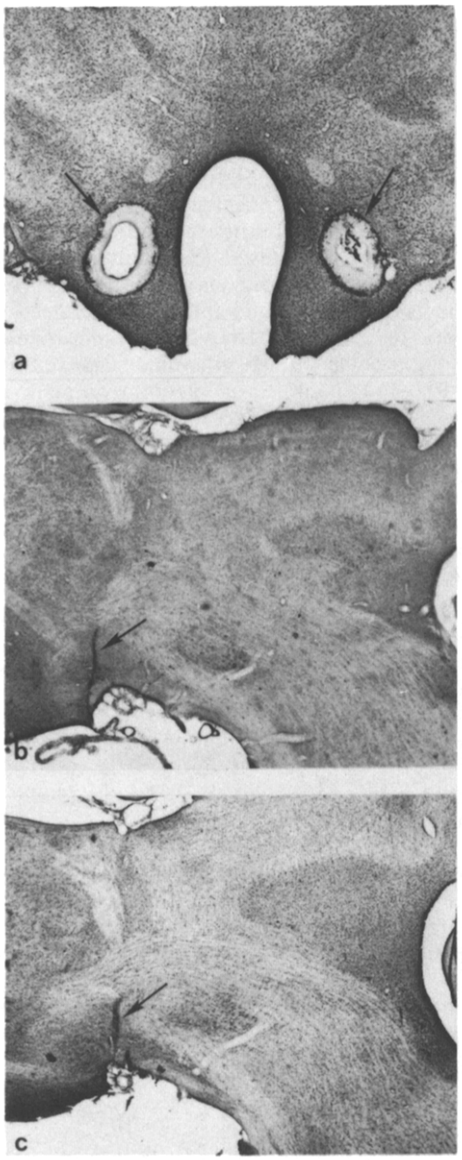

FIG 3 Photomicrograph (a) of a representative bilateral lesion of the lateral perifornical hypothalamus (PFH) This lesion damaged the entire PFH region from the level of the PVN through the level of the ventromedial nucleus and at times as caudal as the anterior portion of the posterior hypothalamic area Tissue damage extended into the medial half of the medial forebrain bundle and into the lateral portions of the dorsomedial and ventromedial nuclei A significant portion of the medial forebrain bundle remained intact Figures b and c depict midline and PFH KCs, respectively, positioned in the caudal hypothalamus These cuts differed primarily in terms of their lateral extent, the midline cut never reached farther than 740 μ lateral to midline [32], while the PFH KC severed tissue from 580 to 1160 μ lateral to midline Note that in some animals, the midline KC, due to its position relative to midline, frequently produced a hole at the midline rather than a fine coronal cut

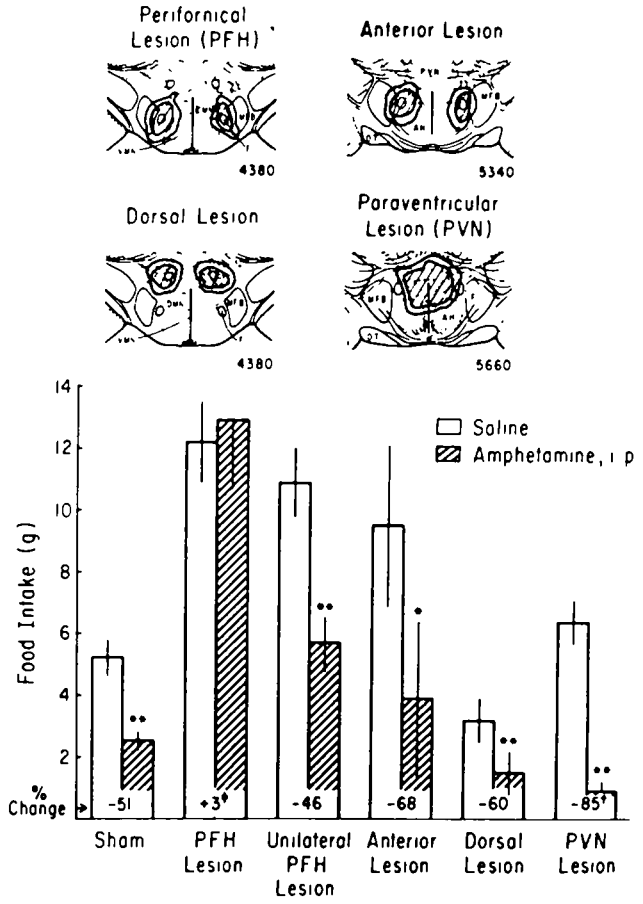

FIG 4 The four coronal drawings of brain sections (adapted from Konig and Klippel [32]) depict the centers of the hypothalamic electrolytic lesions observed in most rats The inner circle denotes the region where tissue was totally destroyed and acellular, and the outer circle denotes the region containing necrotic tissue As noted in the text, the PFH and also the anterior PFH lesions, often dilated the third ventricle The histograms below show the impact of these hypothalamic lesions on the feeding suppressive response induced by IP AMPH injection (0 5 mg/kg) Group mean food intake scores (g±SEM) for the 60-min test are given (**$p<0$ 01, *$p<0$ 05, for comparisons between saline and AMPH scores) In addition, the percent change scores (drug minus saline score, divided by saline score) are also provided within the bars The anorectic response to AMPH was significantly attenuated in the PFH lesion rats (‡$p<0$ 01, compared to the unilateral PFH lesions group) and significantly enhanced in the PVN lesion rats (†$p<0$ 05, compared to the sham group) Abbreviations AH—anterior hypothalamic area, DMN—dorsomedial nucleus, F—fornix, MFB—medial forebrain bundle, OT—optic tract, PVN—paraventricular nucleus, VMN—ventromedial nucleus, ZI—zona incerta

entirely Three of these animals had "dorsal" lesions (Fig 4), which were centered on the mammillothalamic tract and the medial zona incerta and damaged some portion of the DMN and the nucleus reuniens in the thalamus The other three animals sustained "anterior" lesions (Fig 4), which were centered around the fornix at the level of the PVN This anterior lesion remained restricted to the level of the anterior hypothalamic nucleus and extended laterally into the medial half of the medial forebrain bundle It may be distinguished from the on-target PFH lesion by virtue of the fact that it left intact the perifornical region at the level of the ventromedial nucleus

Four animals sustained bilateral PVN lesions These lesions destroyed the entire PVN region and extended lateral to the PVN to the medial extent of the fornix (Fig 4) In one

TABLE 1

FOOD INTAKE SCORES (MEAN ± SEM) AFTER INTRAPERITONEAL SALINE AND FENFLURAMINE (2 0 mg/kg) INJECTION IN 4 HR FOOD DEPRIVED RATS WITH HYPOTHALAMIC LESIONS OR KNIFE CUTS

Group	n	Saline	Fen-fluramine	%-Suppression
Shams	10	6 0 ± 0 6	3 2 ± 0 7*	−52 0 ± 7 4
Lesions				
PFH Lesions	6	11 0 ± 1 7	3 5 ± 0.8*	−61.0 ± 11 8
Unilateral PFH Lesions	4	8.8 ± 1 2	5 3 ± 0 8*	−39 8 ± 1 4
Anterior/ Dorsal Lesion	2	7 3 ± 2 4	4 9 ± 2 3	−32.9 ± 0 2
Perifornical Knife Cut	6	5.8 ± 0 7	1.4 ± 0 4*	−78 0 ± 5 5†

*$p<0$ 001 Comparing saline and fenfluramine food intake scores
†$p<0$ 05 Percent suppression score greater than sham group

of these animals, the lesion also produced extensive damage to the anterior hypothalamic region, and one other animal sustained unilateral damage to the medial aspect of the zona incerta The remaining 10 rats with PVN lesions, sustained either unilateral PVN lesions, partial PVN lesions, or lesions ventral to the PVN. The data from these miscellaneous animals are not reported here

The food intake results obtained with intraperitoneal administration of saline and AMPH, in rats with hypothalamic lesions, are presented in Fig 4 It is apparent from their data that the PFH lesion was the only hypothalamic lesion that attenuated the AMPH anorexic response All other lesion or sham groups exhibited a 46% or greater feeding suppression after 0.5 mg/kg of AMPH compared with saline baseline (at least $p<0.02$), in contrast to the PFH lesion rats which appeared totally unresponsive to AMPH at this dosage. Since the bilateral PFH lesion animals exhibited significantly higher baseline scores than the sham rats, a comparison was made between bilateral PFH lesion rats and the unilateral PFH lesion animals, which also had a high saline baseline (Fig. 4) Analysis of variance showed that the degree of anorexia exhibited by the bilateral PFH lesion group was significantly less than the response observed in the unilateral PFH lesion group, $F(1,17)=9.84$, $p<0$ 01, indicating that the high baseline *per se* was not primary to the loss of responsiveness. Whereas the anterior and dorsal lesion animals seemed normal in their sensitivity to AMPH, the PVN lesion group, compared with the sham rats, actually exhibited a significant enhancement of AMPH-induced feeding suppression, $F(1,14)=15$ 90, $p<0.005$

Table 1 demonstrates the effects of FENF administration on food intake in lesion rats Analysis of variance showed that the degree of anorexia, in terms of percent suppression scores, observed after FENF for the sham group did not differ significantly from the degree of anorexia observed in PFH lesion rats, $F(1,14)=1$ 57, $p>0.10$. Since unilateral PFH and anterior/dorsal lesion groups consisted of small sample sizes, they were not compared to sham animals However, t-tests indicated that all groups, except for the anterior/dorsal group (n=2), exhibited significant decreases in food intake after FENF compared to saline administration ($p<0.001$)

Results from the present study indicate that bilateral destruction of the PFH region disrupts the ability of AMPH, but not FENF, to suppress food intake. Lesions that did not destroy the PFH in its entirety on both sides of the brain, however, did not disrupt AMPH's effectiveness. Although only a small number of animals (n=4) sustained bilateral PVN lesions, these rats exhibited a significantly enhanced responsivity to AMPH. This finding concurs with other studies that have shown ventromedial or anterior hypothalamic damage to potentiate AMPH's action [14, 20, 46, 48, 55]. The mechanism mediating this effect has not been established However, it may be that destruction of the PVN results in the loss of a stimulatory action of AMPH on feeding, which normally would be expected to occur through norepinephrine release in the PVN and to have an attenuating impact on AMPH's anorectic action.

One noticable additional effect of unilateral and bilateral PFH lesions is that this brain manipulation greatly increased saline baseline feeding (Fig. 4). Generally, this effect has not been reported previously [23,50], perhaps due to the fact that the present experiment utilized a 4-hr rather than a 24-hr food deprivation schedule and thus provided an opportunity for an enhanced baseline score to be observed. One study, however, has shown recovered rats with far-lateral hypothalamic lesions to consume large amounts of food after saline or AMPH administration [61]. This stimulatory effect may be attributed to local cellular damage in the PFH or lateral hypothalamic regions, rather than to the severing of passing or terminating fibers. Findings described below reveal no such high baseline eating in animals with mid-lateral coronal KCs in the caudal hypothalamus

Perifornical hypothalamic lesions had little impact on FENF-induced anorexia (Table 1). This supports the findings of others that no hypothalamic lesion effectively blocks this drug's effect [6,23] In the case of midlateral hypothalamic lesions, Blundell and Leshem [6] have demonstrated an enhanced anorectic response after FENF. A similar tendency in this direction has been obtained with far-lateral hypothalamic lesions [23], and in the present study, an analysis (not shown) of FENF minus saline (difference) scores revealed increased FENF response. This difference results primarily from the fact that the PFH lesion animals consumed larger quantities of mash in the saline condition

EXPERIMENT 3

Numerous studies have shown that the feeding suppressive effect of AMPH requires the release of endogenous catecholamines, since depletion of brain catecholamines with alpha-methyl-p-tyrosine or 6-hydroxydopamine decreases AMPH's anorectic potency [13, 23, 26, 35, 37, 52] If the PFH region is the primary site mediating AMPH-induced anorexia, as suggested by Experiment 2, then coronal KCs that sever ascending catecholamine fibers just caudal to the PFH area should also disrupt AMPH's ability to suppress feeding. In the next experiment, discrete KCs were placed in the caudal hypothalamus just behind the PFH region, and the effect of these midlateral KCs on AMPH anorexia was compared with the effect of more medially-placed KCs.

METHOD

Subjects

A total of 51 rats received either KC surgery (n=37) or sham surgery (n=14). Animals were individually housed in

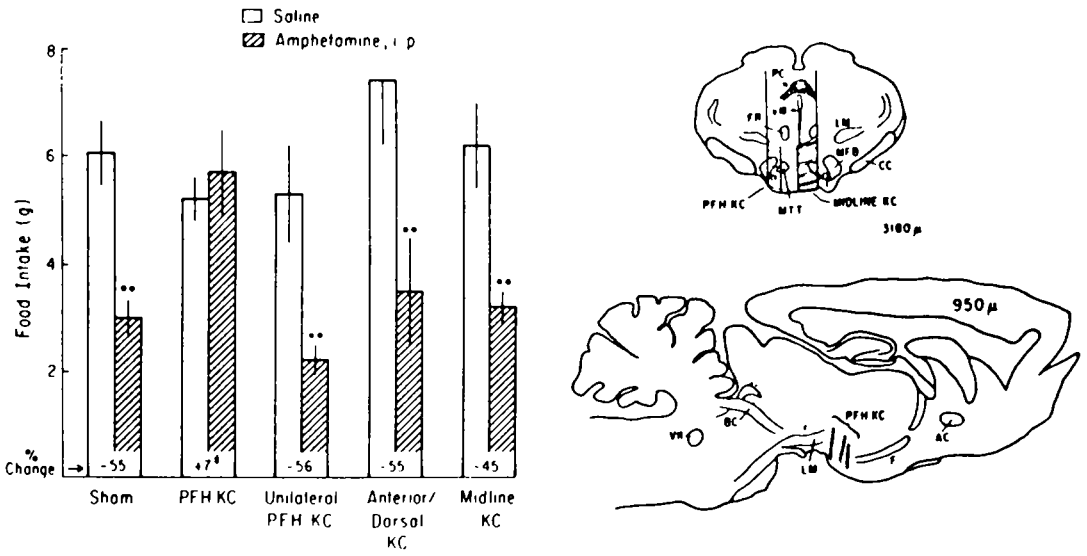

FIG 5 The upper right figure is a coronal drawing of the rat brain at the level of the caudal hypothalamus (approximately 3180 μ with respect to the Konig and Klippel [32] atlas) The left side of this coronal drawing depicts the region severed by the PFH KC, and the right side illustrates the midline KC The lower drawing depicts a sagittal view of the rat brain, approximately 950 μ lateral to midline Three actual on-target PFH KCs are traced on the drawing and can be seen to sever tissue in the caudal hypothalamus in the midlateral plane of the fornix The histogram presents feeding responses (mean±SEM) of sham and 4 KC groups tested with IP injection of saline and AMPH (0 5 mg/kg) All groups, except the PFH group, exhibited a significant suppression of food intake after AMPH relative to saline baseline (**$p<0$ 001) Comparison between percent suppression scores for sham and PFH KC groups revealed a significantly attenuated anorectic response to AMPH injection in the PFH KC animals (‡$p<0$ 001) Abbreviations AC—anterior commissure, BC—brachium conjunctivum, CC—crus cerebri, F—fornix, FR—fasciculus retroflexus, LM—medial lemniscus, MFB—medial forebrain bundle, MTT—mammillothalamic tract, PC—posterior commissure, PFH KC—perifornical KC, r—red nucleus, VIII—third ventricle, VII—seventh cranial nerve

hanging wire-mesh cages and were maintained on the sweetened milk-mash diet Water was available ad lib

Surgery

Using the wire encephalotome developed by Sclafani [53], animals were anesthetized (Nembutal 60 mg/kg) and received either bilateral perifornical KCs (PFH KCs), midline KCs, or a sham surgical procedure. For the midline KC, the knife guide tip was directed to a point +5 2 mm anterior to lambda line (the line interconnecting the lambdoidal sutures located approximately 1 7 mm caudal to lambda)/1 4 mm LAT/−9 2 mm DV, with the nosebar set horizontal with interaural line The wire knife which protruded a length of 2 5 mm in the medial direction and 1.5 mm in the ventral direction, was extended out through the tip of the guide and then, over a distance of 4.0 mm, was raised and lowered three times The PFH KC used a slightly smaller knife measuring 2.0 mm medial and 1.3 mm ventral from the knife guide tip. For this KC, the nosebar was set horizontal to interaural line, and the guide was lowered into the brain using coordinates −3 0 mm AP with respect to bregma/2 5 mm LAT/−9.6 mm DV. The knife was then extended and raised (×3) 3.4 mm Sham animals were similarly treated, except that the guide was lowered into the brain to approximately 3.0 mm dorsal to the site of the cuts, and the wire knife was not extended.

For tests with centrally-injected AMPH, some PFH KC and midline KC rats also received a 23-gauge stainless steel cannula implant with a screw-on top In this case, the incisor bar was set 3.1 mm above interaural line, and the cannula tip was aimed at the perifornical region using coordinates: −1.5 mm AP/1.5 mm LAT/−8.7 mm DV. The cannula was then fixed to the skull using stainless steel hooks and acrylic cement

Behavioral Testing

Since these rats were also used in another experiment [42], AMPH and FENF tests began 4–6 weeks after KC surgery. Noncannulated rats received 2–4 weeks of testing with AMPH and FENF using the 4-hr food deprivation schedule described above. Fifteen min before the animals were given fresh mash, they received intraperitoneal injections of either 0 5 mg/kg AMPH, 2.0 mg/kg FENF, or saline (1 ml/kg) Food intake was measured 60 min postinjection. Animals that had received PFH cannula implants were tested for their responsiveness to central, as well as peripheral, administration of AMPH. On testing days, PFH cannulated rats were food deprived for 4 hr. Fifteen min before food delivery, they received either a central injection of saline (0.5 μl) or 150 nM AMPH (55 3 μg in 0.5 μl sterile saline) or a peripheral injection of saline (1.0 ml/kg) or AMPH (0.5 mg/kg) Food intake was measured 60 min postinjection After all drug tests, animals were sacrificed, perfused, and brains were removed for histological study

RESULTS AND DISCUSSION

As depicted in Figs 3c and 5, animals that sustained PFH KCs exhibited bilateral cuts positioned in the caudal hypothalamus, posterior to the level of the VMN These cuts generally extended just lateral to the fornix, into the medial aspect of the medial forebrain bundle (1160 μ, with respect to Konig and Klippel [32]) and medial to the fornix, towards the mammillothalamic tract (580 μ). Ventrally, these cuts extended below the level of the fornix, to between 0.0 and 0 3

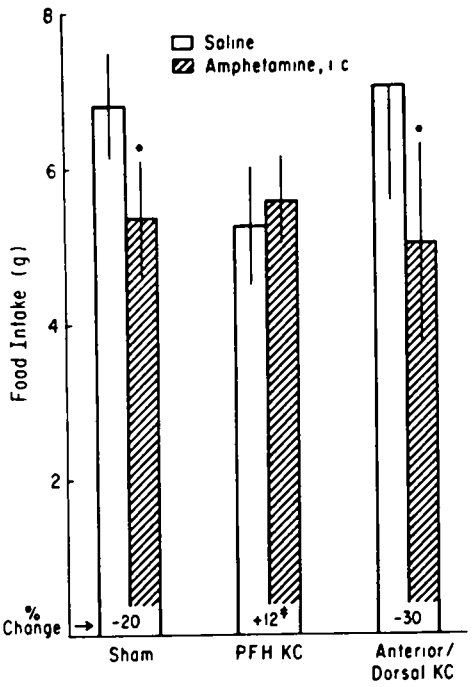

FIG 6 Mean (±SEM) feeding responses (grams) to saline and AMPH administered intracranially (IC) to the PFH region after 4 hr of food deprivation See Figs 3 and 5 for description of KCs After PFH injection of AMPH, both the sham and anterior/dorsal KC rats, but not the PFH KC animals, decreased their food intake compared to after saline injection (*$p<0$ 05) In terms of percent suppression scores, the PFH KC rats exhibited a significantly attenuated anorectic response to AMPH compared to sham rats (‡$p<0$ 001), whereas the anterior/dorsal KC rats responded normally

mm from the base of the brain, and dorsally, they extended to the dorsal border of the hypothalamus Some animals (n=7) sustained this midlateral KC on only one side of the brain (unilateral PFH KCs), with the contralateral side exhibiting tissue damage only medial to the fornix. The bilateral midline KC (Figs. 3b and 5) was very similar to the midlateral PFH KC in its anterior-posterior and dorsal-ventral position. Relative to its medial-lateral extent, it severed tissue from midline to approximately 740 μ lateral, in contrast to the more lateral PFH KC which extended from 580 μ to 1160 μ lateral. Additional animals sustained bilateral KCs that were either anterior (n=3) or dorsal (n=3) to the PFH region The anterior KC animals sustained particularly large KCs which severed through the VMN and DMN approximately 1 5 mm rostral to the PFH KC and extended almost as far dorsal as the anterior aspect of the habenula The dorsal KC rats sustained KCs that did not fall as ventral as the level of the VMN. These cuts severed tissue at the very caudal aspect of the zona incerta and in the fields of Forel, and extended dorsally into the ventromedial nucleus of the thalamus.

Figure 5 shows that bilateral PFH KCs in the posterior level of the hypothalamus disrupted feeding suppression induced by peripheral AMPH injection. That is, analysis of variance of percent suppression scores of the sham (n=14), PFH KC (n=12), and midline KC (n=12) rats indicated that the hypothalamic KC groups differed significantly, $F(4,46)=17.01$, $p<0.001$. Simple comparisons showed that the PFH KC group exhibited a significantly attenuated anorectic response to AMPH as compared to sham animals, $F(1,46)=51.84$, $p<0.001$, in contrast to the other KC groups which responded normally to AMPH.

Figure 6 presents results obtained with injections of AMPH directly into the PFH region. In this experiment, animals sustaining sham (n=10), PFH KC (n=9), anterior/dorsal KC (n=6), or midline KC (n=2) surgery were tested and cannula tip location was verified histologically in these animals. Analyses of the sham, PFH KC, and anterior/dorsal KC groups, demonstrated significantly different responses to AMPH in terms of percent suppression scores, $F(2,22)=7.86$, $p<0.01$. Individual comparisons revealed a significantly attenuated response in the PFH KC rats, $F(1,22)=9.50$, $p<0.01$, in contrast to an apparently normal response for the sham and anterior/dorsal KC rats, $F(1,22)=0$ 93. Although the midline KC rats were not included in the statistical analyses due to their small sample size, both animals in this KC group clearly retained their anorectic response to AMPH, exhibiting a 30% and 35% suppression of feeding (data not shown) No central data from unilateral PFH KC rats is available since none of these animals were cannulated. Table 1 shows that, in contrast to AMPH, FENF's anorectic potency remained intact after PFH KCs and in fact was significantly enhanced, $F(1,14)=6.04$, $p<0.05$.

The present results demonstrate that KCs severing fibers coursing through the midlateral perifornical region of the caudal hypothalamus are effective in disrupting the feeding suppressive action of AMPH injected peripherally, as well as directly into the PFH region. In contrast, KCs that severed tissue anterior, dorsal, or medial to the midlateral PFH area were without effect. In one other KC study with peripherally injected AMPH, a cut positioned more rostral and medial to our PFH KC appeared to have some attenuating effect on AMPH's anorectic action, which just missed statistical significance ([54] and Sclafani, personal communication). In comparing and interpreting these two studies and any future KC studies, one needs to take into account not only the precise location and extent of the KC, but also the drug dose, diet used, and level of deprivation Our finding that PFH KCs left intact and actually enhanced FENF anorexia, while abolishing AMPH anorexia, reveals a pharmacological specificity which directs our attention towards ascending catecholamine projections in the PFH, in contrast to serotonergic mechanisms believed to mediate FENF's action [3]. The significantly enhanced responsiveness to FENF in these PFH KC rats may reflect a possible antagonism between serotonergic and dopaminergic systems in this midlateral hypothalamic brain area, where both monoamine systems are known to project [23].

GENERAL DISCUSSION

Results of the present experiment support the hypothesis that the perifornical region of the hypothalamus mediates AMPH-induced anorexia Electrolytic lesions to the PFH region, at the level of the ventromedial nucleus, decreased feeding suppression induced by AMPH administered peripherally (0.5 mg/kg) This effect appeared to be specific to this midlateral hypothalamic region, since lesions that focused damage within the medial hypothalamus, specifically the PVN, did not attenuate AMPH's effect. Likewise, lesions just anterior or dorsal to the PFH region did not affect the

drug response. Coronal KCs that severed fibers traversing the PFH area, at the level of the caudal hypothalamus, were also able to attenuate AMPH's effect, whether this drug was administered peripherally or directly to the PFH region. A variety of other cuts had no effect: namely, lateral cuts anterior to the level of the ventromedial nucleus, or cuts in the zona incerta region These results suggest that AMPH's anorexigenic action is mediated in part by the perifornical region, and that fibers crucial for drug response course through the midlateral caudal hypothalamus as they pass between the midbrain and the PFH region In contrast, the PFH lesions and PFH KCs that disrupted AMPH anorexia did not attenuate feeding suppression from FENF administration In fact, the PFH KC significantly enhanced FENF-induced anorexia.

It should be noted that the present experiment has utilized testing conditions quite different from those of most previous studies in this area of research For example, all studies that have examined the effects of LH lesions on AMPH-induced anorexia have used 16–24 hr food deprivation schedules (in contrast to 4 hr in the present study) This severe schedule, which has been questioned in terms of its physiological relevance to normal food intake regulation [4], has been employed in conjunction with injections of AMPH at somewhat higher doses of 1–2 mg/kg [6, 12, 23, 39, 50] In the present experiment, a lower 0 5 mg/kg dose of AMPH was chosen to minimize AMPH's stimulatory action on locomotion, which at higher dose levels clearly plays an increasingly predominant role in this drug's feeding suppressive effect [41] Similarly, use of a milder 4-hr food deprivation paradigm would be expected to attenuate AMPH's stimulatory effect, which is known to be greatly potentiated by extended food deprivation periods [9]

The possibility exists that, in addition to the PFH, extra-hypothalamic areas may be involved in AMPH-induced anorexia Hypothalamic manipulations used in the present study may have damaged fibers which pass between the hindbrain and forebrain. Dopaminergic systems in two forebrain structures, specifically, the striatum and nucleus accumbens, are believed to mediate two of AMPH's behavioral effects, namely, stereotypy and locomotor activity [2, 10, 17, 19, 25, 31, 33, 57] Some investigators suggest that AMPH anorexia may be an indirect consequence of AMPH's locomotor effect, rather than result from direct action on catecholaminergic feeding mechanisms [5, 15, 16, 41, 56, 59] Since the lesions and KCs in the present study may have also destroyed interconnections between midbrain and forebrain that are crucial to some of AMPH's actions, additional experiments are required to determine the relationship between these midlateral hypothalamic lesions and KCs and possible effects upon forebrain catecholamine levels and whether forebrain amine changes are associated with the loss of AMPH's feeding effects

A variety of evidence counters the proposal, however, that these extra-hypothalamic, forebrain structures are primary mediators of drug-induced feeding suppression With regard to the striatum, AMPH injections directly to the striatum have no suppressive effect on feeding [34] and can actually elicit feeding [59] Second, ventral noradrenergic bundle lesions, which leave intact primary dopaminergic projections to the forebrain [21], reliably attenuate AMPH-induced anorexia [1, 11, 37, 51], without affecting AMPH's stimulation of locomotor activity [47,51] As demonstrated in a related study, ventrally-placed pontine KCs, which lie caudal to all dopamine cell groups, also attenuate AMPH-induced anorexia [44] With respect to destruction of dopaminergic innervation to the striatum with local administration of the neurotoxin 6-hydroxydopamine, results are conflicting An earlier study indicated that this treatment had no effect on anorexia induced by peripheral AMPH administration [51], while a more recent report indicates dopamine depletion in the caudate can attenuate AMPH response [30] Also consistent with this dissociation of AMPH's locomotor and feeding effects is the evidence that bilateral destruction of the nucleus accumbens itself effectively attenuates AMPH's motor-stimulatory action, but does not alter the feeding suppression [33], and lateral hypothalamic lesions, as well as alpha-methyl-p-tyrosine treatment, are reported to decrease AMPH-induced anorexia, without changing this drug's arousal effects [8,18]

Although some evidence may argue for extra-hypothalamic mediation and locomotor involvement in amphetamine's anorectic action [41], additional evidence suggests that hypothalamic feeding mechanisms regulating feeding behavior play an important role First, direct injections of AMPH to the PFH produces the strongest degree of feeding suppression of any brain site tested [34,38], having no apparent impact on locomotor behavior (Leibowitz, unpublished data) In fact, injections of catecholaminergic blockers to this brain site disrupt anorexia induced by peripheral injection of AMPH [35] Finally, it is reported that the binding characteristics of ^{3}H-AMPH in the hypothalamus is highly correlated with the feeding suppressive properties of various phenylethylamine anorectics, and apparently unrelated to the potencies of these anorectics in stimulating locomotor behavior [45]

The results from the present study also support a hypothalamic site of action for AMPH, specifically the PFH First, lesions in the PFH area and KCs just caudal to this region abolished anorexia induced by peripheral injection of AMPH at a relatively low dose This effect was anatomically specific to the PFH region, since lesions just rostral to the PFH or in the medial hypothalamus did not affect drug response Also, Experiment 3 demonstrated that PFH KCs not only abolished anorexia resulting from peripheral administration of AMPH, but similarly affected the anorectic potency of AMPH injected directly into the PFH These effects of PFH lesions and KCs were drug specific, since they did not decrease the anorectic potency of FENF These findings, therefore, along with other evidence described above, strongly support the existence of a hypothalamic mechanism for feeding suppression, that is, a catecholaminergic system within the PFH region, which plays a major and direct role in mediating the anorectic action of AMPH, particularly at low dose levels

The present study has also attempted to outline the course, within the diencephalon, taken by fibers mediating catecholamine and AMPH feeding suppression The KC results indicate that these fibers follow a relatively straight course through the midlateral caudal hypothalamus, that is, along the perimeter of the fornix within the most medial aspect of the medial forebrain bundle Although the present study does not differentiate whether these fibers are ascending or descending, preliminary data obtained with direct PFH injection of dopamine indicate that caudal PFH KCs, which abolish AMPH anorexia, leave intact the feeding suppressive effect of dopamine, a post-synaptic receptor phenomenon [37] Thus, a viable hypothesis is that the crucial fibers severed by the cuts are *ascending* catecholaminergic fibers that course rostrally from the lower brainstem into the

midlateral hypothalamic region and terminate in the perifornical region at the level of the ventromedial nucleus. This PFH area is dense with catecholamine fibers [1, 28, 29, 37] and is the area most sensitive to local injection of AMPH which presumably acts via the release of endogenous catecholamines to inhibit feeding [34,35]. Other recent evidence [44], supported by earlier studies at the midbrain level [1, 11, 22, 23, 27, 37], suggest that the catecholamine fibers ascending to the PFH region originate from the ventral medullary noradrenergic/adrenergic and ventral mesencephalic dopaminergic cell groups and assume a relatively ventral and midlateral position through the entire brainstem.

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REFERENCES

1 Ahlskog, E J Food intake and amphetamine anorexia after selective forebrain norepinephrine loss *Brain Res* **82:** 211–240, 1974
2 Asher, I M and G K Aghajanian 6-Hydroxydopamine lesions of olfactory tubercles and caudate nuclei Effect on amphetamine-induced stereotyped behavior *Brain Res* **82:** 1–12, 1974
3 Blundell, J E and S L Burridge Control of feeding and the psychopharmacology of anorectic drugs In *The Treatment of Obesity*, edited by J Munro Lancaster MTP Press, 1979, pp 53–84
4 Blundell, J E and C J Latham Behavioural pharmacology of feeding In. *Drugs and Appetite*, edited by T Silverstone New York Academic Press, 1982, pp 41–80
5 Blundell, J E and C J Latham Characterisation of adjustments to the structure of feeding behavior following pharmacological treatment Effects of amphetamine and fenfluramine and the antagonism produced by pimozide and methergoline *Pharmacol Biochem Behav* **12:** 717–722, 1980
6 Blundell, J E and M B Leshem Central action of anorexic drugs Effects of amphetamine and fenfluramine in rats with lateral hypothalamic lesions *Eur J Pharmacol* **28:** 81–88, 1974.
7 Booth, D A Mechanism of action of norepinephrine in eliciting an eating response on injection into the rat hypothalamus *J Pharmacol Exp Ther* **160:** 336–348, 1968
8 Campbell, B A. and L A Baez Dissociation of arousal and regulatory behaviors following lesions of the lateral hypothalamus *J Comp Physiol Psychol* **87:** 142–149, 1974.
9 Campbell, B A and H C Fibiger Potentiation of amphetamine-induced arousal by starvation *Nature* **233:** 424–425, 1971
10 Carey, R J Differential effects of limbic versus striatal dopaminergic loss on motoric function *Behav Brain Res* **7:** 283–296, 1983
11 Carey, R J Effects of selective forebrain depletions of norepinephrine and serotonin on the activity and food intake effects of amphetamine and fenfluramine *Pharmacol Biochem Behav* **5:** 519–523, 1976
12 Carlisle, H J Differential effects of amphetamine on food and water intake in rats with lateral hypothalamic lesions *J Comp Physiol Psychol* **58:** 47–54, 1964
13 Clineschmidt, B V and P R Bunting Differential effects of pharmacological agents on monoaminergic systems on drug-induced anorexia *Prog Neuropsychopharmacol Biol Psychiatry* **4:** 327–339, 1980
14 Cole, S Increased suppression of food intake by amphetamine in rats with anterior hypothalamic lesions *J Comp Physiol Psychol* **61:** 302–305, 1966
15 Cole, S Interaction of food deprivation with different measures of amphetamine effects *Pharmacol Biochem Behav* **10:** 235–238, 1979
16 Cole, S The relationship of amphetamine-induced anorexia and freezing under free-feeding conditions *Pharmacol Res Comm* **4:** 71–76, 1972
17 Costall, B , C D. Marsden, R J. Naylor and C J. Pycock Stereotyped behavior patterns and hyperactivity induced by amphetamine and apomorphine after discrete 6-hydroxydopamine lesions of extrapyramidal and mesolimbic nuclei. *Brain Res* **123:** 89–111, 1977
18 Cox, R H., Jr and R. P. Maickel. Differential effects of aMT on anorectic and stimulatory action of amphetamines *Res Commun Chem Pathol Pharmacol* **12:** 621–626, 1975.
19 Creese, I and S. D Iversen. The pharmacological and anatomical substrates of amphetamine response in the rat. *Brain Res* **83:** 419–436, 1975
20 Epstein, A N Suppression of eating and drinking by amphetamine and other drugs in normal and hyperphagic rats *J Comp Physiol Psychol* **32:** 37–45, 1959
21 Fallon, J H and R Y Moore Catecholamine innervation of the basal forebrain IV Topography of the dopamine projection to the basal forebrain and neostriatum *J Comp Neurol* **180:** 545–580, 1978
22 Fibiger, H C , A G Phillips and R A Clouston Regulatory deficits after unilateral electrolytic or 6-OHDA lesions of the substantia nigra *Am J Physiol* **225:** 1282–1287, 1973
23 Fibiger, H C., A P. Zis and E G McGeer Feeding and drinking deficits after 6-hydroxydopamine administration in the rat Similarities to the lateral hypothalamic syndrome *Brain Res* **55:** 135–148, 1973
24 Garrattini, S and R Samanin (Eds). *Central Mechanisms of Anorectic Drugs* New York· Raven Press, 1978
25 Groves, P M and G V Rebec Biochemistry and behavior. Some central actions of amphetamine and antipsychotic drugs *Annu Rev Psychol* **27:** 91–129, 1976
26 Heffner, T G and L S Seiden The effect of depletion of brain dopamine by 6-hydroxydopamine on tolerance to the anorexic effect of d-amphetamine and fenfluramine in rats *J Pharmacol Exp Ther* **208:** 134–143, 1979
27 Heffner, T G , M J Zigmond and E M. Stricker Effects of dopaminergic agonists and antagonists on feeding in intact and 6-hydroxydopamine-treated rats *J Pharmacol Exp Ther* **201:** 386–399, 1977
28 Hokfelt, T , K Fuxe, M Goldstein and O. Johansson Immunohistochemical evidence for the existence of adrenaline neurons in the rat brain *Brain Res* **66:** 235–251, 1974
29 Jacobowitz, D M and M Palkovits Topographic atlas of catecholamine and acetylcholinesterase-containing neurons in the rat brain I Forebrain (telencephalon, diencephalon) *J Comp Neurol* **157:** 13–28, 1974
30 Joyce, E M and S D Iversen Striatal dopamine depletion attenuates anorexia produced by D-amphetamine *Soc Neurosci Abstr* **9:** 1172, 1983
31 Kelly, P H , P W Seviour and S D Iversen Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum *Brain Res* **94:** 507–522, 1975
32 Konig, J F R and R A Klippel *The Rat Brain* Huntington, NY Krieger Publishing Co , 1974

33 Koob, G K, S J Riley, S C Smith and T W Robbins Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat *J Comp Physiol Psychol* **92:** 917–927, 1978

34 Leibowitz, S F Amphetamine possible site and mode of action for producing anorexia in the rat *Brain Res* **84:** 160–167, 1975a

35 Leibowitz, S F Catecholaminergic mechanisms of the lateral hypothalamus their role in the mediation of amphetamine anorexia *Brain Res* **98:** 529–545, 1975

36 Leibowitz, S F Paraventricular nucleus A primary site mediating adrenergic stimulation of feeding and drinking *Pharmacol Biochem Behav* **8:** 163–175, 1978

37 Leibowitz, S F and L L Brown Histochemical and pharmacological analysis of catecholaminergic projections to the perifornical hypothalamus in relation to feeding inhibition *Brain Res* **201:** 315–345, 1980

38 Leibowitz, S F and C Rossakis Analysis of feeding suppression produced by perifornical hypothalamic injection of catecholamines, amphetamines, and mazindol *Eur J Pharmacol* **53:** 69–81, 1978

39 Leshem, M Morphine-induced anorexia in lateral hypothalamic rats *Psychopharmacology (Berlin)* **75:** 48–53, 1981

40 Lewander, T Characteristics and possible mechanisms of tolerance to the anorexigenic effects of amphetamine and fenfluramine in rats In *Anorectic Agents Mechanisms of Action and Tolerance*, edited by S Garattini and R Samanin New York Raven Press, 1981, pp 79–85

41 Lyon, M and T Robbins The action of central nervous system stimulant drugs A general theory concerning amphetamine effects In *Current Developments in Psychopharmacology*, vol 2, edited by W B Essman and L Valzelli Holliswood, NY Spectrum Publications, 1975, pp 79–163

42 McCabe, J T, M DeBellis and S F Leibowitz Clonidine-induced feeding Analysis of central sites of action and fiber projections mediating this response *Brain Res* **309:** 85–114, 1984

43 McCabe, J and S F Leibowitz Hindbrain catecholamine projections to the perifornical hypothalamus Their role in the mediation of drug-induced anorexia and hyperphagia *Soc Neurosci Abstr* **6:** 784, 1980

44 McCabe, J T and S F Leibowitz Determination of the course of brainstem catecholamine fibers mediating amphetamine anorexia *Brain Res* **311:** 211–224, 1984

45 Paul, S M, B Hulihan-Giblin and P Skolnick (+)-Amphetamine binding to rat hypothalamus Relation to anorexic potency of phenylethylamines *Science* **218:** 487–490, 1982

46 Pecile, A, V R Olgiati and C Netti Hypersensitivity of rats to anorectic agents after lesions in the ventromedial hypothalamus *Arch Int Pharmacodyn Ther* **226:** 48–55, 1977

47 Quattrone, A, C Bendotti, M Recchia and R Samanin Various effects of d-amphetamine in rats with selective lesions of brain noradrenaline-containing neurons or treated with penfluridol *Comm Psychopharmacol* **1:** 525–531, 1977

48 Reynolds, R W The effect of amphetamine on food intake in normal and hypothalamic hyperphagic rats *J Comp Physiol Psychol* **52:** 682–684, 1959

49 Rowland, N, S M Antelman and D Kocan Differences among 'serotonergic' anorectics in a cross-tolerance paradigm Do they all act on serotonin systems? *Eur J Pharmacol* **81:** 57–66, 1982

50 Russek, M, A M Rodriquez-Zendejas and P Teitelbaum The action of adrenergic anorexigenic substances on rats recovered from lateral hypothalamic lesions *Physiol Behav* **10:** 329–333, 1973

51 Samanin, R, C Bendotti, S Bernasconi, E Borroni and S Garattini Role of monoamines in the anorectic activity of mazindol and d-amphetamine in the rat *Eur J Pharmacol* **43:** 117–124, 1977

52 Samanin, R, S Bernasconi and S Garattini The effect of selective lesioning of brain catecholamine-containing neurons on the activity of various anorectics in the rat *Eur J Pharmacol* **34:** 373–375, 1975

53 Sclafani, A Neural pathways involved in the ventromedial hypothalamic lesion syndrome in the rat *J Comp Physiol Psychol* **77:** 70–96, 1971

54 Sclafani, A and C N Berner Hyperphagia and obesity produced by parasagittal and coronal hypothalamic knife-cuts Further evidence for a longitudinal feeding inhibitory pathway *J Comp Physiol Psychol* **91:** 1000–1018, 1977

55 Stowe, F R, Jr and A T Miller The effect of amphetamine on food intake in rats with hypothalamic hyperphagia *Experientia* **13:** 114–115, 1957

56 Stricker, E M and M J Zigmond Recovery of function after damage to central catecholamine-containing neurons A neurochemical model for the lateral hypothalamic syndrome In *Progress in Psychobiology and Physiological Psychology*, vol 6, edited by J M Sprague and A N Epstein New York Academic Press, 1976, pp 121–188

57 van Rossum, J M, C L E Broekkamp and A J J Pijnenberg Behavioral correlates of dopaminergic function in the nucleus accumbens In *Advances in Biochemical Psychopharmacology* vol XXXI, edited by E Costa and G I Gessa New York Raven Press, 1977, pp 201–207

58 Weingarten, H P, P-K Chang, and K R Jarvie Reactivity of normal and VMH-lesion rats to quinine-adulterated foods Negative evidence for negative finickiness *Behav Neurosci* **97:** 221–233, 1983

59 Winn, P, S F Williams and L J Herberg Feeding stimulated by very low doses of d-amphetamine administered systemically or by microinjection into the striatum *Psychopharmacology (Berlin)* **78:** 336–341, 1983

60 Wolgin, D L and P Teitelbaum Role of activation and sensory stimuli in recovery from lateral hypothalamic damage in the cat *J Comp Physiol Psychol* **92:** 474–500, 1978

61 Zigmond, M J, T G Heffner and E M Stricker The effect of altered dopaminergic activity on food intake in the rat Evidence for an optimal level of dopaminergic activity for behavior *Prog Neuropsychopharmacol Biol Psychiatry* **4:** 351–362, 1980