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Evidence for Ascending Noradrenergic Mediation of Hypothalamic Hyperphagia[1]

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KAPATOS, G. AND R. M. GOLD. *Evidence for ascending noradrenergic mediation of hypothalamic hyperphagia.* PHARMAC. BIOCHEM. BEHAV. 1(1) 81–87, 1973.–Rats sustaining unilateral ablation of the ventral ascending noradrenergic bundle, in combination with a contralateral parasagittal knife cut rostrolateral to the ventromedial nucleus of the hypothalamus (VMN), became obese. Ablation of the ventral noradrenergic (NA) bundle was effective at both mammillary and midbrain levels. The weight gains produced by this asymmetrical technique were comparable to those obtained following bilateral parasagittal knife cuts. Rats with unilateral mammillary lesions that spared the ventral NA bundle or unilateral midbrain lesions which only partially destroyed the ventral NA bundle, in combination with the contralateral parasagittal knife cut, did not become obese. The neural substrate damaged in the production of hypothalamic hyperphagia thus appears to be that part of the ascending ventral NA bundle which projects medially through the effective parasagittal knife cut locus rostrolateral to the VMN.

Hyperphagia Hypothalamus Obesity Mammillary Noradrenaline

BILATERAL lesions in the vicinity of the ventromedial nucleus of the hypothalamus (VMN) can produce dramatic hyperphagia and, as a result, obsesity in rats [3,14]. Bilateral parasagittal knife cuts rostrolateral to VMN [1, 9, 25] also produce hyperphagia and obesity. In unpublished work, Gold has localized the most effective parasagittal knife cut locus to the frontal planes midway between the paraventricular and ventromedial nuclei (Figs. 30–32 in König and Klippel [17]). In addition, horizontal knife cuts dorsal to VMN [22], and large bilateral lesions at the extreme caudal end of the hypothalamus in the vicinity of the mammillary nuclei, can produce hyperphagia and obesity [12,15]. These studies suggest that the critical fibers destroyed in hypothalamic obesity may originate at a mammillary, midbrain, or brainstem site, and project rostrally through the hypothalamus. These fibers may run in the lateral hypothalamus (LH) as a component of the medial forebrain bundle (MFB), or they may pass diffusely through the medial hypothalamus. At the rostral end of the hypothalamus the fibers, it appears, must turn medially (or laterally) and dorsally through the effective knife cut loci. A projection in the opposite (caudal) direction is also possible.

Recent data, using an asymmetrical lesion technique, have clearly demonstrated that feeding inhibition is indeed mediated by a longitudinal projection [11]. A unilateral parasagittal knife cut rostralateral to VMN was combined with a contralateral unilateral electrolytic lesion in the mammillary area. The rats rapidly gained weight at a rate equivalent to that which follows bilateral parasagittal knife cuts.

The only fibers lesioned bilaterally were those that pass through both the knife cut region and the mammillary area lesion. All other fibers were only damaged unilaterally. Thus, a common neural system appears to be interrupted by both the parasagittal rostrolateral to VMN knife cut and the mammillary area lesion.

The mammillary ablation in the previous study unilaterally destroyed the mammillary nuclei and the medial region of the MFB [11]. In Experiment 1 of the present study

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asymmetrical lesions are used to investigate the possible importance to hypothalamic hyperphagia of fiber systems efferent and afferent to the mammillary bodies. Experiment 2 also uses asymmetrical lesions to further trace the critical projections in the midbrain, and relates hypothalamic hyperphagia to recent histochemical and pharmacological data regarding the ascending monoamine pathways and their possible role in the control of food intake [19,28].

EXPERIMENT 1

The mammillary nuclei are innervated afferently by the fornix, MFB, and mammillary peduncle, while efferent projections are via the principle mammillothalamic tract. The principle mammillothalamic tract ascends from the mammillary bodies and divides into the mammillothalamic and mammillotegmental tracts [18]. Both the mammillotegmental tract and the mammillary peduncle are, respectively, major descending and ascending fiber systems linking the hypothalamus and the midbrain tegmental nuclei [6,18]. The medial forebrain bundle carries fibers which appear to project from the septum to the mammillary nuclei [16,24].

In this study lesions were made in the principle mammillothalamic tract (in order to destroy both mammillothalamic and mammillotegmental projections), the mammillary peduncle, the mammillary nuclei, or the adjacent MFB. Unilateral lesions of one of the four loci were always combined with a unilateral controlateral electrolytic VMN lesion or parasagittal rostrolateral to VMN knife cut.

Method

Animals and diets. Animals were individually housed, female Carworth CFE rats, 85–95 days old at the time of surgery. A high fat diet consisting of 67% (by weight) Purina laboratory meal and 33% Crisco brand hydrogenated vegetable shortening was available ad lib from an 8-cm dia. glass cup secured to a corner of each cage. Tap water from inverted bottles was also available ad lib. Details of diet preparation and intake measures were as described previously [10]. Twice each week the rats were weighed, food and water intakes were determined by difference weights, and fresh food and water were provided. Clean cages and fresh litter were provided at frequent intervals, and room temperature was maintained at 72°–75°F (22–24°C).

Surgery and Histology. Parasagittal knife cuts rostrolateral to VMN were produced with a 3 mm long razor blade knife [10]. Electrolytic lesions were produced via a 0.25 mm dia. stainless steel insulated wire anode with a 0.2–0.5 mm conical tip exposed. The top of the incisor bar was always 3 mm below the center of the ear bars. Anterior, lateral,and vertical stereotaxic reference points were,respectively, ear bar center, midsagittal sinus and dura. Asymmetrically lesioned animals received either a unilateral electrolytic ventrodmedial hypothalamic (VMN) lesion (A 6.5, L 0.5, V 8.2), or a unilateral rostrolateral to VMN parasagittal knife cut (A 6.5, L 0.9, V to base). This was combined with a contralateral unilateral lesion placed in one of four loci: the principle mammillothalamic tract (A 5.0, L 0.75, V 7.8); the mammillary peduncle (A 3.6, L 0.7, V 8.45); the mammillary nuclei (A 4.7, L 0.6, V 8.2); or the MFB at the level of the mammillary bodies (A 4.7, L 1.2, V 8.0). Unilateral control animals received only the unilateral VMN lesion or parasagittal knife cut, while the bilateral controls received bilateral parasagittal hypothalamic knife cuts. Sham operations consisted of ether anesthesia, placement in the stereotaxic instrument, and exposure of the dura.

After 5 weeks of postoperative ad lib feeding on the high fat diet, all lesioned animals were perfused, and frozen frontal plane brain sections were stained with cresyl violet for cells or a Weigert Weil stain for fibers.

Results

Mean body weights and food intakes for 5 weeks following recovery from postoperative weight loss (if any) are shown in Fig. 1. Mean body weight gains are also shown in Table 1.

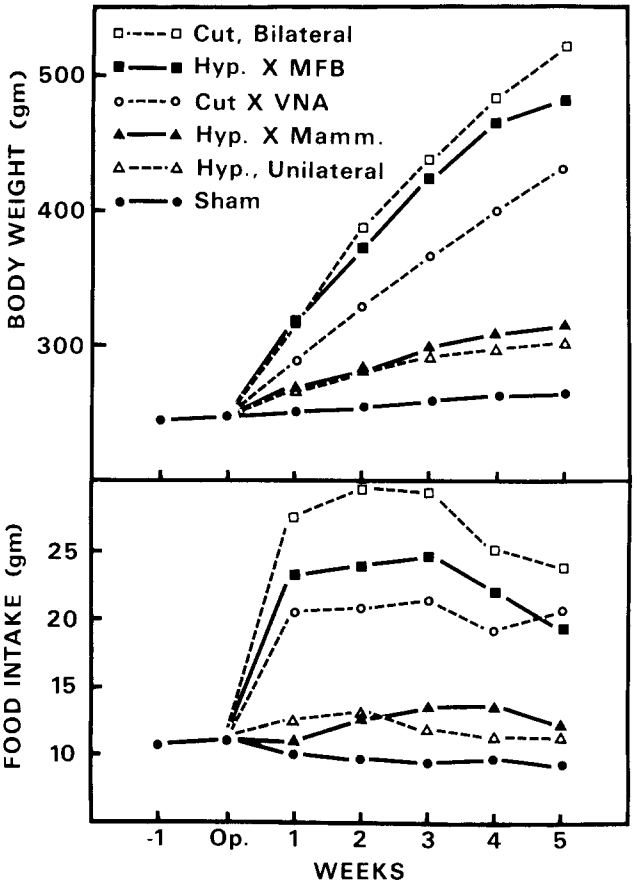

FIG. 1. Mean body weights and food intakes (high fat diet). Cut=parasagittal knife cut rostrolateral to the ventromedial hypothalamus (VMN; Hyp.=either a unilateral knife cut or VMN lesion; X=crossed combination; MFB=medial forebrain bundle; Mamm.= mammillary nuclei and fiber systems; VNA=ascending ventral noradrenergic bundle.

Rats having unilateral VMN lesions or unilateral parasagittal knife cuts displayed modest weight gains (means 1.4

and 1.6 g/day). As in the previous report [11], the difference between these two groups was not significant ($p>0.01$, Mann Whitney U Test [27] and their data were pooled. This pooled unilateral control group gained weight more rapidly than the sham operated controls (mean, 0.5 g/day, $p<0.01$). Asymmetrical combinations of a unilateral VMN lesion or knife cut and a contralateral lesion that spared the MFB but severed; the principle mammillothalamic tract, the mammillary peduncle, or destroyed the medial and lateral mammillary nuclei, all resulted in weight gains similar to those of the unilateral control group (means; 1.7, 1.9, and 1.9 g/day, respectively). As a pooled group, the weight gain of the 10 asymmetrically lesioned rats just described did not differ significantly from the 8 unilaterally lesioned controls ($p>0.1$). In contrast, rats with the crossed combination of a unilateral electrolytic VMN lesion or parasagittal knife cut and a contralateral electrolytic lesion which spared the mammillary nuclei and projections, but severed the MFB at the level of the mammillary bodies, gained weight rapidly and became obese (mean 6.3 g/day, $p<0.01$). This rate of weight gain is essentially identical to that produced by the bilateral parasagittal knife cuts (6.7 g/day, $p<0.01$). Animals sustaining the crossed combination of a unilateral knife cut or VMN lesion in combination with a lesion that destroyed the mammillary nuclei as well as the MFB also became obese. They gained weight neither faster nor slower than animals in which the contralateral lesion was restricted to the MFB

TABLE 1

MEAN WEIGHT GAINS OVER 5 WEEKS FOLLOWING RECOVERY FROM SURGERY

Group	Mean Weight Gain (g/day)	N
Control Procedures		
Bilateral parasagittal hypothalamic knife cuts	6.7	9
Unilateral hypothalamic parasagittal knife cut (U Cut)	1.6	4
Unilateral VMN Lesion (U VMN)	1.4	4
Sham operation	0.5	11
Lesions of Mammillary Nuclei and Projections		
U Cut or U VMN combined with a contralateral lesion of the principle mammillothalamic tract	1.7	3
U Cut or U VMN combined with a contralateral lesion of the mammillary peduncle	1.9	4
U Cut or U VMN combined with a contralateral lesion of the mammillary nuclei	1.9	4
Lesions of the Ascending Ventral Noradrenergic Bundle (VNA)		
U Cut or U VMN combined with a contralateral lesion of the VNA at the mammillary level which spared the mammillary nuclei	6.3	7
U Cut or U VMN combined with a contralateral lesion of the VNA at the mammillary level which also damaged the mammillary nuclei	6.5	5
U Cut combined with a contralateral lesion of the VNA in the midbrain	5.6	4
U Cut combined with a contralateral midbrain lesion that only partially ablated the VNA bundle	2.8	2

(means 6.5 and 6.3 g/day, $p>0.1$). Thus, unilateral damage to the mammillary bodies neither produces, enhances, or impairs obesity.

As noted above, there was no significant weight gain difference between unilateral parasagittal knife cuts and unilateral VMN lesions. Similarly, when combined with a contralateral MFB lesion, there was no significant weight gain difference between unilateral parasagittal knife cuts (n =3) and unilateral VMN lesions (n = 4, $p>0.1$). This is further justification for pooling unilateral VMN lesion and parasagittal knife cut groups.

Anatomical findings. Reconstructions of representative lesions are shown in Fig. 2. Ablations of the principle mammillothalamic tract (Fig. 2A) were localized to, and in all 3 cases severed, the origins of both the mammillothalamic and mammillotegmental tracts. The MFB, fornix, and the mammillary nuclei in particular were consistently spared by these lesions.

Lesions of the mammillary peduncle (Fig. 2B), posterior to the mammillary nuclei, were restricted exlcusively to the peduncle, with the exception that 2 of the 4 animals also sustained partial damage to the fasciculus retroflexus. Although the mammillary nuclei were spared damage, there was degeneration in the lateral and medial mammillary nuclei ipsilateral to the lesion, as previously described by Cowan, Guillery and Powell [6].

Destruction of the mammillary bodies typically involved both the medial and lateral mammillary nuclei as well as the mammillary peduncle (Fig. 2C). These lesions extended rostrally to the premammillary nuclei and caudally to the interpeduncular nucleus, which in one case was destroyed unilaterally along with the fasciculus retroflexus. The MFB was spared.

Lesions destroying the MFB (Fig. 2D) extended rostrally to the level of the premammillary nuclei and caudally to the level of the interpeduncular nucleus. In all 7 cases the MFB was completely severed and the mammillary nuclei and projections were spared. In isolated cases there was minimal damage to the medial lemiscus, the internal capsule, the zona compacta of the substantia nigra, or the fields of Forel.

All rostrolateral to VMN parasagittal knife cuts, both unilateral and bilateral, met the anatomical criteria for knife cuts that induce obesity as localized by Gold ([19] and unpublished). Unilateral VMN lesions typically destroyed the ventromedial nucleus and immediately adjacent tissue, but without crossing the midline or extending lateral to the fornix. On occasion, however, the unilateral VMN lesion was more dorsal than intended and spared all but the dorsal edge of the VMN, while destroying the dorsomedial nucleus (DMN). Figure 2E shows such a unilateral VMN lesion which, in combination with a contralateral lesion of the MFB, produced marked hyperphagia and rapid weight gains (8.1 g/day).

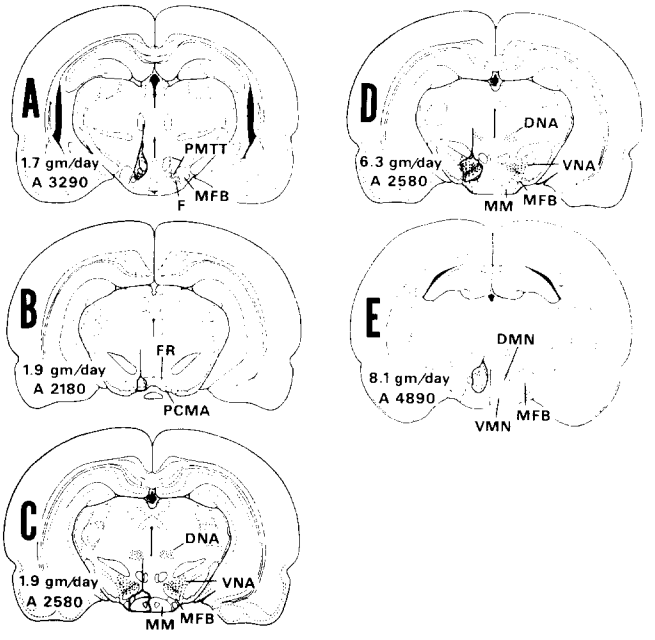

FIG. 2. Reconstructions of representative lesions superimposed on frontal sections of the Konig and Klippel atlas [17]. Weight gains are means over 5 weeks. A, principle mamillothalamic tract; B, mammillary peduncle; C, mammillary nuclei; D, medial forebrain bundle. A through D were combined with either a contralateral parasagittal knife cut rostrolateral to the ventromedial hypothalamus (VMN) or a contralateral electrolytic VMN lesion. E, an atypical VMN lesion which spared most of the ventromedial hypothalamic nucleus but ablated the dorsomedial hypothalamic nucleus. This lesion combined with a contralateral lesion of the medial forebrain bundle produced rapid weight gains. Abreviations: DNA=ascending dorsal noradrenergic bundle; DMN=dorsomedial hypothalamic nucleus; F=fornix; FR=fasciculus retroflexus; MFB=medial forebrain bundle; MM=mammillary nuclei; PCMA= mammillary peduncle; PMTT=principle mammillothalamic tract; VNA=ascending ventral noradrenergic bundle; VMN=ventromedial hypothalamic nucleus.

Discussion

In a previous report [11], it was shown that the fibers which must be destroyed for the production of hypothalamic hyperphagia course longitudinally through the mammillary area and the vicinity of the VMN. Experiment 1 of the present study demonstrates conclusively that destruction of neither the mammillary bodies nor their efferent or afferent projections are involved in hypothalamic hyperphagia and obesity. In contrast, animals with unilateral electrolytic lesions of the posterior MFB combined with a contralateral unilateral electrolytic VMN lesion or parasagittal knife cut did become hyperphagic and obese. These asymmetrically lesioned rats displayed weight gains equivalent to those of animals sustaining bilateral parasagittal knife cuts. It can be concluded from these data that the neural system involved in hypothalamic hyperphagia projects longitudinally within the MFB.

If lesions or knife cuts near the VMN and lesions in the caudal MFB produce obesity by severing one and the same longitudinal neural pathway, then frontal plane knife cuts or electrolytic lesions caudal to VMN but rostral to the mammillary nuclei should also sever the pathway. Attempts to produce hypothalamic obesity with bilaterally symmetrical cuts or lesions have produced contradictory results, perhaps because more than one neural system involved in feeding is interrupted. Large bilateral lesions in the mammillary area can produce hyperphagia and obesity [11, 12, 15]. These lesions typically encroach on the medial hypothalamus and more laterally on the medial portion of the MFB. Large bilateral frontal cuts immediately caudal to

the VMN produce only a modest weight gain and only if the lateral as well as medial areas of the hypothalamus are severed [13], while cuts restricted to either the medial or lateral hypothalamus alone produce no effect, aphagia, or hypophagia [2, 13, 23, 26]. The apparent discrepancy between these small or negative weight gains and our data may be due to our use of a bilaterally asymmetrical rather than bilaterally symmetrical surgical procedure. The major advantage of this approach is that bilateral damage only occurs to those neural systems which pass through both lesion loci. This allows a more selective destruction to individual neural pathways. A more discriminative behavioral deficit should thus be obtainable, and the unlesioned side of the brain at each lesion locus is available for histological assistance.

One must still account for the conflicting data of previous studies that used bilaterally symmetrical lesions or knife cuts. Some of the studies report hypothalamic hyperphagia [11, 12, 13] while others report aphagia or hypophagia [2,23] or no effect [26]. A tentative hypothesis to account for these differences involves the discrete location within the MFB of the separate monoamine pathways as described by Ungerstedt [28].

At the level of the caudal VMN the most dorsolateral portion of the MFB contains dopaminergic fibers which arise from the substantia nigra and project to the corpus striatum. The destruction of these nigro-striatal dopaminergic fibers produces a period of aphagia and adipsia surpassing that produced by lesions of the more medial portion of the medial forebrain bundle [8, 21, 29]. Bilaterally symmetrical surgery caudal to VMN may therefore produce aphagia if the frontal knife cut or lesion severs the dorsolateral (dopaminergic) portion of the medial forebrain bundle, even if satiety fibers are also severed. If the surgery does not produce damage to the dorsolateral MFB, but does sever satiety fibers located more medially in the MFB, hyperphagia and obesity should occur. Unpublished data from our laboratory has shown that bilateral electrolytic lesions of the entire posterior MFB produce an initial period of aphagia and adipsia in aggrement with the data of Albert, Storlien, Wood and Ehman [2]. These same animals later became hyperphagic and obese on a high fat diet. This finding is quite similar to data presented by Carlisle and Stellar [5], in that their animals which sustained damage to both the VMN and LH were at first aphagic and adipsic, but later became hyperphagic if a high fat diet was used.

EXPERIMENT 2

Experiment 1 demonstrated that hypothalamic obesity results from damage to fibers that course longitudinally within the MFB and bypass the mammillary bodies. Recent histochemical mapping of the monoamine pathways has shown that at the level of the mammillary bodies the MFB contains ascending dopaminergic (DA), noradrenergic (NA), and serotonergic (5-HT) fibers which arise from nuclei in the brainstem and midbrain tegmentum [28]. In Experiment 1 the lesions of the MFB which produced hyperphagia and obesity when combined with contralateral parasagittal knife cuts may have damaged all of these ascending monoamine systems. However, of the monoamines only NA has been implicated as possibly playing a role in the inhibition of feeding in the rat [4,19].

Ungerstedt [28] has separated the ascending NA axons into a dorsal and ventral bundle. The dorsal bundle innervates the cortex and hippocampus, while the ventral bundle supplies NA terminals to the pons, medulla, and more importantly to the entire hypothalamus. At the level of the posterior interpeduncular nucleus these two bundles are separate from each other and from the DA and 5-HT systems. In Experiment 2, lesions of the ascending ventral NA bundle were combined with contralateral parasagittal knife cuts rostrolateral to VMN in order to determine what role, if any, these ascending NA fibers play in hypothalamic hyperphagia.

Method

Except as noted below, the methods were as in Experiment 1. Asymmetrically lesioned animals received a unilateral parasagittal knife cut in combination with a contralateral electrolytic lesion of the ascending ventral NA pathway.

In order to produce lesions which conformed to the dimensions of the ventral NA bundle, (see FIG. 4A), two electrode placements were used: A 2.5, L 1.3, V 7.0 and A 2.5, L 1.6, V 6.6.

Control data for rats receiving either unilateral or bilateral parasagittal knife cuts or sham operations were taken from Experiment 1, which was run concurrently.

Results

Mean body weights and food intakes for 5 weeks following recovery from postoperative weight loss (if any) are shown in Fig. 1 (Cut X VNA group). Mean body weight gains are shown in Table 1.

Animals with the asymmetrical combination of a unilateral parasagittal knife cut and a contralateral electrolytic lesion of the ascending ventral NA bundle became hyperphagic and obese (mean weight gain, 5.6 g/day), in comparison to the unilateral or sham operated animals (p's<0.01). The weight gains were similar to but significantly lower than those found following bilateral knife cuts (mean 6.7 g/day, $p<0.05$), although one asymmetrically lesioned animal did display a weight gain of 6.2 g/day.

Anatomical findings. The ascending ventral NA bundle as localized by Ungerstedt [28] was ablated in four of six animals (Fig. 3, A-D) with damage also occurring in varying degrees to the lateral portion of the superior cerebellar peduncle and the recticular formation. The lesions typically extended rostrally to the interpeduncular nucleus, and caudally to the level of the trigmental nerve. Minimal damage produced by the lesion or the electrode track may also have occurred in the ascending dorsal NA bundle. The animal sustaining maximum damage to the dorsal NA bundle (Fig. 3D) displayed the lowest rate of weight gain of animals in this asymmetrical group (5.0 g/day). Gold [8] has previously described a critical midbrain area, which when lesioned produced aphagia and adipsia. The ascending dorsal NA bundle is situated within this critical midbrain region. Since all four animals appear to have damage to the dorsal NA bundle, this may account for the failure of these lesions to produce as great a rate of weight gain as some of the other procedures. Alternatively, NA fibers at the periphery of the ventral bundle may have been spared by these small lesions. These possible explanations are supported by Experiment 1, where lesions of the ascending ventral NA bundle at the mammillary level, which did not

encroach on the dorsal NA bundle (Fig. 2D), produced weight gains which were no different from those produced by bilateral knife cuts (Fig. 1).

Figure 3E and F are reconstructions of two midbrain lesions which only partially destroyed the ascending ventral NA bundle. The lesion in Fig. 3E destroyed the ascending ventral NA bundle. The lesion in Fig. 3E destroyed only the lateral portion of the ventral NA bundle, while that of Fig. 3F ablated only the medial portion. Both these lesions produced similar modest weight gains, which seems to indicate that no one portion of the ventral bundle is specifically involved in the inhibition of feeding, but rather that the inhibitory fibers project diffusely within the entire bundle.

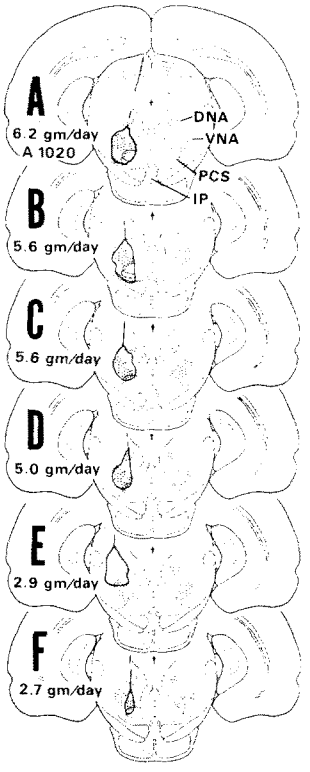

FIG. 3. Reconstructions of individual lesions in the ascending ventral noradrenergic bundle. Each lesioned animal also had a contralateral parasagittal knife cut rostrolateral to the ventromedial hypothalamus (VMN). Rates of weight gain are over a 5 week period. Abbreviations: DNA=ascending dorsal noradrenergic bundle; IP=interpeduncular nucleus; PCS=superior cerebellar peduncle; VNA=ascending ventral noradrenergic bundle.

GENERAL DISCUSSION

Unilateral ablation of the ascending ventral noradrenergic (NA) pathway at a midbrain or mammillary level, in combination with a contralateral parasagittal knife cut, resulted in hyperphagia and obesity. These data are in agreement with Ahlskog and Hoebel's [4] demonstration that bilateral destruction of the ascending ventral NA bundle at the midbrain level produces hyperphagia and obesity. Unilateral lesions in the midbrain which only partially ablated the ventral NA bundle produced only modest hyperphagia when combined with contralateral parasagittal knife cuts. Further rostral, unilateral lesions which spared the ventral NA pathway as it ascends within the MFB, but destroyed the mammillary nuclei or their fiber systems, did not produce obesity when combined with contralateral parasagittal knife cuts.

The neural substrate which must be lesioned to produce hypothalamic hyperphagia therefore may be the ascending ventral NA bundle. This bundle projects rostrally from NA cell groups in the medulla and pons [7,28]. The NA brainstem nuclei have been shown to possess neural connections with the nuclei of autonomic nerves, such as the nucleus tractus solitarius, which receives oropharangeal afferent taste fibers via the glossopharyngeal, lingual, and vagus nerves [20,28]. These brainstem nuclei could thereby receive hunger related information by way of the peripheral nervous system, and conduct this information via the ascending ventral NA bundle to the hypothalamus where an integration of food related sensory cues might occur.

From the brainstem NA nuclei the ventral NA bundle ascends through the recticular formation, along the medial lemniscus, and continues rostrally within the MFB from which NA fibers then turn medially to innervate the hypothalamus [28]. Some of these medially projecting fibers appear to be interrupted by the parasagittal hypothalamic knife cuts or by the more traditional electrolytic VMN lesions.

There are no NA terminals within the VMN itself [28]. The degree of hyperphagia and obesity following VMN lesions has been shown to correlate positively with the size of the lesion [3], suggesting fibers of passage adjacent to the VMN may be critical. Frontal knife cuts anterior to the VMN can produce hyperphagia, quite possibly by severing the same fibers as rostrolateral to VMN parasagittal knife cuts [13,23].

Destruction of the MFB at the level of the mammillary nuclei results in a depletion of NA terminals ipsilaterally in the entire hypothalamus. Lesions of the MFB just rostral to the mammillary bodies do not produce a depletion of hypothalamic NA terminals, with the exception of the paraventricular nucleus and the preoptic area [28]. The NA fibers to the hypothalamus thus appear to turn medially within the hypothalamus long before they reach the level they innervate. Since parasagittal knife cuts at the caudal end of the hypothalamus which would sever the medially projecting fibers to the hypothalamus, do not produce hyperphagia and obesity [9], the medially projecting NA fibers that are interrupted in hypothalamic hyperphagia may innervate more rostral structures such as the paraventricular nucleus. If the fibers that are critically damaged in hypothalamic obesity normally inhibit feeding, then the loci containing the neurons thay they inhibit must be spared by lesions that produce obesity. Thus, if the fibers involved in the inhibition of feeding do indeed ascend from brainstem NA nuclei, then the VMN and adjacent loci may not be the recipient of these inhibitory NA terminals, but rather the fibers may course near the VMN and project to more rostrally located structure (s).

Finally, the conclusion that destruction of the ventral NA bundle may be responsible for hypothalamic hyperphagia has been based on the destruction, albeit at several

levels and with asymmetrical lesions, of loci at which the maps prepared by Ungerstedt [28] place the ventral bundle. Damage to the ventral bundle was not quantified directly by histo-fluorescent or biochemical techniques. Also, the electrolytic lesions and knife cuts used do not selectively damage adrenergic fibers. It is entirely possible that some pathway other than the ventral bundle, but which runs a parallel course, is responsible for hypothalamic hyperphagia when destroyed.

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