Pharmacology Biochemistry & Behavior, Vol. 6, pp. 203–214.

A Correlational Analysis of the Effects of Surgical Transections of Three Components of the MFB on Ingestive Behavior and Hypothalamic, Striatal, and Telencephalic Amine Concentrations[1]

LOIS J. MCDERMOTT, GEORGE F. ALHEID, ANGELOS E. HALARIS AND SEBASTIAN P. GROSSMAN[2]

Committee on Biopsychology, University of Chicago, Chicago, IL 60637

(Received 20 December 1976)

MCDERMOTT, L. J., G. F. ALHEID, A. E. HALARIS AND S. P. GROSSMAN. *A correlational analysis of the effects of surgical transections of three components of the MFB on ingestive behavior and hypothalamic, striatal, and telencephalic amine concentrations.* PHARMAC. BIOCHEM. BEHAV. 6(2) 203–214, 1977. – A retractable wire knife was used to transect medial or lateral components of the MFB or its lateral projections to the striatum and amygdaloid complex. All cuts produced significant depletions of NE, DA, and 5-HT from telencephalon and striatum but little or no effect on hypothalamic NE or 5-HT. Two of our cuts resulted in aphagia and adipsia, the third in hyperphagia and obesity. A detailed correlational analysis of the magnitude and direction of the behavioral and biochemical consequences of our cuts indicated that the ingestive behavior of all of our experimental animals (including animals which had been aphagic and adipsic after surgery as well as animals which were hyperphagic and obese) was positively correlated with the concentration of DA in striatum and telencephalon and negatively correlated with telencephalic 5-HT. Less consistent evidence for facilitatory noradrenergic influences on food intake was also obtained. Our results suggest that the regulation of food intake may be the result of an interaction between telencephalic serotonergic mechanisms and dopaminergic pathways which exert opposite effects on ingestive behavior.

Medial forebrain bundle, ingestive behavior Medial forebrain bundle, brain amines Norepinephrine, MFB transection Serotonin, MFB transection Dopamine, MFB transection Striatum, ingestive behavior Telencephalon, ingestive behavior

IT HAS long been known that damage to adjacent hypothalamic areas results in opposite effects on ingestive behavior. Lesions of the ventromedial hypothalamus (VMH) produce hyperphagia and obesity [34]. Lesions of the lateral hypothalamus (LH), dorsal and lateral to the VMH, produce aphagia, adipsia, and emaciation [5]. These findings prompted Stellar [62] to suggest that food intake was regulated by the reciprocal action of excitatory and inhibitory mechanisms in the hypothalamus.

The uniqueness of these hypothalamic influences on food and water intake has been questioned by more recent reports of the effects of surgical, electrolytic, or pharmacological lesions in various extrahypothalamic structures on food or water intake. Persistent aphagia and adipsia have been reported following electrolytic lesions in the globus pallidus [46], midbrain tegmentum [8,21], and substantia nigra [35,68]. Hyperphagia and/or hyperdipsia have been reported after lesions in the mammillary region [24], septum [32], and portions of the mesencephalon [1, 51, 60].

That some or all of the effects of these lesions may be due to an interruption of fiber systems which project to or through the hypothalamus is suggested by a number of recent experimental observations, including (a) hyperphagia and/or hyperdipsia following surgical knife cuts in the coronal plane anterior [26], posterior [26, 31, 33] and lateral [3,58] to the VMH or after asymmetric electrolytic lesions in the ventromedial and mammillary region of the diencephalon [23] and (b) aphagia and adipsia after surgical knife cuts along the lateral border of the diencephalon [28,29], or asymmetric lesions in the globus pallidus and LH [66].

These experimental findings are congruent with earlier suggestions that the effects of medial as well as lateral hypothalamic lesions on food and water intake may be due to an interruption of fibers of passage rather than the

[1] This research was supported in part by USPHS. NIMH Grant MH 10130.
[2] Send reprint requests to S. P. Grossman, Department of Behavioral Sciences, University of Chicago, Chicago, IL 60637.

destruction of local perikarya (e.g., [11,46]; see [27] for review). What is not clear at this point is the nature, origin and projection of the fiber systems that may be responsible for the effects of hypothalamic lesions on ingestive behavior.

The areas of the hypothalamus where lesions most consistently affect food or water intake are traversed by a number of diffuse fiber systems, including the medial forebrain bundle (MFB), nigrostriatal bundle (NSB), pallidofugal and corticofugal fiber systems and several sensory projection systems. The aminergic components of these fiber systems [47] (i.e., the dorsal and ventral noradrenergic bundles, the medial and lateral serotonergic bundles, and the nigrostriatal and mesolimbic dopaminergic bundles) in particular have been implicated in the regulation of food and water intake by the results of numerous recent investigations which have shown that intracranial injections of compounds which preferentially destroy or inactivate aminergic neurons can result in pronounced effects on food and/or water intake. Ahlskog and associates [1,2] have reported that local injections of the neurotoxin 6-hydroxydopamine (6-OHDA) into lateral portions of the tegmentum which are traversed by the ventral noradrenergic projection to the hypothalamus [52,68] depletes NE from hypothalamus and results in mild hyperphagia and obesity. Others have reported hyperphagia after intraventricular injections of compounds which reversibly (p-chlorophenylalanine) or irreversibly (5,7-dihydroxytryptamine) deplete brain serotonin [10,56]. Aphagia and adipsia have been reported after intraventricular [63, 64, 70, 71]; intracisternal [9,12]; intranigral [17, 18, 43, 68]; intrahypothalamic [18, 43, 61] or intrastriatal [49] injections of the neurotoxin 6-hydroxydopamine (6-OHDA) which destroys catecholaminergic pathways.

The results of these pharmacological studies have implicated ascending amine pathways that ascend through the brainstem in the regulation of food and water intake but the interpretation of these results is controversial. Intracerebral injections of compounds such as 6-OHDA do not affect any one aminergic pathway selectively and produce non-specific neurotoxic effects on all neural tissue which may be severe at the relatively high concentrations that are typically used in these experiments [54]. The pharmacological specificity of these effects is therefore open to serious question. Intraventricular and intracisternal injections produce relatively few generalized neurotoxic effects, but convincing evidence of neural reactions in the immediate vicinity of the ventricular system is notably lacking. These injections do not, however, selectively attack any one amine system (although the specificity of their effects can be significantly increased by pretreatments with uptake blockers such as desmethylimipramine) and provide inconclusive evidence of the site of action of 6-OHDA since the aminergic pathways are diffusely distributed to most portions of the brain. There are significant regional differences in the distribution of specific amines in the brain but this, by itself, provides no evidence that any particular behavioral effect is due to a selective depletion of any specific portion of the brain. There are, moreover, serious questions concerning the behavioral specificity of the effects of intraventricular or intracisternal injections since the more or less complete destruction or inactivation of one or more of the amines in the entire brain produces complex general behavioral disturbances (e.g., loss or arousal, extreme activation, etc.) which in and of themselves may be responsible for many or all of the observed changes in food or water intake [65].

A number of investigators [1, 13, 14, 19, 42, 50, 51] have attempted to circumvent some of these problems by examining the relationship between behavioral and biochemical effects of electrolytic lesions in various portions of the brainstem that are traversed by specific portions of the ascending aminergic pathways. Some have reported hyperdipsia after tegmental lesions which depleted forebrain serotonin [14,42] or norepinephrine [51]. Others have reported hyperphagia after tegmental lesions which depleted hypothalamic NE [1] or aphagia and adipsia after lesions of the hypothalamus, globus pallidus, substantia nigra which depleted striatal and/or telencephalic dopamine [19, 43, 50]. Only a few investigators have discussed the relationship between the severity of the behavior and biochemical consequences of the lesions and attempted even a limited correlational analysis of these effects [13, 19, 43].

The present experiments were designed to provide data for a detailed correlational analyses of the biochemical and behavioral consequences of three surgical procedures which have been shown to produce distinct effects on food and water intake. On the basis of recent anatomical and histochemical data [36, 40, 52], an attempt was made to interfere selectively with three anatomically and to some extent biochemically distinct components of the MFB. Using microsurgical knife cut techniques that have been developed and perfected in our laboratory, the following pathways were interrupted: (a) the laterally coursing projections of the MFB to the striatum and amygdala (a procedure known to produce long-term aphagia and adipsia as well as persisting deficits in response to glucoprivic and hydrational challenges) [28,29]; (b) components of the MFB which ascend to forebrain in the lateral aspects of that diffuse bundle (a procedure known to produce only transient disruptive effects on food and water intake) [3,53] and (c) medial components of the MFB (a procedure known to result in hyperphagia and/or hyperdipsia) [31]. Three regions of the brain (hypothalamus, striatum, and forebrain) were assayed for the residual concentrations of serotonin, norepinephrine, and dopamine, after the behavioral consequences of each of the transections had been established. Correlational analyses of the behavioral and biochemical consequences of the transactions were performed to demonstrate possibly existing functional relationships.

METHOD

Animals

The animals were male albino rats of the Sprague-Dawley strain (Holtzman, Madison, Wisconsin), housed singly in a temperature controlled colony which was on a 12 hr light–dark schedule (lights on 700 hours). The animals weighed 345–380 g at the time of surgery.

Surgery

Knife cuts were made under Nembutal anesthesia using an encephalotome constructed of 27 ga stainless-steel hypodermic needle stock as previously described [58]. The knife shaft was stereotaxically placed at one of three locations in the trajectory of the medial forebrain bundle and a 150 μ diameter spring steel wire knife was then extended from the slightly bent tip of the guide cannula.

One of three cuts was made bilaterally in each of the animals, according to the following coordinates from the de Groot [16] atlas of the rat brain.

(a) Parasagittal cuts (PS) along the medial edge of the internal capsule. Bilateral PS cuts were made in 14 rats using a knife that was 2.0 mm long and dropped 0.4 mm from the tip of the guide shaft. The knife was extended caudally in a parasagittal plane (L = 2.2) from H = −1.5 and lowered to the base of the brain at AP = 6.0. The knife thus cut across all laterally coursing projections of the MFB in a plane extending from the anterior hypothalamus to the mammillary bodies, and from the thalamus to the base of the brain, along the medial aspect of the internal capsule. Ten of these operated rats were used for behavioral testing and biochemical assays. The brains of the four remaining animals were used for histological confirmation of the placement of the cuts.

(b) Coronal cuts across fibers of the lateral MFB (LMFB). Bilateral LMFB cuts were made in 18 rats with a knife of an overall length of 1.2 mm. The knife dropped 0.7 mm from the tip of the guide shaft. The knife was extended at L = 2.6 along a coronal plane (AP = 4.6) toward the midline and lowered from H = 1.8 to the base of the brain, thus cutting across lateral components of the MFB as they ascend or descend through the IC and lateral hypothalamus just anterior to the mammillary bodies. Twelve of these rats were used for behavioral testing and biochemical assays. The brains of the other six rats of this group were used for histological confirmation of the placement of the cuts.

(c) Coronal cuts across the fibers of the medial MFB (MMFB). Bilateral MMFB cuts were made in 21 rats with a knife of an overall length of 1.2 mm. The wire dropped 0.7 mm from the tip of the guide shaft. The knife was extended toward the midline at L = 2.0 in a coronal plane (AP = 4.6) and lowered to the base of the brain, thus cutting across the medial fibers of the MFB as they pass through a part of the hypothalamus that is bordered by the zona incerta, dorsally, the internal capsule laterally, the fornix and mammilothalamic tract medially, and the base of the brain, ventrally. Seventeen operated rats were used for behavioral tests and biochemical assays. The remaining four were used for histological confirmation of the placement of the cuts.

(d) Control operations. Control operations were performed on ten rats which were used as controls in the behavioral tests and biochemical assays. These animals were anesthetized, placed into the stereotaxic apparatus, an incision was made in the scalp, holes were drilled through the skull and a stainless steel insect pin was used to pierce the dura and cortex.

Measures of Ingestive Behavior

Twenty-four hour ad lib food and water intake as well as body weight were recorded daily for all animals. Standard pellet food (Teklad 6% fat) was always available on the floor of the cage, and tap water was available in glass bottles with standard drinking tubes. Animals which did not eat or drink at least 5 g of food and water for two consecutive days after surgery were given a liquid diet by intragastric intubation, as described by Teitelbaum and Epstein [67]. During the period of intragastric feeding wet mash was also available on the floor of the cage. The consumption of this preferred diet was monitored in order to determine the minimum quantity of intragastric feeding required to maintain life (and thus assure optimal recovery). Daily food intake was recorded periodically until 45 days after surgery. Daily water intake was recorded periodically until Day 60. Body weight was recorded for 115 days after surgery.

Biochemistry

Fifty-two rats were used for biochemical assays. All animals were sacrificed 115 days after surgery, except for five animals with LMFB cuts which were sacrificed on Day 10 because of a severe loss of body weight and general debilitation. Of the 52 aimals used, 10 had PS cuts, 12 had LMFB cuts, 17 had MMFB cuts and 10 were controls which had undergone control surgery. The brains of three unoperated rats which had been maintained on ad lib food and water intake and had not undergone any behavioral tests were also assayed.

The rats were sacrificed by decapitation, their brains quickly removed and dissected on ice. Brain regions were weighed, quickly frozen and stored in liquid nitrogen. The concentration of NE, DA and 5HT was determined in striatum and telencephalon and NE and 5HT in hypothalamus by ion exchange chromatography. Brain regions were homogenized in 15 ml ice cold 0.4 N perchloric acid with 0.25 ml 4% disodium (ethylenedinitrilo) tetraacetate and 0.2 ml 2% ascorbic acid in each tube. After centrifugation, the supernatant was adjusted to pH 6.5 and passed onto Amberlite (CG-50) columns. The amines were eluted from the columns in 4 ml 1 N hydrochloric acid. Catecholamines were oxidized as described by Barchas *et al.* [6]. The five animals with LMFB cuts which were sacrificed on Day 10 were assayed only for striatal DA and hypothalamic NE.

Brain regions were dissected according to the following procedure. After the brain was removed from the calvarium, the olfactory bulbs were dissected and discarded. The brain was divided into three sections by making coronal cuts at the rostral and caudal edges of the olfactory tubercles. The left and right striata were removed from the middle section by trimming away the cortex along the corpus callosum, removing the septum by cutting along the ventricles, and removing the amygdala by a horizontal cut. The cortical tissue surrounding the striatum, including the frontal lobes, was combined with the remaining cortex of the other two sections to constitute the tissues of the telencephalon. The hypothalamus was dissected from the diencephalon by making a coronal cut just caudal to the mammillary bodies to remove the midbrain. The thalamus was removed and discarded from this section by cutting horizontally at the dorsal edge of the fornix on the anterior aspect of this section.

Histology

The brains of 14 rats were used to obtain histological verification of the accuracy of the surgical procedures. Data from these animals were not included in behavioral or biochemical tests because the rats were killed ten days after surgery to permit optimal histological staining of glial-cell formations. The animals were killed with an overdose of Nembutal and perfused intracardially with a 10% formol-saline solution. The brains were removed from the calvaria and stored for seven days in a similar solution. They were then frozen and sectioned through the area of the knife cuts. The sections were mounted on glass slides and stained with cresyl violet. Of these animals, four had bilateral PS cuts, six received LMFB cuts, and four MMFB cuts.

TABLE 1

GROUP MEANS (G) FOR MEASURES OF INGESTIVE BEHAVIOR ±SE

Cuts	n	Days of Aphagia	Body Weight Day 2	Body Weight Day 10	Body Weight Day 115	Food Intake Day 2	Food Intake Day 10	Food Intake Day 45	Water Intake Day 2	Water Intake Day 10	Water Intake Day 45
PS	10	5.0 ± 2.4	*324** ± 23	*384*‡ ± 20	470 ± 54	*3** ± 5	33 ± 10	29 ± 3	*4** ± 3	43 ± 14	44 ± 12
LMFB	12	5.3 ± 5.0	*332*† ± 35	339 ± 51	478 ± 59	*13*‡ ± 13	17 ± 16	34 ± 7	*18*† ± 19	26 ± 23	50 ± 16
MMFB	17	0.1 ± .3	377 ± 24	404 ± 25	*584*† ± 80	*34*‡ ± 14	*40** ± 7	*40*† ± 11	44 ± 19	*53*‡ ± 9	*66*† ± 13
CONT	10	0.0 ± .0	373 ± 24	417 ± 25	491 ± 38	28 ± 2	29 ± 2	29 ± 3	40 ± 5	46 ± 9	52 ± 9

*$p<0.001$
†$p<0.01$
‡$p<0.05$

TABLE 2

MEAN REGIONAL CONCENTRATIONS OF MONOAMINES (NG/G) ±SE

Cuts	Striatum n	Striatum NE	Striatum DA	Striatum 5HT	Hypothalamus n	Hypothalamus NE	Hypothalamus 5HT	Telencephalon n	Telencephalon NE	Telencephalon DA	Telencephalon 5HT
PS	9	*179** ± 83	*1901** ± 529	*498** ± 164	10	*1748*† ± 181	1514 ± 517	9	*318** ± 46	*363** ± 183	*461*† ± 87
LMFB	7	*276*† ± 52	*4627** ± 2169§	*535*‡ ± 245	7	2011 ± 683§	1744 ± 248	5	*292** ± 87	*595** ± 135	596 ± 208
MMFB	13	*287*‡ ± 64	*7618*‡ ± 1470	*528*‡ ± 49	13	1956 ± 351	1882 ± 652	16	*276** ± 89	*505** ± 119‖	*347** ± 104
CONT	13	372 ± 65	9674 ± 2029	706 ± 112	13	2092 ± 246	1428 ± 508	12	478 ± 43	785 ± 63	613 ± 100

*$p<0.001$
†$p<0.01$
‡$p<0.05$
§n=11
‖n=10

RESULTS

1. Parasagittal (PS) Cuts Along the Medial Edge of the Internal Capsule

(a) Ingestive behavior (Table 1). Ten animals with PS cuts consumed, on the average, 2.5 g of food (91% less than controls) on the second day after surgery ($p<0.001$). All but one of the animals were aphagic after surgery ($\bar{X}$ = 5.0 days, range ± 1–7 days) and all ten rats required intragastric feeding for several days ($\bar{X}$ = 5.5 days). By the 10th day after surgery, the mean daily food intake for the operated group was not significantly different from that of controls.

Water intake and body weight were also reduced by the PS cuts. Nine of the operated animals were adipsic ($\bar{X}$ = 6.2 days, range 2–8 days) and consumed 3.7 ml of water on the average (90.1% less than controls) ($p<0.001$) on the second postoperative day. Water intake returned to control levels by Day 10.

On the second day after surgery, the animals with PS cuts, weighed, on the average, 46 g less than prior to surgery ($p<0.01$) and significantly less (13.8%) than controls ($p<0.001$). Twenty days after surgery and on subsequent days there were no significant differences in body weight between animals with PS cuts and controls, although the mean body weight for the operated group remained somewhat lower than control values.

(b) Biochemistry (Table 2). PS cuts resulted in profound amine depletions in striatum and telencephalon, but had little or no effect on hypothalamic tissue. In the striatum, DA was depleted to 19.7% of control values ($p<0.001$), NE was reduced to 48.1% of controls ($p<0.001$) and 5HT was reduced to 70.5% of controls ($p<0.01$). The same cuts significantly depleted the telencephalon of DA (46.2% of controls, $p<0.001$), NE (69.0% of controls, $p<0.001$) and 5HT (74.2% of control, $p<0.01$). Hypothalamic NE was also slightly depleted to 83.6% of control ($p<0.01$).

(c) Correlations (Table 3). The effects of PS cuts on food and water intake as well as body weight were not reliably correlated with any of the biochemical effects of the cuts (see Table 3), except that the number of days of aphagia and body weight on the second day after surgery

TABLE 3

CORRELATIONS BETWEEN INGESTIVE BEHAVIOR AND REGIONAL CONCENTRATION OF MONOAMINES FOR ANIMALS WITH PS CUTS

	n	Days of Aphagia	Body Weight			Food Intake			Water Intake		
			Day 2	Day 10	Day 115	Day 2	Day 10	Day 45	Day 2	Day 10	Day 60
Striatum											
NE	9	−0.04	0.05	0.03	0.27	0.33	−0.63	−0.12	0.34	−0.28	−0.62
DA	9	−0.12	0.17	0.04	0.49	0.27	−0.30	0.25	0.19	0.23	−0.31
5HT	9	−0.14	0.41	0.05	0.10	0.30	0.07	−0.57	0.26	0.02	−0.12
Hypothalamus											
NE	10	−0.45	−0.09	−0.26	0.14	−0.17	−0.36	0.05	−0.29	−0.35	−0.39
5HT	10	−0.08	0.03	0.16	0.42	−0.02	0.38	0.02	0.00	0.17	0.02
Telencephalon											
NE	9	−0.32	0.32	0.36	0.16	0.20	0.65	0.05	0.30	*0.68**	0.07
DA	8	*−0.69**	*0.69**	0.02	−0.18	0.59	−0.19	−0.14	0.50	−0.03	0.19
5HT	9	0.65	−0.43	−0.31	−0.35	−0.11	−0.59	−0.50	−0.18	−0.49	−0.58

*$p<0.05$

were correlated reliably ($p<0.05$) with telencephalic dopamine. There also was some indication of a relationship between food and water intake on Day 10 (i.e., after recovery from aphagia and adipsia) and telencephalic norepinephrine, but the correlation coefficients were only marginally significant ($p<0.06$ and 0.04 respectively).

2. Coronal Cuts Across the Fibers of the Lateral MFB (LMFB)

(a) Ingestive behavior (Table 1). On the second day after surgery, the 24 hr ad lib food intake of 12 rats with LMFB cuts was 53.7% smaller than that of controls ($p<0.01$). Water intake was reduced to 54.9% of controls ($p<0.01$). The body weight of the operated animals was also significantly lower ($p<0.01$) than that of controls on Day 2 (Table 1).

Ten animals were aphagic and adipsic after surgery. Although intragastric feedings were administered two or three times per day, five of these animals displayed no evidence of recovery by the 10th postoperative day. At this time the body weight of these aphagic animals had decreased by an average of 75.6 g below preoperative body weight. The controls had increased their body weight by 58.3 g in the same period. Because of this precipitous drop in weight and a correlated general deterioration of their physical condition, these five animals were decapitated on Day 10 while still aphagic and their brains were assayed for monoamine concentrations. The other seven animals of this group (which were aphagic for only 2.1 days, on the average, range 0–5 days, and hypophagic for eight days) recovered their normal voluntary ingestive behavior within 10 days after surgery and ingested amounts of food and water on Day 10 which were not significantly different than those consumed by controls. By Day 10, the body weights of the seven surviving rats with LMFB had also recovered to control levels.

(b) Biochemistry (Table 2). In animals with LMFB cuts, the striatum was depleted of DA (to 47.8% of control; $p<0.001$), NE (74.2% of control; $p<0.01$) and 5HT (74.5% of control; $p<0.05$). The telencephalon was depleted of NE (to 61.1% of control; $p<0.001$) and DA (to 75.7% of control; $p<0.001$). Telencephalic 5HT was not reliably affected. The LMFB cuts had no significant effects on hypothalamic NE or 5HT.

(c) Correlations (Table 4). The pronounced behavioral effects of LMFB cuts were consistently positively correlated with the magnitude of the depletions of striatal dopamine. Major negative correlations between the biochemical and behavioral effects of this cut were computed for telencephalic 5HT, indicating that a reciprocal relationship between striatal DA and telencephalic 5HT may influence food and water intake. It is interesting that the duration of aphagia in these animals was positively correlated with telencephalic 5HT and negatively correlated with striatal DA.

3. Coronal Cuts Across Fibers of the Medial MMFB (MMFB)

(a) Ingestive behavior (Table 1). Seventeen animals with MMFB cuts consumed 34.3 g of food on the average, on Day 2, an increase of 16.3% over the mean of the control group. Two of the experimental animals were aphagic and adipsic for four days. When the data from these animals was excluded from the analysis, the food intake of the experimental group averaged 35.8 g, 27.4% larger than that of the control group on Day 2 ($p<0.01$). On Day 10, the average intake of the experimental group (including the two animals which had been aphagic and adipsic was 39.9% greater than the intake of the control group ($p<0.001$). A significant ($p<0.01$) difference in food intake between the experimental and control groups persisted on Day 45.

The water intake of our rats with MMFB cuts was slightly greater than that of the controls (see Table 1). The difference between the experimental and control groups was statistically reliable ($p<0.01$) on Day 60 but not on Days 2 or 10. The slight increases in water intake that were seen in rats with MMFB cuts almost certainly reflect that prandial and digestive needs of hyperphagic animals rather

TABLE 4

CORRELATIONS BETWEEN INGESTIVE BEHAVIOR AND REGIONAL CONCENTRATIONS OF MONOAMINES FOR ANIMALS WITH LMFB CUTS

	n	Days of Aphagia	Body Weight			Food Intake			Water Intake		
			Day 2	Day 10	Day 115	Day 2	Day 10	Day 45	Day 2	Day 10	Day 60
Striatum											
NE	7	0.25	−0.38	0.02	0.07	−0.68	−0.36	−0.71	−0.62	−0.39	−0.38
DA	11	*−0.68*§	*0.69*§	*0.74*‡	*0.78**§	*0.69*§	*0.66*§	−0.14*	*0.52*§	*0.64*§	0.64*
5HT	7	0.25	−0.19	−0.17	−0.17	0.15	−0.12	−0.33	0.07	−0.30	−0.22
Hypothalamus											
NE	11	*−0.72*‡	0.56	0.58	0.33*	0.43	*0.60*§	−0.71*	0.39	0.69	−0.44*
5HT	7	−0.24	0.40	0.42	0.45	0.72	0.65	0.32	0.64	0.32	0.45
Telencephalon											
NE	7	0.03	−0.11	−0.02	−0.15	−0.30	−0.61	*−0.85*§	−0.51	−0.42	−0.27
DA	7	0.10	0.10	−0.32	0.52	0.41	−0.48	−0.51	0.61	0.37	0.22
5HT	7	*0.79*§	−0.73	*−0.90*‡	*−0.93*‡	−0.67	*−0.82*§	*−0.83*‡	−0.19	−0.28	−0.55

*n=7
‡$p<0.01$
§$p<0.05$

TABLE 5

CORRELATIONS BETWEEN INGESTIVE BEHAVIOR AND REGIONAL CONCENTRATIONS OF MONOAMINES FOR ANIMALS WITH MMFB CUTS

	n	Days of Aphagia	Body Weight			Food Intake			Water Intake		
			Day 2	Day 10	Day 115	Day 2	Day 10	Day 45	Day 2	Day 10	Day 60
Striatum											
NE	13	N/A	0.44	0.25	0.20	0.27	−0.24	−0.10	0.37	0.06	0.14
DA	13	N/A	*0.63*†	0.33	−0.10	*0.72*†	0.42	−0.24	*0.72*†	0.44	0.00
5HT	14	N/A	0.44	0.47	0.07	0.00	0.27	0.24	0.24	*0.55*‡	0.35
Hypothalamus											
NE	13	N/A	−0.21	0.16	−0.08	−0.11	0.20	0.02	−0.62	−0.19	−0.21
5HT	13	N/A	0.03	0.16	0.19	−0.08	0.40	0.27	−0.01	0.18	0.21
Telencephalon											
NE	16	N/A	0.29	0.06	−0.35	0.41	0.27	−0.27	0.28	0.25	0.32
DA	10	N/A	0.20	0.14	−0.13	−0.01	0.40	0.04	0.17	0.17	−0.27
5HT	15	N/A	0.16	−0.21	*−0.60*‡	*0.54*‡	0.17	*−0.56*‡	0.44	0.00	−0.47

†$p<0.01$
‡$p<0.05$

than true hyperdipsia. Rats with MMFB cuts also weighed more than the controls, throughout the experimental observation period. On Day 85 the experimental rats were 62 g heavier on the average than the controls ($p<0.05$). On Day 115 the difference had increased to 94 g ($p<0.01$). At this time, the operated animals weighed on the average, 84.5% more than on the day before surgery, whereas the controls were only 33.1% heavier. The weight gain for the seven heaviest experimental animals was 114%, 110%, 94%, 89%, 77%, 76%, and 67% above preoperative body weight. The largest control animal was only 37% heavier. It is noteworthy that significant hyperphagia and obesity occurred in these male rats even though they were maintained on standard laboratory chow.

(b) Biochemistry (Table 2). MMFB cuts significantly ($p<0.001$) depleted all three amines from the telencephalon (5HT = 56.6% of control; DA = 64.2% of control; NE = 58.4% of control). Striatal amine levels were reduced less severely (DA = 78.7% of control; NE = 78.2% of control; 5HT = 74.5% of control). Nevertheless, the effect was statistically reliable ($p<0.05$) in each case. The cuts produced no significant effects ($p>0.1$) on hypothalamic amine concentrations.

(c) Correlations (Table 5). In contrast to the aphagia and adipsia seen after LMFB cuts, MMFB cuts produced hyperphagia and obesity. However, a correlational analysis of the behavioral and biochemical effects of MMFB cuts revealed significant relationships between telencephalic 5HT and striatal DA and food and water intake which were similar to those observed in the aphagic animals (ingestive

TABLE 6

CORRELATIONS BETWEEN INGESTIVE BEHAVIORAL AND REGIONAL CONCENTRATIONS OF MONOAMINES FROM POOLED DATA FOR ALL ANIMALS SUSTAINING DAMAGE TO COMPONENTS OF THE MFB

	n	Days of Aphagia*	Body Weight			Food Intake			Water Intake		
			Day 2	Day 10	Day 115	Day 2	Day 10	Day 45	Day 2	Day 10	Day 60
Striatum											
NE	29	*−0.54‡*	*0.54‡*	0.28	0.37	*0.53‡*	0.10	0.25	*0.50‡*	0.09	0.19
DA	33	*−0.73†*	*0.79†*	*0.52†*	*0.58†*	*0.88†*	*0.49‡*	*0.50‡*	*0.84†*	*0.49‡*	*0.60†*
5HT	30	−0.10	0.23	0.16	0.01	0.10	0.10	0.01	0.15	0.15	0.06
Hypothalamus											
NE	34	*0.49‡*	0.27	0.21	0.10	0.22	0.24	−0.07	0.25	0.28	−0.16
5HT	30	−0.27	0.29	0.25	0.36	0.23	0.42	0.35	0.26	0.27	0.30
Telencephalon											
NE	30	0.10	−0.02	0.01	−0.34	0.02	0.10	*−0.40§*	−0.11	0.14	−0.03
DA	23	*−0.75†*	*0.53‡*	0.06	0.09	*0.49‡*	0.03	0.13	*0.48‡*	0.25	0.23
5HT	29	*0.47§*	−0.32	*−0.50‡*	*−0.67†*	−0.21	*−0.45‡*	*−0.55†*	−0.17	−0.29	*−0.44‡*

*Data from LMFB and PS cuts only.
†$p<0.001$.
‡$p<0.01$.
§$p<0.05$.

behavior was positively correlated with the concentration of striatal DA and negatively correlated with telencephalic 5HT). Neither telencephalic NE nor DA (which were reliably affected by the MMFB cuts) appeared to be reliably correlated with the observed changes in ingestive behavior.

4. Correlations Between Regional Amine Concentrations and Measures of Ingestive Behavior for all Animals Sustaining Damage to the Fibers of the MFB

Our knife cuts involved three different portions of the MFB. Each cut resulted in some damage to NE, DA and 5HT systems but resulted in different patterns of regional depletions which suggests that different components of the three major aminergic pathways were damaged. The PS cuts resulted in very large depletions of striatal DA and NE with large to moderate depletions of telencephalic amines. The MMFB cuts produced only a slight depletion of striatal amines but very significant changes in telencephalic amines especially telencephalic 5HT. The LMFB cuts caused profound depletion of striatal DA with only moderate changes in striatal NE and 5HT and forebrain DA and NE and no change in forebrain 5HT. (See Table 2 for details.)

These cuts also resulted in a variety of effects on food and water intake and body weight. Transient aphagia and adipsia were observed in animals with PS cuts. LMFB cuts appeared to produce more persistent and profound inhibitory effects on food and water intake although some animals of this group showed only slight deficits. Animals with MMFB cuts were hyperphagic, and obese.

The surprising agreement of the results of our correlational analyses in three independent groups of animals which sustained quite different biochemical depletions and seemingly opposite behavioral effects suggests that food intake may be influenced by a neural system that relies on a reciprocal interaction of dopaminergic and serotonergic pathways. Depending on the nature of the imbalance, either aphagia or hyperphagia results when the normal relationship between the two influences is disrupted. An attempt to test this general hypothesis by examining the correlations between regional amine concentrations and food intake, using pooled data from all of our hyperphagic and aphagic animals provided substantial support for this interpretation.

Analysis of the data shown in Table 6 suggests the presence of several consistent relationships between ingestive behavior (and body weight) and the concentrations of brain amines. The most consistent of these is a strong and reliable positive correlation between striatal dopmaine and food as well as water intake (and body weight). It is particularly interesting that this relationship holds not only for Day 2 (the only reference point that is clearly within the immediate postsurgical period when both the PS and LMFB cuts produce significant inhibitory effects on food as well as water intake) but also for all subsequent points of analysis (i.e., 10, 45, 60, or 115 days after surgery).

The second major relationship between the behavioral and biochemical effects of our cuts which emerges from the analysis of the pooled data from all experimental animals (Table 6) is a significant negative correlation between food and water intake (and body weight) and telencephalic serotonin. Similar correlations were seen in the LMFB group (Table 4) (made up of rats that were initially aphagic and adipsic) and in the MMFB group (Table 5) (made up of rats that were hyperphagic after surgery). These observations suggest that telencephalic serotonergic projections may normally exert inhibitory influences on ingestive behavior.

The only other correlations that emerged from our analysis of pooled data indicate a positive relationship between the short-term behavioral effects of our cuts and their depleting effects on telencephalic DA and striatal NE. On Day 2 after surgery, food and water intake as well as body weight were lowest in animals which had the most severe depletions of NE (as well as DA, see above) from the striatum and DA (but not NE) from the telencephalon. These relationships (unlike the persisting correlations be-

tween striatal DA or telencephalic 5HT) do not characterize data from longer surgery-test intervals, indicating that mechanisms specifically concerned with some of the short-term effects of our cuts may be involved.

Histology

Analysis of cresyl violet stained sections of 15 brain from 5 animals with PS cuts, 6 with LMFB cuts, and 4 with MMFB cuts, confirms that the knife cuts were placed in the brains of these animals at the intended sites as described in the methods sections of this paper and as reported in earlier papers from this laboratory [26, 28, 29, 33]. See Fig. 1 for representative samples of histology and diagrammatic representations of the three cuts.

The PS cuts (Fig. 1A) lay bilaterally in a parasagittal plane at L = 2.0 and extended from AP = 6.2 to AP = 4.2 and from the thalamus to the base of the brain. The LMFB cuts (Fig. 1B) lay in a coronal plane just anterior to the mammillary bodies at AP = 4.6 and resulted in massive damage to fibers of the MFB that ascend or descend in the medial segments of the internal capsule. The MMFB cuts (Fig. 1C) lay in a coronal plane just anterior to the mammillary bodies and resulted in damage of medial fibers of the MFB as they course through the lateral hypothalamus in an area bounded by the internal capsule, medial lemniscus, fornix, and base of the brain.

DISCUSSION

(a) Dopamine and Ingestive Behavior

Numerous reports of the effects of electrolytic, surgical, or chemical lesions in a variety of brain structures, have suggested that the disruption of ingestive behaviors seen after damage to the lateral hypothalamus as well as many extrahypothalamic areas, may be due to a disruption of dopaminergic pathways and more specifically, the depletion of striatal DA [12, 17, 18, 19, 43, 44, 50, 63, 64, 68, 70, 71]. A few investigators have reported that the concentration of striatal DA is correlated with measures of ingestive behavior [19, 20, 43].

In the present series of experiments, small knife cuts in the trajectory of the MFB produced a variety of effects on ingestive behavior and neurochemistry. Parasagittal cuts along the lateral border of the diencephalon resulted in transient aphagia and adipsia and loss of body weight and significant depletions of striatal and telencephalic DA. Coronal cuts across the fibers of the lateral medial forebrain bundle (LMFB) resulted in a more persistent syndrome of aphagia and adipsia in some animals and weight loss accompanied by severe depletions in striatal DA and a moderate decrease in telencephalic DA. Coronal cuts across the fibers of the medial MFB resulted in hyperphagia and obesity and moderate depletions of telencephalic and striatal DA. Examination of pooled data from the two groups of animals which were aphagic and adipsic during the immediate, postsurgical period demonstrated significant correlations between striatal DA and the duration of aphagia and adipsia ($r = -.605$, $p<0.001$), food intake ($r = .781$, $p<0.001$), water intake ($r = .671$, $p<0.001$), and body weight ($r = .585$, $p<0.01$). This is in excellent agreement with the results of a recent study of the role of striatal projections in food and water intake [4]. Examination of the correlational data from animals with MMFB cuts, which overate and became obese, indicated that the concentrations of striatal DA was also significantly correlated with food intake ($r = .724$), water intake ($r = .722$) and body weight ($r = .632$) during the initial postoperative period that is characterized by moderate hyperphagia and hyperdipsia. When the data from all the experimental animals were pooled, significant correlations between striatal DA and all measures of ingestive behavior were observed. This provides further support for the hypothesis that striatal dopaminergic mechanisms contribute to the effects on ingestive behavior that were seen after our transections (see Table 6).

These observations are congruent with the hypothesis [20] that dopaminergic, nigrostriatal projections, may play an important role in the normal regulation of food intake. The data suggest, furthermore, that the apparently disinhibitory effects of VMH lesions as well as the inhibitory effects of LH lesions on food intake may relfect, at least in part, a dysfunction of specific dopaminergic components of the striatum.

Our results also suggest, however, that dopaminergic pathways to extrastriatal portions of the brain may also play an important function in the regulation of food and water intake and body weight. Our behaviorally effective cuts resulted in significant ($p<0.001$) depletions of telencephalic DA and our correlational analysis indicated that the magnitude of this biochemical effect of our cuts correlated well with their short-term effects on ingestive behaviors and body weight (Table 6). Indeed, in one of our transiently aphagic adipsic groups (rats with parasagittal cuts along the lateral border of the diencephalon) the magnitude of the behavioral effects correlated well with telencephalic DA levels but not with striatal DA levels (Table 3).

(b) Serotonin and Ingestive Behavior

Several recent reports of the effects of quite different experimental interventions have suggested that serotonergic mechanisms may exert important inhibitory effects on food intake [9, 13, 56]. In the present study, small knife cuts in the trajectory of medial components of the MFB produced hyperphagic and increased weight gain, accompanied by a significant ($p<0.001$) depletion of telencephalic 5HT (to 57% of control). Striatal 5HT was only moderately depleted (to 75% of control) and hypothalamic 5HT showed an increase (132% of control) that was not statistically reliable ($p<0.10$). Our PS and LMFB cuts produced aphagia and adipsia and weight loss, accompanied by smaller but statistically significant ($p<0.01$) depletions of telencephalic and striatal 5HT (75% of control). It is interesting that telencephalic concentrations of 5HT were negatively correlated with ingestive behavior in animals which were aphagic (see Table 4) as well as in animals which overate and became obese (see Table 5). An analysis of pooled data from all animals which sustained damage to the MFB also indicates a negative correlation between ingestive behavior and telencephalic 5HT. These findings support the hypothesis that changes in serotonergic mechanisms which project to the telencephalon may have contributed to the disruption of food and water intake regulation seen after all our transections.

Analysis of the effects of MMFB cuts indicated correlations between telencephalic 5HT and food intake on Day 2 ($r = .54$) and Day 45 ($r = -.56$) which were of comparable magnitude but opposite in direction. This apparently paradoxical result may be due to a release of

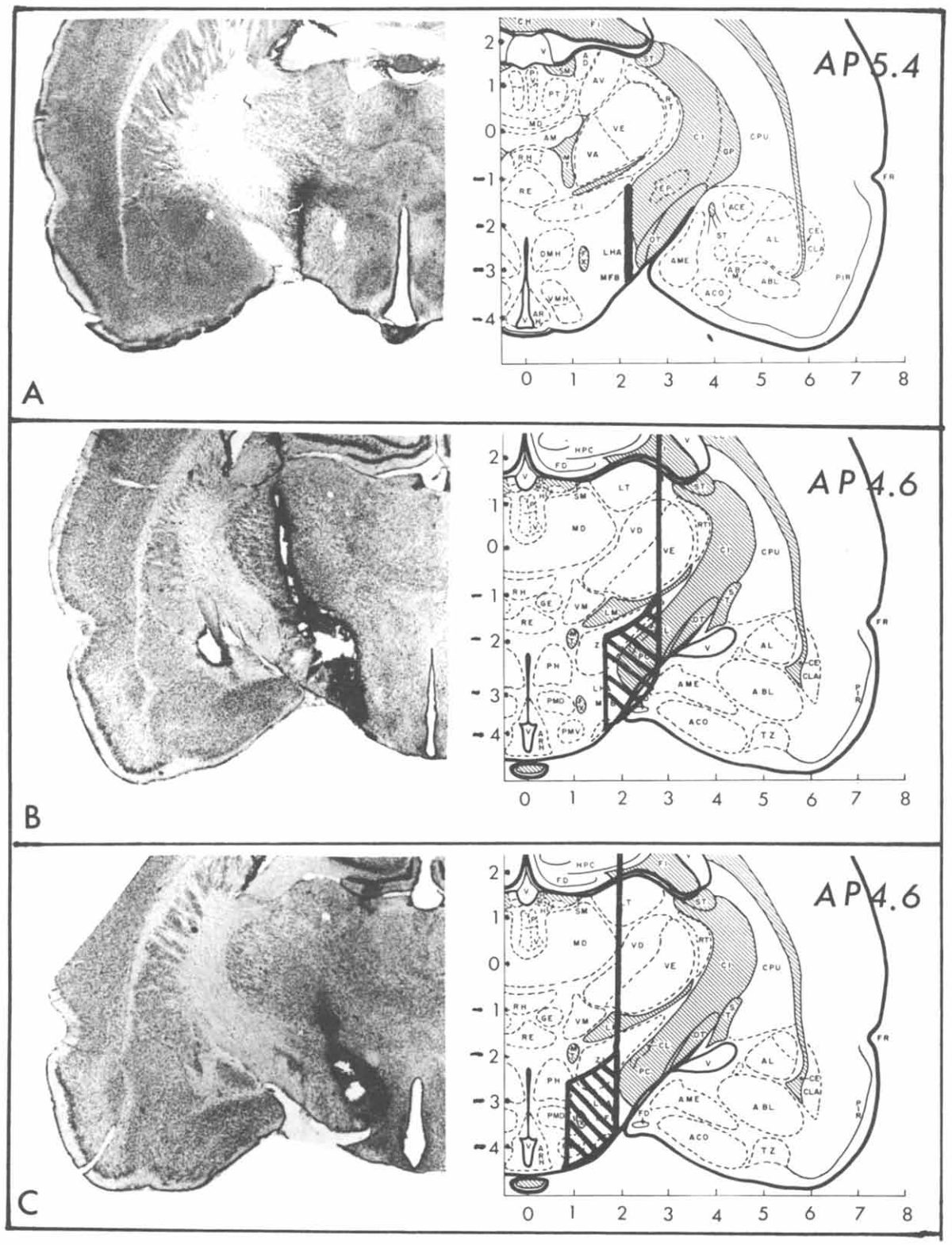

FIG. 1. Photomicrographs and schematic representations, based on the deGroot [16] atlas of the rat brain, of representative knife cuts which transect three components of the medial forebrain bundle (MFB): (A) A parasagittal cut along the lateral edge of the diencephalon (PS), (B) a coronal cut of lateral components of the MFB as they course through the internal capsule (LMFB), and (C) a coronal cut of medial components of the MFB as they course through the lateral hypothalamic and perifornical area (MMFB).

5HT from injured axons during the first days after surgery, followed by degeneration of the injured axons and depletion of the amine [45,72]. If serotonergic pathways contribute important inhibitory influences on food intake, the hypothesized release of 5HT from injured axons should have resulted in a decrease as the amine stores became depleted. Inspection of data from individual animals provided some support for this hypothesis. Of the five rats which were most obese 115 days after surgery, three ate less than the average of the control group on the second day after surgery. These three animals also had particularly severe depletions of telencephalic 5HT. A similar pattern of effects (i.e., initial hypophagic followed by increased food intake) has been reported in two studies which examined the effects of food intake of drugs which selectively destroyed serotonergic neurons [48,56].

Our results are also congruent with the demonstration of inhibitory effects of intracranial injections of serotonin on food intake [38] and the anorexic effects of systemic fenfluramine (which increases 5HT release [15]).

(c) Interactions of Dopamine and Serotonin

The pattern of correlational results discussed above indicates that serotonergic components of the telencephalon and dopaminergic components of the striatum and/or telencephalon may exert opposite influences on ingestive behavior, depletion of forebrain 5HT being accompanied by increased food intake and depletions of striatal or telencephalic DA accompanied by decreased food and water intake.

An anatomical basis for such an interaction between serotonergic and dopaminergic mechanisms has been demonstrated. Serotonergic terminals of axons which originate in the raphé nuclei have been observed at the sites of origin and termination of the two major dopaminergic systems, and it has been suggested that serotonergic mechanisms may modulate dopaminergic activity in the striatum and/or forebrain (for review, see [57]).

Further support for a functional interaction of dopaminergic and serotonergic pathways in the control of ingestive behavior, comes from biochemical studies which have shown that intracerebral injections of 6OHDA (which causes degeneration of DA neurons) increased the levels of 5-hydroxyindoleacetic acid (5HIAA), a metabolite of 5HT in the brain, suggesting increased utilization of 5HT [57]. More specifically, 5HIAA concentrations have been reported to be negatively correlated with weight gain in rats after medial hypothalamic lesions which effected forebrain NE and 5HT concentrations [13]. This suggests that the deficits in food intake and body weight that is seen after 6OHDA lesions may be accompanied by increased 5HT activity. This is congruent with our finding that food intake and body weight of animals with PS, LMFB or MMFB cuts is negatively correlated with the concentrations of telencephalic 5HT but positively correlated with striatal and telencephalic DA.

(d) Norepinephrine and Ingestive Behavior

Evidence for an involvement of noradrenergic brainstem pathways in the control of ingestive behavior was reported as early as 1960 when Grossman demonstrated that intrahypothalamic injections of NE elicited eating in sated rats [25]. Similar results have been obtained with microinjections of NE into the globus pallidus [46,69]. Subsequent research utilizing intracranial injections of alpha and beta adrenergic compounds, suggests that noradrenergic mechanisms may be involved not only in the elicitation but also in the inhibition of food intake (for review, see [39]). Investigators using a variety of techniques which deplete the brain of norepinephrine (electrolytic lesions, knife cuts, injections of 6OHDA, 6OHDOPA, or guanethidine) have reported results which support such hypotheses [1, 2, 7, 22, 37, 55, 61, 75].

The results of the present study do not provide additional support for the hypothesis that noradrenergic components of the hypothalamus or telencephalon play a significant role in the inhibition of food or water intake. Although comparable depletions of telencephalic NE were produced by each of the three knife cuts, hyperphagia and obesity was observed in only the animals with MMFB cuts. Within this group, the magnitude of effect was not correlated with the degree of telencephalic NE depletion. Hypothalamic NE was essentially unchanged in the animals with MMFB cuts. These observations are in excellent agreement with several recent reports. Grossman *et al.* [30] observed significant depletions of NE from telencephalon as well as hypothalamus after knife cuts in the tegmentum that resulted in hyperphagia but found comparable depletions in rats with similar cuts that did not overeat after surgery and failed to find evidence for a correlation between the biochemical and behavioral effects of these cuts in the animals which did become hyperphagic. Osumi *et al.* [51] failed to produce hyperphagia with electrolytic brainstem lesions which significantly depleted hypothalamic or forebrain NE. Lorden *et al.* [41] did observe obesity after NE depleting electrolytic lesions in the tegmentum but could not duplicate the effect with local injections of 6OHDA which produced more severe effects on hypothalamic NE.

It has been suggested [56] that a disruption of noradrenergic mechanisms may prevent the appearance of hyperphagia after pharmacological treatments which deplete brain serotonin. The results of our present experiments indicate, however, that hyperphagia and obesity is seen in animals which sustained significant concurrent depletions of NE and 5HT from telencephalon. Grossman *et al.* [30] have observed hyperphagia after tegmental knife cuts which depleted hypothalamic as well as forebrain NE and 5HT in roughly comparable proportions, except for a significant difference in the magnitude of the 5HT depletion from forebrain.

Some of our data (see Tables 4 and 6) can be interpreted to suggest that noradrenergic components of the striatum and/or hypothalamus may also have facilitatory influences on food intake as some investigators have suggested [59,61]. A closer look at our correlational analysis suggests, however, that the apparent positive relationships between norepinephrine and ingestive behavior may be secondary to the relation between food intake and dopamine and 5HT because striatal NE is correlated with striatal DA and hypothalamic NE is correlated with telencephalic 5HT.

In summary, the results of this study support the hypothesis that ingestive behavior depends on the reciprocal interaction of dopaminergic and serotonergic mechanisms which innervate the telencephalon and/or striatum.

REFERENCES

1. Ahlskog, J. E. and B. G. Hoebel. Overeating and obesity from damage to a noradrenergic system in the brain. *Science* **182:** 166–168, 1973.
2. Ahlskog, J. E., P. K. Randall and B. G. Hoebel. Hypothalamic hyperphagia: Dissociation from hyperphagia following destruction of noradrenergic neurons. *Science* **190:** 399–401, 1975.
3. Albert, D. and L. Storlien. Hyperphagia in rats with cuts between the ventromedial and lateral hypothalamus. *Science* **165:** 599–600, 1969.
4. Alheid, G. F., J. Kelly, L. McDermott, A. Halaris and S. P. Grossman. The effects of striatal knife cuts on eating and drinking. *Neurosci. Abstr.* **2:** No. 406, 285, 1976.
5. Anand, B. and J. Brobeck. Hypothalamic control of food in rats and cats. *Yale J. biol. Med.* **24:** 123–140, 1951.
6. Barchas, J., E. Erdelyi and P. Angwin. Simultaneous determination of indole- and catecholamines in tissues using a weak cation-exchange resin. *Anal. Biochem.* **50:** 1–17, 1972.
7. Berger, B. D., C. D. Wise and L. Stein. Norepinephrine: Reversal of anorexia in rats with lateral hypothalamic damage. *Science* **172:** 281–284, 1971.
8. Blatt, B. and M. Lyon. The interrelationship of forebrain and midbrain structures involved in feeding behavior. *Acta neurol. scand.* **44:** 576–595, 1968.
9. Breese, G., R. Smith, B. Cooper and L. Grant. Alteration in consummatory behavior following intracisternal injections of 6-hydroxydopamine. *Pharmac. Biochem. Behav.* **1:** 319–328, 1973.
10. Breisch, S., F. Zemlan and B. Hoebel. Hyperphagia and obesity following serotonin depletion by intraventricular p-chlorophenylalanine. *Science* **192:** 382–385, 1976.
11. Brobeck, J. Mechanisms of the development of obesity in animals with hypothalamic lesions. *Physiol. Rev.* **26:** 541–559, 1946.
12. Cooper, B., J. Howard, L. Grant, R. Smith and G. Breese. Alteration of avoidance and ingestive behavior after destruction of central catecholamine pathways with 6OHDA. *Pharmac. Biochem. Behav.* **2:** 639–649, 1974.
13. Coscina, D., D. Godse and H. Stancer. Neurochemical correlates of hypothalamic obesity in rats. *Behav. Biol.* **16:** 365–372, 1976.
14. Coscina, D. V., L. D. Grant, S. Balagura and S. P. Grossman. Hyperdipsia following serotonin-depleting midbrain lesions. *Nature New Biol.* **235:** 63–64, 1972.
15. Costa, E., A. Groppetti and A. Revuelta. Action of fenfluramine on monoamine stores of rat tissues. *J. Pharmac. Chemother.* **41:** 57, 1971.
16. deGroot, J. The rat forebrain in stereotaxic coordinates. *Verh. K. ned. Akad. Wet.* **52:** 1–40, 1959.
17. Fibiger, H., B. Lonsbury, H. Cooper and L. Lytle. Early behavioral effects of intraventricular administration of 6-hydroxydopamine in rat. *Nature New Biol.* **236:** 209–211, 1972.
18. 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.
19. Glick, S. D., S. Greenstein and D. H. Waters. Lateral hypothalamic lesions and striatal dopamine levels. *Life Sci.* **14:** 747–750, 1974.
20. Glick, S. D. and M. E. Stanley. Neurochemical correlate of body weight in rats. *Brain Res.* **96:** 153–155, 1975.
21. Gold, R. M. Aphagia and adipsia following unilateral and bilaterally asymmetrical lesions in rats. *Physiol. Behav.* **2:** 211–220, 1967.
22. Gold, R. M. Hypothalamic obesity: The myth of the ventromedial nucleus. *Science* **182:** 488–489, 1973.
23. Gold, R., P. Quackenbush and G. Kapatos. Obesity following combination of rostrolateral to VMH cut and contralateral mammillary area lesion. *J. comp. physiol. Psychol.* **79:** 210–218, 1972.
24. Graff, H. and E. Stellar. Hyperphagia, obesity and finickiness. *J. comp. physiol. Psychol.* **55:** 418–484, 1962.
25. Grossman, S. P. Eating or drinking elicited by direct adrenergic or cholinergic stimulation of hypothalamus. *Science* **132:** 301–302, 1960.
26. Grossman, S. P. Changes in food and water intake associated with an interruption of the anterior or posterior fiber connections of the hypothalamus. *J. comp. physiol. Psychol.* **75:** 23–31, 1971.
27. Grossman, S. P. Role of the hypothalamus in the regulation of food and water intake. *Psychol. Rev.* **82:** 200–224, 1975.
28. Grossman, S. P. and L. Grossman. Food and water intake in rats with parasagittal knife cuts medial or lateral to the lateral hypothalamus. *J. comp. physiol. Psychol.* **74:** 148–156, 1971.
29. Grossman, S. P. and L. Grossman. Persisting deficits in rats "recovered" from transections of fibers which enter or leave the hypothalamus laterally. *J. comp. physiol. Psychol.* **85:** 515–527, 1973.
30. Grossman, S. P., L. Grossman and A. Halaris. Effects on hypothalamic and telencephalic NE and 5HT of tegmental knife cuts that produce hyperphagia or hyperdipsia in the rat. *Pharmac. Biochem. Behav.* **6:** 101–106, 1977.
31. Grossman, S. P. and J. W. Hennessy. Differential effects of cuts through the posterior hypothalamus on food intake and body weight in male and female rats. *Physiol. Behav.* **17:** 89–102, 1976.
32. Harvey, J. A. and H. F. Hunt. Effects of septal lesions in the rat as indicated by water consumption and operant responding for water reward. *J. comp. physiol. Psychol.* **59:** 49–56, 1965.
33. Hennessy, J. W. and S. P. Grossman. Overeating and obesity produced by interruption of the caudal connections of the hypothalamus: evidence of hormonal and metabolic disruption. *Physiol. Behav.* **17:** 103–110, 1976.
34. Hetherington, A. and S. Ranson. Hypothalamic lesions and adiposity in the rat. *Anat. Rec.* **78:** 149–172, 1940.
35. Iversen, S. D. The effects of surgical lesions to frontal cortex and substantia nigra on amphetamine responses in rats. *Brain Res.* **31:** 295–311, 1971.
36. 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.
37. Kapatos, G. and R. M. Gold. Evidence for ascending noradrenergic mediation of hypothalamic hyperphagia. *Pharmac. Biochem. Behav.* **1:** 81–87, 1973.
38. Lehr, D. and W. Goldman. Continued pharmacologie analysis of consummatory behavior in the albino rat. *Eur. J. Pharmac.* **23:** 197–210, 1973.
39. Leibowitz, S. F. Brain catecholaminergic mechanisms for control of hunger. In: *Hunger: Basic Mechanisms and Clinical Implications,* edited by D. Novin, W. Wyrwicka and G. Bray. New York: Raven Press, 1976, pp. 1–18.
40. Lindvall, O. and A. Bjorklund. The organization of the ascending catecholamine systems in the rat brain as revealed by the glyoxylic acid fluorescence method. *Acta physiol. scand. Suppl.* **412:** 1–48, 1974.
41. Lorden, J., G. A. Oltmans and D. L. Margules. Central noradrenergic neurons: differential effects on body weight of electrolytic and 6-hydroxydopamine lesions in rats. *J. comp. physiol. Psychol.* **90:** 144–155, 1976.
42. Lorens, S. A., J. P. Sorenson and L. M. Yunger. Behavioral and neurochemical effects of lesions in the raphé system of the rat. *J. comp. physiol. Psychol.* **77:** 48–52, 1971.
43. Marshall, J. F., J. S. Richardson and P. Teitelbaum. Nigrostriatal bundle damage and the lateral hypothalamic syndrome. *J. comp. physiol. Psychol.* **87:** 808–830, 1974.

44. Marshall, J. and P. Teitelbaum. A comparison of the eating in response to hypothermic and glucoprivic challenges after nigral 6OHDA and LH electrolytic lesions in the rat. *Brain Res.* **55**: 229–233, 1973.
45. Moore, R. and A. Heller. Monoamine levels and neuronal degeneration in rat brain following lateral hypothalamic lesions. *J. Pharmac. exp. Ther.* **156**: 12–22, 1967.
46. Morgane, P. Electrophysiological studies of feeding and satiety centers in the rat. *Am. J. Physiol.* **201**: 839–844, 1961.
47. Morgane, P. Anatomical and neurobiochemical basis of the central nervous control of physiological regulation and behavior. In: *Neural Integration of Physiological Mechanisms and Behavior,* edited by G. J. Mogenson and F. R. Calaresu. University of Toronto Press, 1975.
48. Myers, R. Impairment of thermoregulation, food and water intake in the rat after hypothalamic injections of 5,6-dihydroxytryptamine. *Brain Res.* **94**: 491–506, 1975.
49. Neill, D. B. and C. L. Linn. Deficits in consummatory responses to regulatory challenges following basal ganglia lesions in rats. *Physiol. Behav.* **14**: 617–624, 1975.
50. Oltmans, G. and J. Harvey. LH syndrome and brain catecholamine levels after lesions of the nigrostriatal bundle. *Physiol. Behav.* **8**: 69–78, 1972.
51. Osumi, Y., R. Oishi, H. Fujiwara and S. Takaori. Hyperdipsia induced by bilateral destruction of the locus coeruleus in rats. *Brain Res.* **86**: 419–427, 1975.
52. Palkovits, M. and D. M. Jacobowitz. Topographic atlas of catecholamine and acetylcholinesterase-containing neurons in the rat brain. II. Hindbrain (Mesencephalon, Rhombencephalon). *J. comp. Neurol.* **157**: 29–42, 1974.
53. Paxinos, G. and D. Bindra. Hypothalamic knife cuts: Effects on eating, drinking, irritability, aggression, and copulation in the male rat. *J. comp. physiol. Psychol.* **79**: 219–229, 1972.
54. Poirier, L., P. Langelier, A. Roberge, R. Boucher and A. Kitsikis. Non-specific histopathological changes induced by the intracerebral injection of 6-hydroxydopamine (6OHDA). *J. Neurol. Sci.* **16**: 401–416, 1972.
55. Richardson, J., N. Cowan, R. Hartman and D. Jacobowitz. On the behavioral and neurochemical actions of 6-hydroxydopa and 5,6-dihydoxytryptamine in rats. *Res. Communs chem. pathol. Pharmac.* **8**: 29–45, 1974.
56. Saller, C. and E. Stricker. Hyperphagia and increased growth in rats after intraventricular injections of 5,7-dihydroxytryptamine. *Science* **192**: 386–388, 1976.
57. Samanin, R. and S. Garattini. Serotonergic system in the brain and its possible functional connections with other aminergic systems. *Life Sci.* **17**: 1201–1210, 1975.
58. Sclafani, A. and S. P. Grossman. Hyperphagia produced by knife cuts between the medial and lateral hypothalamus in the rat. *Physiol. Behav.* **4**: 533–538, 1969.
59. Singer, G., S. Armstrong, B. Evans and G. Burnstock. Comparison of the effects of intracranial injections of 6OHDA and guanethidine on consummatory behavior and monoamine depletion. *Pharmac. Biochem. Behav.* **3**: SUPPL. 1, 91–106, 1975.
60. Skultety, F. Hyperphagia after midbrain lesions involving the medial lemniscus. *Expl Neurol.* **38**: 6–19, 1973.
61. Smith, G., A. Strohmayer and D. Reis. Effects of lateral hypothalamic injections of 6-hydroxydopamine on food and water intake in rats. *Nature New Biol.* **235**: 27–29, 1972.
62. Stellar, E. The Physiology of motivation. *Psychol. Rev.* **61**: 5–22, 1954.
63. Stricker, E., M. Friedman and M. Zigmond. Glucoregulatory feeding by rats after intraventricular 6-hydroxydopamine or lateral hypothalamic lesions. *Science* **189**: 895–897, 1975.
64. Stricker, E. M. and M. J. Zigmond. Effects on homeostasis of intraventricular injections of 6-hydroxydopamine in rats. *J. comp. physiol. Psychol.* **86**: 973–994, 1974.
65. 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.
66. Teitelbaum, P. Motivation and control of food intake. In: *Handbook of Physiology.* Section 6: Alimentary Canal (Vol. 1), edited by C. F. Code. Washington, DC: American Physiological Society, 1967.
67. Teitelbaum, P. and A. N. Epstein. The lateral hypothalamic syndrome: Recovery of feeding and drinking after lateral hypothalamic lesions. *Psychol. Rev.* **69**: 74–90, 1962.
68. Ungerstedt, U. Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigrostriatal dopamine system. *Acta physiol. scand.* **82**: SUPPL. 367, 95–122, 1971.
69. Wagner, J. W. and J. de Groot. Changes in feeding behavior after intracerebral injections in the rat. *Am. J. Physiol.* **204**: 483–487, 1963.
70. Zigmond, M. J. and E. M. Stricker. Deficits in feeding behavior after intraventricular injections of 6-hydroxydopamine in rats. *Science* **177**: 1211–1213, 1972.
71. Zigmond, M. J. and E. M. Stricker. Recovery of feeding and drinking by rats after intraventricular 6-hydroxydopamine or lateral hypothalamic lesions. *Science* **182**: 717–719, 1973.