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Deficits in Food and Water Intake after Knife Cuts that Deplete Striatal DA or Hypothalamic NE in Rats[1]

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ALHEID, G. F., L. MCDERMOTT, J. KELLY, A. HALARIS, AND S. P. GROSSMAN *Deficits in food and water intake after knife cuts that deplete striatal DA or hypothalamic NE in rats.* PHARAC. BIOCHEM. BEHAV. 6(3) 273–287, 1977. – Knife cuts ventral or medial to the striatum were used to interrupt some of the principal connections of this structure. All of the cuts depleted striatal dopamine and produced aphagia and adipsia but there was no indication that the two classes of effects were always correlated. Cuts medial to the striatum produced the most severe DA depletions, persistent aphagia and adipsia, and the full complement of deficits in responding to glucoprivic and hydrational challenges that characterize rats that have recovered from lateral hypothalamic lesions. Cuts ventral to posterior portions of the striatum produced comparable periods of aphagia and adipsia (but few of the persisting impairments in responsiveness to regulatory challenges) even though their effect on striatal DA was relatively small (the average depletion was 51% compared to 89% for rats with cuts medial to the striatum). A second group of rats with cuts below more anterior aspects of the striatum sustained severe DA depletions (70%) but only very brief periods of aphagia and adipsia and only slight deficits in responding to osmotic challenges. The effects of the DA depleting cuts were compared with the behavioral consequences of coronal cuts in the midbrain tegmentum which selectively depleted hypothalamic norepinephrine. These cuts did not produce reliable effects on either food or water intake but abolished the normal feeding response to 2-deoxy-d-glucose without affecting the response to insulin. A correlational analysis of the biochemical and behavioral results of our cuts indicated a significant positive relationship between drinking in response to cellular thirst stimuli and hypothalamic NE as well as striatal DA. The postoperative body weights of our experimental animals were positively correlated with striatal dopamine and negatively related to hypothalamic norepinephrine.

Aphagia Adipsia Dopamine Norepinephrine Serotonin 2-Deoxy-d-glucose Insulin Hunger Thirst

LESIONS in the lateral hypothalamus (LH) of rats and various other species produce severe and often persistent impairments in ingestive behavior [49]. Several independent lines of recently obtained evidence suggest that an interruption of fibers of passage rather than the destruction of cellular components of the area may be responsible for the effect of LH damage. For example, lesions rostral [37] or caudal [17, 24, 50] to the hypothalamus also produce aphagia and surgical transection of the lateral connections of the hypothalamus reproduce the full syndrome of persisting deficits in ingestive behavior that have been seen after LH lesions [20,21] (see [19] for a detailed review of relevant data).

It has recently been suggested that the effects of LH lesions on ingestive behavior may be specifically related to an interruption of the dopaminergic nigrostriatal pathway (NSB), because electrolytic as well as chemical lesions in the nucleus of origin of this fiber system [33,50] as well as very severe general depletions of brain dopamine (DA) stores [47,55] produce aphagia and adipsia and some (though apparently not all) of the deficits in behavioral reactivity to glucoprivic and hydrational challenges that characterize rats with LH lesions.

The similarities between the behavioral deficits of rats with LH lesions and chemically or surgically produced striatal dopamine depletions are numerous (see [48] for a review) but a closer look at the evidence suggests possibly important differences. Both experimental preparations are somnolent shortly after surgery and at least some components of the initial aphagia and adipsia may be due to this general lack of endogenous arousal [30]. Severe central DA depletions result in persisting arousal deficits that may well be responsible for the relatively mild deficits in responsiveness to glucoprivic and hydrational challenges that have been observed in these animals as recently proposed [48]. What is not so clear is whether the typically more severe

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impairments seen in rats with LH lesions are due to similar arousal deficits. These animals display some evidence of sensory neglect throughout the period of gradual recovery of voluntary ingestive behavior but appear quite alert and responsive to environmental stimulation [35]. We [20,21] have found that knife cuts along the lateral border of the lateral hypothalamus produce aphagia and adipsia (as well as the complete syndrome of persisting deficits seen after LH lesions) in animals which display only very transient evidence of sensory or arousal dysfunctions. More recently, we [3] have found that surgical transections of pathways that enter or leave the striatum ventrally result in persisting aphagia and adipsia but few, if any, persisting impairments in responsiveness to glucoprivic or hydrational challenges. Conversely, we have found that lesions in the zona incerta [51,52] or interruption of ascending norepinephrine (NE) projections [23] produce many of the specific impairments in responding to glucoprivic and hydrational challenges without significantly interfering with ad libitum food or water intake.

These observations suggest that the residual deficits in responding to glucoprivic or hydrational challenges that are typically seen after LH lesions may not merely reflect an incomplete recovery of the same neural mechanisms that are responsible for the initial aphagia and adipsia but, instead, a dysfunction of quite specific regulatory mechanisms that involve distinct central pathways. In the present experiments, the role of noradrenergic, and serotonergic (5HT) projections to the hypothalamus, and dopaminergic projections to the striatum in the regulation of ingestive behavior was therefore further explored. To this end, the relationship between the biochemical (striatal DA, hypothalamic NE, and 5HT) and behavioral (food and water intake, response to regulatory challenges) effects that result from several surgical interventions known to interrupt hypothalamic and striatal afferents was evaluated.

METHOD

Animals

Fifty-nine male albino rats of the Sprague-Dawley strain (Holtzman, Madison, Wisconsin) were used. They weighed 350–400 g at the beginning of the experiment. The animals were individually housed in an air conditioned colony with a 12 hr light/dark cycle (lights on at 0600 hr). They were maintained on a 6% fat Teklad Mouse and Rat Pellet diet, and tap water which was available in glass bottles with stainless steel nozzles.

Surgery

Surgery was performed under Nembutal anesthesia using a retractable wire knife. The apparatus and procedure have been previously described [44]. Briefly, a 27 gauge guide cannula was stereotaxically lowered into the brain until its tip reached the desired coordinates. A 150 μ spring steel wire was then extended from the tip of the guide which was slightly bent so that the wire projected at an angle of about 90° to the guide. The entire assembly was lowered to transect fibers of passage. The wire was then retracted and the guide cannula removed from the brain. The procedure was repeated on the contralateral side of the brain. Four different knife cuts were made.

Parasagittal hypothalmaic knife cuts (PH). Cuts were made in a parasagittal plane at the lateral edge of the LH (n = 8). The cuts were designed to interrupt the lateral coursing connections of the hypothalamus without producing significant direct damage to cellular components of the LH. The wire was extended caudally 2.5 mm at AP = 6.0 H = 0.5, L = ±2.0 (using coordinates from the deGroot, 1959 atlas of the rat brain, [11]) and lowered 2.5 mm.

Anterior ventral striatal knife cuts (AV). Cuts were made adjacent to the ventral surfaces of the globus pallidi and caudate nuclei (n = 14). The cuts were designed to undercut the anterior striatum but avoid damage to the internal capsule. The guide tube was lowered stereotaxically at an angle of 30° to the horizontal plane (slanting laterally from dorsal to ventral) at AP = 8.0, H = 0.0, L = ±2.0. The wire was extended 2.0 mm caudally and the guide tube lowered 3.0 mm in the direction of the guide cannula axis.

Posterior ventral striatal knife cuts (PV). These cuts were designed to undercut the striatum, but were placed more posteriorly than the AV cuts in order to include striatal axons imbedded in the internal capsule (n = 14). Damage to the optic tract was avoided. The guide cannula was lowered at an angle of 30° as described above for the AV cuts, but the guide cannula was implanted at AP = 7.0, H = 0.5, L = 2.0. The wire knife was extended 2.0 mm in the caudal direction and the guide lowered 3.0 mm in the direction of the guide axis.

Midbrain knife cuts (MB). Transections in the coronal plane were made in the midbrain in an area known to contain ascending NE fibers, but posterior to the cells of origin for the NSB (n = 11). The guide cannula was lowered to AP = 0.8, H = 1.5, L = 2.0. The wire was extended medially in a coronal plane for 1.5 mm, and the assembly lowered vertically to H = −3.5. The wire was then retracted and the guide removed from the brain.

Controls (C). Twelve rats were used as operated controls. Anesthesia was administered to these animals, the scalp was incised, and holes drilled through the skull as in all experimental animals. The wound was then closed and the rats returned to their home cages.

Recovery. Following surgery each animal had ad lib access to food and water. Five fresh food pellets were placed on the floor of the cage. The pellets were inspected twice daily for tooth marks. The duration of aphagia was defined as the average between the time when tooth marks were first observed and the time a full pellet (approximately 3 g) was ingested. The latter event almost always occurred within 12–36 hr of the former. The duration of adipsia was determined by monitoring water intake to the nearest ml. The period in which water intake exceeded 5 ml was scored as the end of adipsia (spillage averaged 1 ml or less). If rats failed to eat within 48 hr after surgery, intragastric feeding was initiated. This involved the intubation of 15 ml of a liquid diet, consisting of milk, sugar, egg, and several drops of liquid multiple vitamins (Polyvisol) two or three times a day. Intragastric feeding was continued until voluntary ingestive behavior occurred with sufficient regularity to maintain stable body weight. The first regulatory challenges were administered a minimum of 2 weeks following recovery of voluntary eating and drinking. Successive tests were scheduled at least one week apart. Posttest recovery of food and water intake to baseline was required before additional tests were performed.

Response to regulatory challenges. (Listed in the order of administration).

Water intake during food deprivation. Twenty-four hr water intake in the absence of food was recorded in the

home cage and compared with the animals' intakes during the previous 24 hr when food was present, and with the intakes of similarly deprived controls.

Glucoprivation (2DG). Experimental animals and controls were tested for their ability to increase eating after intraperitoneal (IP) injections of 2-deoxy-d-glucose (2DG) (750 mg/kg, 10% solution w/v in distilled water) administered between 1000–1100 hr. The food intake in the first 6 hr following the injection was compared with that recorded on the previous day following injections of a comparable volume of isotonic saline. Both food and water were available ad lib.

Glucoprivation (insulin). Animals were tested for their ability to increase eating after IP injections of 5 U of regular insulin (Iletin, Lilly Co.) administered at 1000–1100 hours. The food intake in the first 6 hr after the injection was compared with that following injections of comparable volumes of isotonic saline.

Cellular dehydration. The water intake of experimental and control animals was measured 3, 6, and 24 hr following IP injections of 5 ml of 2 M NaCl, administered at 1000–1100 hours. Food and water were available ad lib. The control test consisted of injections of 5 ml of 0.15 M (isotonic) saline (IP).

Extracellular dehydration. Two tests for drinking responses to polyethylene glycol (Carbowax, compound 20-M, Union Carbide) (PG) were given. In the first, 5 ml of 30% PG (w/v) in isotonic saline were injected subcutaneous (SC) at 1000 hr. The subsequent intake of isotonic saline was measured 3, 6, 8, 14, and 24 hr after the injection. In the second test, 5 ml of 30% PG (w/v) were given at 2200 hr and the intake of isotonic saline measured 3, 6, 8, 14, 17, 22, and 24 hr. Food was not available during these tests. Isotonic saline was used rather than distilled water in these tests since it has been shown that water consumption in response to PG induces an osmotic imbalance that inhibits further fluid intake prior to the repletion of extracellular fluid. Fluid ingestion after PG was compared with the intake of isotonic saline following SC placebo injections of 5 ml of isotonic saline. Since these tests required food deprivation, experimental and control tests were separated by no less than one week of ad lib access to food and water.

Histology. Animals were killed with an overdose of Nembutal and perfused intracardially with isotonic saline followed by a 10% formol-saline solution. Following fixation in formol saline, brains were removed from the calvaria and sectioned at 50 μ on a freezing microtome. When sections were cut in a plane transverse to the plane of the knife cut – e.g., coronal sections of PH, AV and PV cuts – every fifth section was saved throughout the extent of the knife cut. When sections were cut parallel to the plane of the cut – e.g., parasagittal sections of PH cuts or coronal sections of MB cuts – every section was retained in the region of the cut. All brain sections were stained with cresyl violet to aid in the identification of the glial cell formation which characterizes the location of the knife cuts. To facilitate analysis, knife cuts were reconstructed by tracing the image from a microprojector onto atlas pages.

Biochemical assays. Rats were sacrificed by decapitation, the brains quickly removed and dissected on ice. Brain regions were weighed and stored in liquid nitrogen until assayed. DA was determined in pooled striata from the right and left hemisphere. The concentration of NE and 5HT in the hypothalamus was determined from single samples. 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 supernatent was adjusted to PH 6.5 and passed onto Amberlite (CG-50) columns. The amines were eluted from the columns in 4 mls IN hydrochloric acid. Monoamines (MA) were oxidized according to the methods described by Barchas *et al.* [4].

Brain regions were dissected according to the following procedure: after removal of the brain from the calvarium, coronal cuts were made perpendicular to the cortex at the rostral and caudal edges of the olfactory tubercle. The left and right striata were then obtained from the resulting section by trimming away the cortex along the corpus callosum, removal of the nucleus accumbens and olfactory tubercle by a horizontal cut ventral to the striatum, and removal of the septum by cutting along the lateral ventricles. The hypothalamus was dissected by a cut in the coronal plane just caudal to the mammillary bodies which removed the midbrain and remaining brainstem, and a cut in the horizontal plane at the level of the anterior commissure that removed the thalamus. Laterally, remaining parts of the temporal lobes and cerebral peduncles were then trimmed away.

Data analysis. Product moment correlations were computed between the biochemical (striatal DA, hypothalamic NE, or 5HT) and behavioral effects of our cuts. Correlations were computed separately for each experimental group as well as for a combined sample consisting of all animals which sustained knife cuts. Amine levels were compared with duration of aphagia or adipsia; average body weight (the mean of 6 separate measures taken during 2 months after surgery); food intake following injections of 2DG or insulin; water intake after injections of hypertonic saline, or PG; and during the 24 hr period when all animals were food deprived; and the median from 4 measures of 24 hr food or water intake during the 2 months after surgery. Pretreatment baseline records were used to obtain these food and water intake scores. Because of the large number of correlations computed, coefficients were required to exceed the 0.01 probability level for pairwise comparisons to insure reliability.

RESULTS

Histology

Parasagittal hypothalamic (PH) cuts. The location and extent of the PH cuts were examined in 3 rats. Five additional rats were used for monoamine assay. In all 3 animals, bilaterally symmetric knife cuts were observed at the medial edge of the internal capsule (See Fig. 1). The rostral boundary of the transections was just posterior to the optic chiasm and they extended caudally to the level of the subthalamic nucleus. At the caudal-most level of each cut some damage occurred to the medial tip of the cerebral peduncle and medial portions of the subthalamic nucleus. All cuts extended from the base of the brain into the area of the zona incerta dorsally.

Anterior ventral striatal (AV) cuts. Histological materials from 6 rats were analyzed to characterize the AV cuts. Eight additional animals were used for MA assay. All transections were bilaterally symmetrical just proximal to the ventral surface of the striatum (See Fig. 2). The rostral boundary of these cuts was just anterior to the optic chiasm

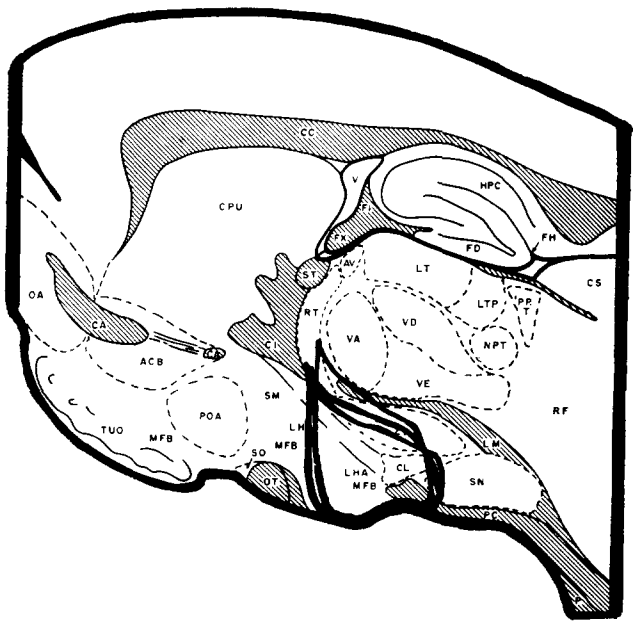

FIG. 1. Parasagittal hypothalamic knife cuts. Outlines represent the common bilateral area intersected by these cuts projected on a sagittal section (lat. = 2.0).

(AP = 8.2) and they extended caudally for 2.0 mm. The cuts did not involve the internal capsule.

Posterior ventral striatal (PV) cuts. Histological materials from 6 rats were analyzed to characterize the PV cuts. Eight additional rats were used for MA assay. The cuts began rostrally at the level of the anterior commissure (AP = 7.4) and extended caudally to the level of the entopeduncular nucleus (AP = 5.4) (See Fig. 3). The rostral portion of these cuts approximated the ventral surface of the striatum. Their posterior extent invaded the rostral aspects of the internal capsule. At this point, some irregularities in the position of these cuts occurred, presumably due to deflection of the wire knife, by heavily myelinated components of the capsule. All cuts traversed the capsule just dorsal to the entopeduncular nucleus, and separated dorsal and ventral components of the postero-lateral globi pallidi and caudate nuclei.

Midbrain knife cuts. The histological data from all 11 rats with MB cuts were analyzed. The portions of all 11 brains anterior to the cuts were used for neurochemical analysis. These transections were placed in the midbrain reticular formation near the level of the oculomotor nucleus. The area affected was just lateral and ventral to the periventricular grey (See Fig. 4). Three rats received cuts that were asymmetric with respect to the AP dimension. In these animals the knife cut on the left occurred 1.5–2 mm more posterior than that on the right. Inasmuch as the behavioral and biochemical results of these 3 cuts were similar in all respects to those of symmetric cuts, their data were included in the subsequent analysis.

Behavioral Observations

Aphagia and adipsia. Following surgery, rats with PH cuts or cuts ventral to the striatum (AV and PV cuts) were aphagic and adipsic (See Table 1). One rat with a PH cut died on the third postoperative day. The data from this animal were not included in Table 1. Rats with PV cuts were aphagic and adipsic significantly longer than animals with AV cuts ($p<0.01$). Parasagittal hypothalamic cuts produced more variable durations of aphagia or adipsia than AV or PV cuts. The sizeable differences between the effects of PH and AV cuts therefore did not attain customary levels of significance ($0.05<p<0.10$). One rat with a PH cut remained adipsic for an extended period and was severely hypodipsic for months thereafter. This animal was not included in subsequent tests of responsiveness to various regulatory challenges because of the general debilitating effects of this deficit.

TABLE 1

MEAN DURATION OF APHAGIA AND ADIPSIA AFTER CENTRAL KNIFE CUTS (DAYS)

	PH	AV	PV
Aphagia	9.14	4.29	9.89*
± SE	2.31	0.82	1.46
N	7	14	14
Adipsia	14.86	6.64	13.86*
± SE	3.87	0.88	1.72
N	7	14	14

*Significantly greater than rats with AV cuts ($p<0.01$).

Food deprivation – drinking. This test was conducted 40 days after surgery. At this time, all but one of the groups of experimental animals consumed quantities of water when food was available ad libitum that were comparable to the intake of the control animals (See Table 2). The exception to this rule, rats with PH cuts, drank reliably ($p<0.001$) less than the controls and less ($p<0.001$) than any of the other 3 experimental groups. When food was withheld for 24 hr. the animals of all experimental and control groups sharply curtailed their water intake ($p<0.01$). Rats with PH cuts continued to drink reliably ($p<0.01$) less than all other groups on this test, attesting to the generality of the deficit seen when food was available. Rats with cuts beneath the posterior aspects of the striatum (PV) which had consumed normal quantities of water when dry food was available ad libitum drank reliably ($p<0.001$) less than controls during 24 hr. of food deprivation. This suggests that a significant impairment in water intake regulation may have been masked in these animals by feeding-associated water needs. Rats with cuts beneath the anterior portions of the striatum (AV) did not show this effect, suggesting that the posterior-most portion of the PV cut may be responsible for its effects on regulatory water intake.

Rats with coronal cuts in the tegumentum (MB) also reduced their water intake more than controls when the ingestive and digestive needs of a dry food diet were removed but the difference did not reach customary levels of statistical significance ($0.10>p>0.05$).

Baseline food and water intake. Food and water intakes were measured 60 days after surgery. A number of samples were obtained throughout a 24 hr period to evaluate the

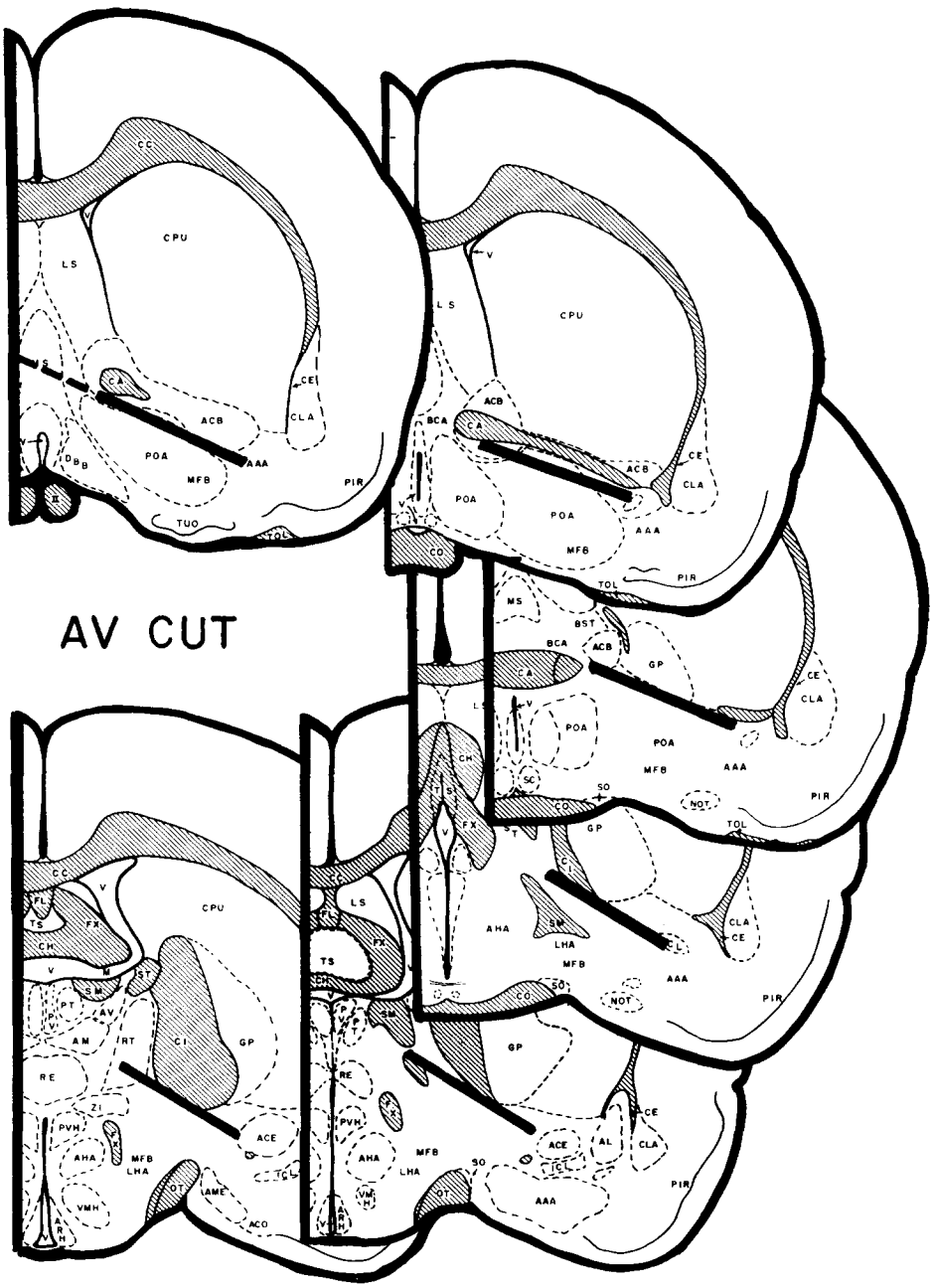

FIG. 2. Schematic diagram of anterior ventral striatal knife cuts.

diurnal pattern of ingestive behavior (See Fig. 5). There was no significant effect ($p>0.10$) of any of the knife cuts on 24 hr food intake, but there was a significant interaction between the effects of the cuts and time of day ($p<0.01$). All rats with knife cuts overate relative controls during the dark part of the light/dark cycle (PH, AV, MB, $p<0.01$; PV, $p<0.05$), but ate less (PH, $p<0.01$; PV, $p<0.05$) during the light part of the cycle. None of the experimental animals drank reliably ($p>0.05$) more than the controls during the dark part of the cycle despite the significant increases in food intake.

Four rats with PV cuts were excluded from this analysis because they failed to eat during this test. Earlier measures of 24 hr food intake indicated that these 4 animals ate normal amounts when food was available on the floor of their home cages but they appeared to find it difficult to obtain food from the wire mesh hoppers used during the present test. Rats with PV cuts also tended to invert their heads while drinking suggesting that a general oral apraxia may have influenced their ingestive behaviors to some extent. Other overt sensory or motor impairments were not observed in these animals who were otherwise active and responsive.

Body weight. Mean body weights in the three months following surgery are shown in Fig. 6. Rats with PH cuts showed the greatest weight reductions after surgery and failed to compensate for this loss during the post-operative observation period ($p<0.01$). Rats with PV cuts also

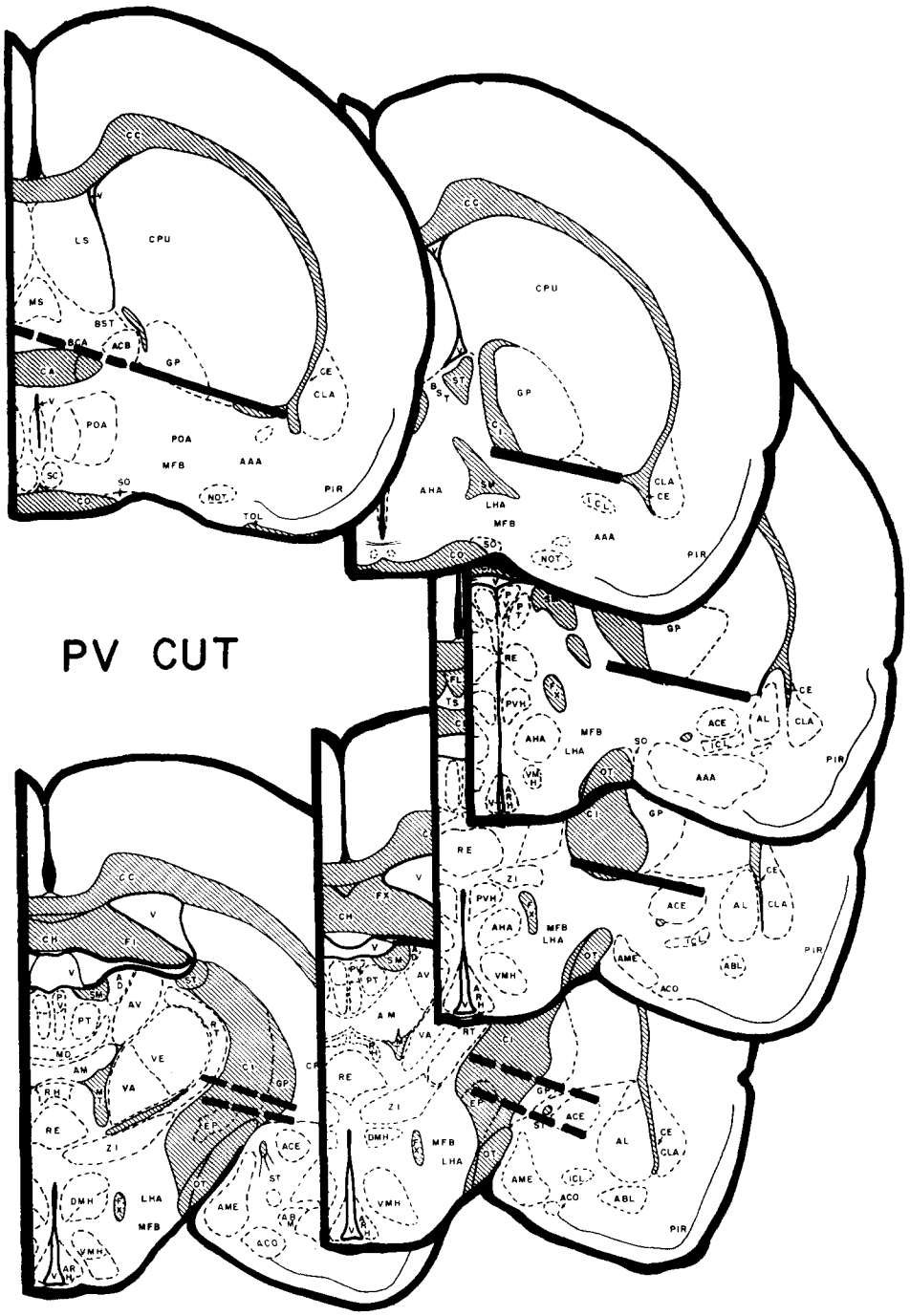

FIG. 3. Schematic diagram of posterior ventral striatal knife cuts. These cuts were variable in their posterior location as indicated by the broken lines at the level where the cut crosses the internal capsule.

weighed less than controls throughout this period ($p<0.05$). Rats with MB cuts increased their body weight relative to controls. This effect was small and variable but was statistically significant over the 3 months postoperative observation period ($p<0.01$).

Glucoprivic challenges. Eating after 2DG or insulin is shown in Table 3. Rats with cuts ventral to the globus pallidus (AV and PV) significantly ($p<0.05$) increased food intake during the 6 hr period after 2DG and after insulin. Both groups ate less than controls after 2DG but this difference was statistically reliable ($p<0.05$) only for rats with PV cuts. Rats with MB cuts failed to increase food intake in response to 2DG, but responded reliably ($p<0.05$) to insulin injections. Their response to insulin was not different ($p>0.10$) from that of the controls. The rats with PH cuts did not reliably ($p>0.10$) increase food intake after 2DG or insulin.

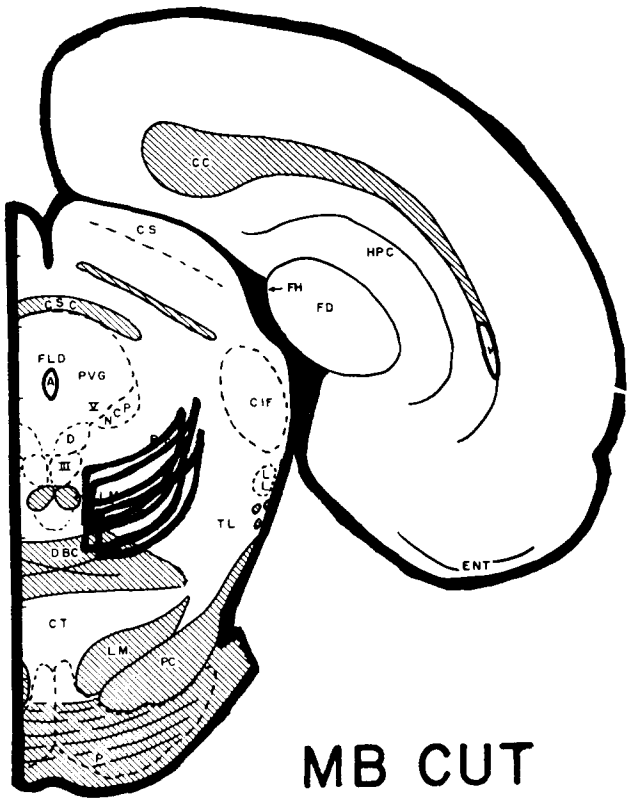

FIG. 4. Midbrain knife cuts. Outlines were projected from several different subjects to indicate variability in cut location. The section shown is at A.P. 0.6. Most cuts fell between 0.8 and 0.4 A.P.

Cellular dehydration. Of all groups tested, only rats with PH cuts failed to significantly increase their water intake 3 or 6 hr after IP injections of 5 ml of 2 M NaCl (See Fig. 7). However, rats with PH, AV or PV cuts drank significantly less than controls ($p<0.01$) throughout the 24 hr test. Only the water intake of rats with MB cuts did not differ reliably from controls levels at any of the intervals measured.

Extracellular dehydration. The 24 hr intake of isotonic saline in the absence of food (before and after the injection of PG) is shown in Fig. 8. Except for rats with PH cuts, all animals significantly increased fluid intake in the 24 hr after the injection of polyethylene glycol ($p<0.01$). Only rats with PH cuts drank significantly ($p<0.05$) less than controls in the 24 hr after either of our two PG tests. One of the rats in the PH group drank as much as the average control; the others increased their intake only very slightly, or drank less than during the control test. After the first PG test (begun in the light part of the cycle) 2 rats with PH cuts became aphagic and required intragastric feeding for several days. These animals were not included in the second PG test that was administered during the dark part of the light-dark cycle.

Light appeared to inhibit drinking after PG. In the first PG test (for all animals except rats with PH cuts) water intake during the period 8–14 hr after PG injection (the first 6 hr of the dark period) was significantly greater ($p<0.01$) than the amount ingested during the first 6 hr after injection. In the second PG test, fluid intake for the first 6 hr exceeded ($p<0.05$) the amount ingested 8–14 hr after PG injection (the first 6 hr of the light period).

Monoamine Assays

DA, NE, and 5HT concentrations. The residual concentrations of striatal DA, hypothalamic NE, and hypothalamic 5HT are shown in Table 4. PH, AV, or PV cuts produced significant depletions of striatal DA. The most severe effects were caused by PH cuts which depleted DA to only 13% of control values ($p<0.001$). There were no significant differences in the DA depletions between PH and AV animals, but each of these groups were depleted to a greater degree ($p<0.05$) than rats with PV cuts. None of the three cuts which preferentially severed striatal connections (PH, AV, PV) had significant effects on hypothalamic NE. Coronal cuts in the midbrain depleted that amine to about 60% of control levels ($p<0.001$). Hypothalamic 5HT was not reduced by any of the cuts. Significantly higher concentrations were found in rats with PH cuts ($p<0.05$) than in controls.

Correlations

Body weight. Significant correlations were obtained between body weights and MA concentrations. For pooled data from all experimental groups body weight was positively correlated with striatal DA ($r = .67$, $n = 32$, $p<0.001$), and negatively correlated with hypothalamic NE ($r = -.53$, $n = 31$, $p<0.001$).

Food intake. Daily food intake and the concentration of hypothalamic NE were negatively correlated in the control animals ($r = -.79$, $n = 10$, $p<0.01$) but positively correlated in the combined experimental group ($r = .56$, $n = 31$, $p<0.001$).

TABLE 2

MEAN 24 HR WATER INTAKE WITH FOOD PRESENT OR ABSENT (ML)

	PH	AV	PV	MB	C
Food Present	19.5*	43.4	36.9	37.1	41.4
± SE	2.14	2.76	3.07	3.25	2.90
N	6	14	14	11	12
Food Absent	5.7*	30.4	12.0*	20.9	31.8
± SE	0.91	3.84	1.60	3.66	3.97
N	6	14	14	11	12

*Significantly lower than controls ($p<0.001$).

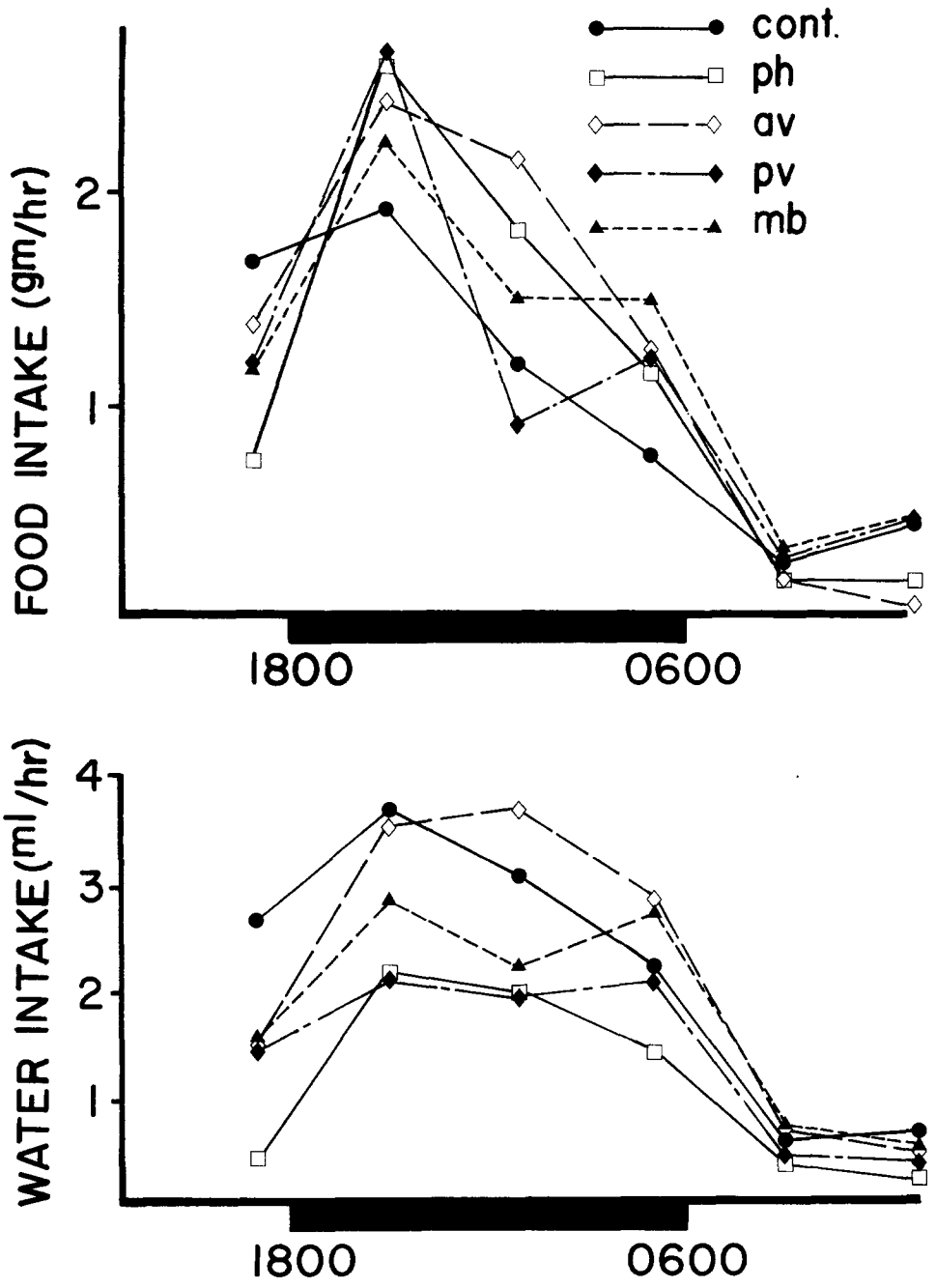

FIG. 5. Light/dark food and water intake. The rate of food and water intake is shown at 4 hr intervals for all animals. The black bar indicates the period in which lights were off.

Water intake. No significant correlations were found between amine concentrations and ad lib water intake, or water intake during food deprivation.

Glucoprivation. No significant correlations were found between amine concentrations and food intake after 2DG or insulin injection.

Intracellular dehydration. Water intake in the first 3 hr after 2 M NaCl was positively correlated with hypothalamic NE in rats with AV cuts ($r = .87$, $n = 8$, $p<0.01$), and in rats with MB cuts ($r = .79$, $n = 10$, $p<0.01$). Water intake after a hypertonic saline challenge was also positively correlated with striatal DA ($r = .61$, $n = 31$, $p<0.001$) and negatively correlated with hypothalamic 5HT ($r = -.61$, $n = 21$, $p<0.01$) when the data from all experimental rats were pooled.

Extracellular dehydration. Cumulative water intake 14 hr after PG injection was negatively correlated with hypothalamic 5HT concentrations for all experimental animals (injection during light, $r = -.54$, $n = 21$, $p<0.01$; injection during dark, $r = -.54$, $n = 21$, $p<0.01$).

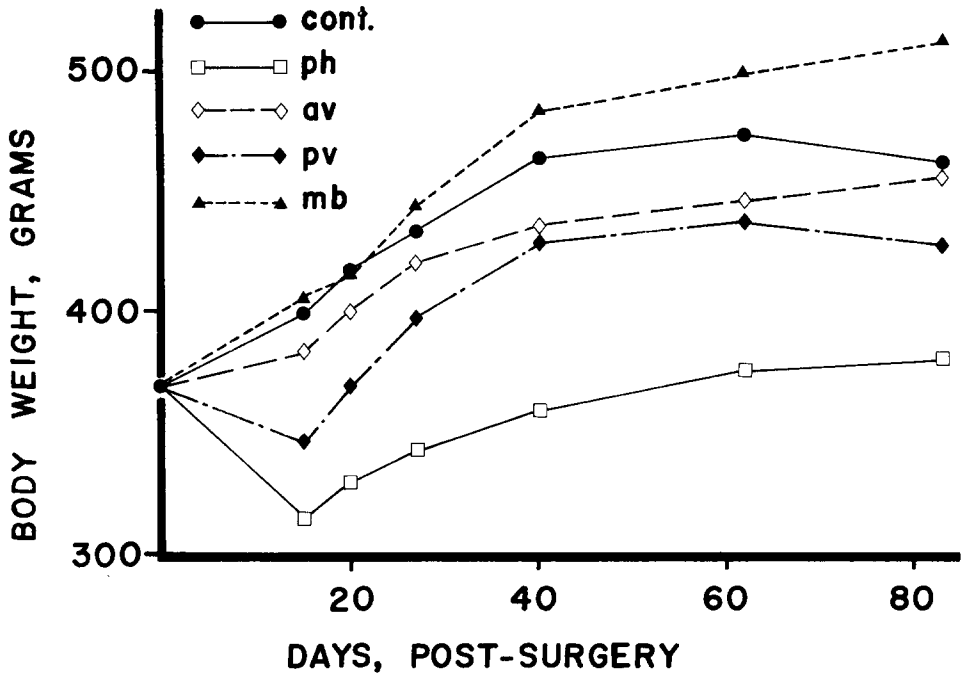

FIG. 6. Effect of knife cuts on mean body weights in the three months following surgery.

DISCUSSION

The results of the present experiments provide further evidence for the conclusion that an interference with afferent or efferent connections of the striatum results in aphagia and adipsia which may persist for several weeks and cause death unless food and water are supplied intragastrically. All three of our cuts which interrupted striatal connections reliably produced this syndrome. However, the full syndrome of persisting deficits in responding to all types of glucoprivic and hydrational challenges which is characteristic of rats that have recovered voluntary ingestive behavior after LH lesions was seen only in rats with parasagittal hypothalamic cuts.

Rats with cuts that severed the ventral connections of the striatum increased their food intake in response to both types of glucoprivic challenges. However, the magnitude of their response to 2DG was not as large as that seen in controls, the reduction being statistically reliable ($p<0.05$) for the PV group. Although small, the impairment in the response to 2DG is of interest because all animals ate normal quantities during the insulin test. Selective impairments in responding to 2DG but not insulin have recently been observed after several other lesions including the zona incerta [52]; and brainstem tegmentum [22].

Rats with cuts beneath the striatum responded normally to polyethylene glycol treatments that sequester extracellular fluids. They also drank after an osmotic challenge but the magnitude of the response was smaller than normal. The only other behavioral abnormality observed in animals with cuts below the striatum was a significant tendency to

TABLE 3

MEAN FOOD INTAKE (G) IN 6 HR AFTER INJECTION OF PLACEBO (0.15M NaCl), 2DG (750 MG/KG), OR INSULIN (5 U)

	PH	AV	PV	MB	C
0.15 M NaCl	2.58	3.29	4.53	4.73	3.96
± SE	0.57	0.35	0.56	0.60	0.45
N	6	14	14	11	12
2DG	4.08†	8.93*	7.41*†	5.32†	11.33*
± SE	0.93	0.96	1.10	1.03	0.83
N	6	14	14	11	12
Insulin	3.00†	7.44*	6.53*	7.32*	7.88*
± SE	1.02	0.63	0.61	1.00	0.37
N	6	8	14	11	12

*Significantly greater than baseline ($p<0.05$).
†Significantly lower than control response ($p<0.05$).

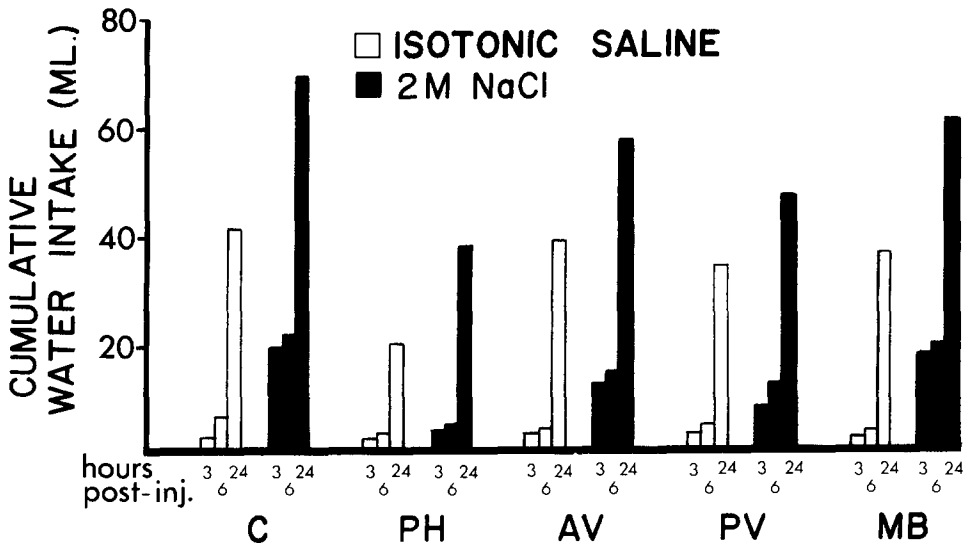

FIG. 7. Drinking in response to injections of hypertonic saline.

drink less during periods of food deprivation and to ingest a larger than normal proportion of their daily food intake during the dark portion of the day-night cycle.

The remarkably complete recovery of our rats with cuts beneath the striatum is of interest in view of the common assumption that persisting deficits in responsiveness to glucoprivic or hydrational challenges reflect incomplete recovery of the same pathways that are responsible for the initial aphagia and adipsia. If duration of aphagia and adipsia is a valid measure of the extent to which feeding – and drinking – related pathways are disrupted, our rats with postero-ventral striatal cuts should have been as severely impaired on subsequent tests of responsiveness to regulatory challenges as the animals with parasagittal hypothalamic cuts. Yet, there were few indications of significant impairments in this group or in the group with similar, more anterior cuts. These observations suggest that different afferent or efferent connections of the striatum may play specific roles in the organization of ingestive behavior.

The effectiveness of our parasagittal cuts along the lateral border of the hypothalamus in producing not only persisting aphagia and adipsia, but also deficits in responding to all types of glucoprivic and hydrational challenges replicates and extends earlier observations [20,21] of the effects of larger cuts in the same plane. The results of the present experiments indicate that the pathway responsible for the effectiveness of these cuts are not as diffusely distributed as originally assumed. They further demonstrate that transection of this connection enhances the circadian rhythm of food intake that is typical of the rat and abolishes not only water [21] but also saline ingestion after polyethylene glycol treatments that sequester extracellular water.

The three cuts which interfered with striatal connections depleted dopamine from the striatum but a causal relationship between the behavioral and biochemical consequences of these cuts could not be established. The duration of the principal behavioral dysfunction (aphagia and adipsia) was not reliably correlated with the concentration of dopamine in the striatum and only one of the three groups which sustained severe dopamine depletions displayed persisting deficits in responding to all glucoprivic and hydrational

TABLE 4

MEAN CONCENTRATION (NG/GM) STRIATAL DA, HYPOTHALAMIC NE, OR 5HT AFTER CENTRAL KNIFE CUTS

	PH	AV	PV	MB	C
Striatal DA	1201*	2832*	4744*	8847	9210
± SE	446	681	466	536	299
N	5	8	8	11	10
Hypothalamic NE	2030	2048	2109	1169*	1952
± SE	150	84	49	126	130
N	5	8	7	10	10
Hypothalamic 5 HT	1969†	1141	1387	887	969
± SE	327	221	50	230	195
N	5	6	6	5	6

*Significantly lower than control ($p<0.001$).
†Significantly greater than control ($p<0.05$).

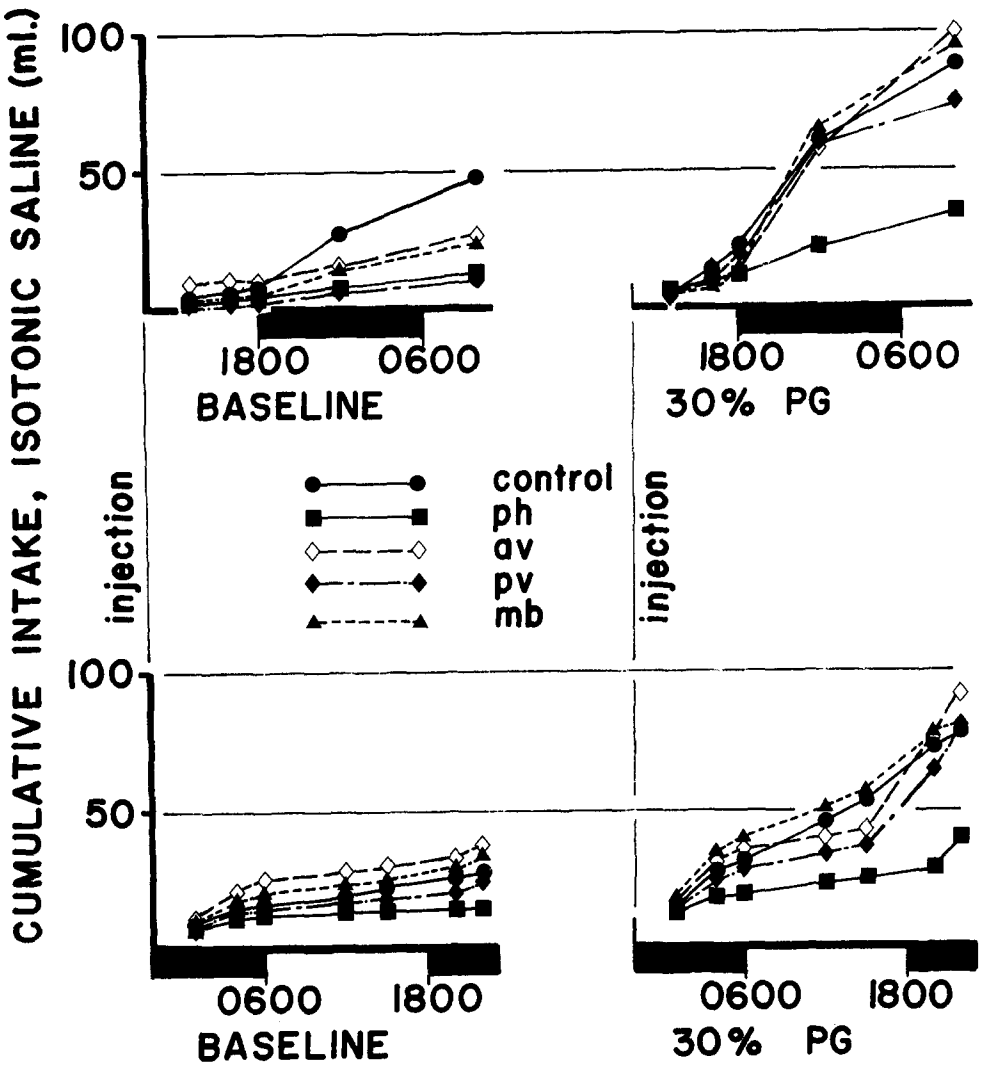

FIG. 8. Drinking of isotonic saline before and after injections of polyethylene glycol (PG). Injections were given either at 1000 hr (top graph) or at 2200 hr (bottom graph). The black bars indicate the periods in which lights were off.

challenges. Within this group, the behavioral and biochemical effects of the cuts were also not reliably correlated.

The failure of our correlational analysis to demonstrate significant relationships between the biochemical effects of these cuts and the duration of aphagia and adipsia does not, of course, prove the null hypothesis. A relation between striatal dopamine and ingestive behavior has been suggested by many different lines of evidence (see [19], and [48], for review) but significant correlational data have been hard to come by. To our knowledge, only one of the many studies which have demonstrated concurrent behavioral and biochemical effects of electrolytic or chemical lesions which affect the nigrostriatal pathway [33] has reported significant correlations between the duration of aphagia or adipsia (the choice of data suggest that the duration of adipsia was the critical variable in this correlation) and the extent of striatal dopamine depletion. Even these investigators failed to obtain reliable correlations between the biochemical consequences of their lesion and any of the persisting regulatory deficits that were observed after the animals had recovered voluntary ingestive behavior. We [36] have observed a significant correlation between the duration of aphagia and adipsia and striatal dopamine depletions after knife cuts across lateral portions of the medial forebrain bundle but also noted that such a relationship did not characterize a group of animals with parasagittal hypothalamic cuts similar to the PH cuts used in the present study [36].

Other workers in this field (e.g., [55]) have argued that significant and persisting behavioral deficits occur only when striatal dopamine has been depleted to such low levels (less than 5% of normal) that the relatively crude assay procedures used in all published research could not possibly detect significant correlations. It is interesting to note, in this connection, that we obtained prolonged aphagia and adipsia as well as the full complement of persisting deficits in responding to glucoprivic and hydrational challenges in our animals with PH cuts that depleted striatal dopamine to 13% of normal on the average. We also recorded aphagia and adipsia of comparable duration in rats with postero-ventral striatal undercuts that depleted striatal dopamine by only 51%. The antero-ventral undercut of the striatum

which produced the shortest period of aphagia and adipsia depleted striatal dopamine much more severely than the behaviorally more effective postero-ventral cut.

The only test which provided evidence of a persisting behavioral impairment in all three groups of animals with cuts that interfered with striatal connections also provided the only indication of a significant relationship between their behavioral and biochemical effects. The magnitude of the response to an osmotic challenge did not correlate reliably with striatal dopamine in any of the three groups but pooled data from all experimental animals indicated a significant relationship. This observation is of particular interest in view of several reports of selective impairments in the responsiveness to osmotic challenges after lesions in the ventral thalamus [12], zona incerta [51], preoptic area [6,40], and globus pallidus [38] which may have interrupted components of the nigrostriatal projection system. Drinking responses to osmotic challenges are also impaired by vagotomy [27] and it is possible that some or all of the effective brain lesions interfere with the transmission of afferents from the vagus to the diencephalon and striatum.

The relationship between striatal dopamine and cellular thirst which our data suggest is supported by a number of reports of impaired responding to osmotic challenges after intrahypothalamic, intranigral, or intrapallidal injections of 6-OHDA which severely deplete striatal dopamine [33]. However, matters are complicated by reports of essentially normal responses to cellular dehydration after intraventricular injections of 6-OHDA that deplete striatal dopamine severely [47] and after central injections of the dopamine blocker haloperidol which were effective in inhibiting drinking responses to extracellular thirst stimuli [45]. The pooling of data from all experimental groups produced several additional results of interest. A significant positive correlation between body weight and striatal dopamine was recorded that is in good agreement with earlier reports of similar correlations in rats with LH lesions [15] as well as normal animals [16]. In addition, we observed a significant negative correlation between body weight and hypothalamic norepinephrine concentration which suggests an interactive system in which the hypothalamic NE component plays an inhibitory function. This is in agreement with recent reports of hyperphagia and obesity after brainstem lesions which deplete hypothalamic NE [1,2] as well as earlier reports of inhibitory effects on food intake of intrahypothalamic [29] or systemic [28] injections of beta-adrenergic compounds. Our observation of a significant negative correlation between food intake and hypothalamic NE in our control animals provides further evidence for an inhibitory function of adrenergic components of the hypothalamus. These observations suggest that noradrenergic hypothalamic pathways which may rely on beta-adrenergic receptor mechanisms [29] and exert inhibitory influences on food intake play a dominant role. There is, however, also considerable evidence for alpha-adrenergic pathways to the diencephalon that carry facilitatory influences on food intake (e.g., [18, 29, 42]). Our knife cuts may have interfered preferentially with this aspect of the system since the overall correlation between food intake and hypothalamic NE was positive for the combined experimental groups. These results suggest that food intake may be regulated, in part, by two noradrenergic hypothalamic mechanisms which exert opposing influences. Other interpretations, including the possibility of statistical artifact, cannot, however, be excluded from consideration at this time, particularly in view of the fact that we have not observed significant correlations between food intake and hypothalamic NE in normal rats or in animals with brainstem lesions which interrupted NE pathways in several other studies [23,36].

The analysis of pooled data from all experimental groups provided one additional set of observations of interest. Several investigators [9,32] have demonstrated that serotonin depleting tegmental lesions produce transient hyperdipsia, suggesting that 5HT might exercise inhibitory effects on water intake. We [23] have recently observed that tegmental lesions which result in hyperdipsia deplete forebrain 5HT more severely than similar lesions that did not affect water intake. In the present experiment, telencephalic 5HT was not assayed, but hypothalamic levels of 5HT were negatively correlated with drinking in response to cellular as well as extracellular thirst stimuli. The influence of the serotonergic projections to the hypothalamus which are responsible for these correlations appears to be subtle since none of our cuts produced hyperdipsia or significant 5HT depletions from hypothalamus. Somewhat paradoxically, significant increases in 5HT were observed after PH cuts. While the exact mechanism for this increase has not been explained, similar increases in monoamine content have been observed after 6-OHDA injections, or injections of 5,6-dihydroxytryptamine that initially deplete more rostral structures [33,5]. Increases in 5HT require an extended recovery period, and may be due to axonal sprouting [5,14].

Our coronal cuts through the midbrain reticular formation failed to produce reliable effects on ad libitum food and water intake. These cuts were designed to interrupt the ascending noradrenergic projections to the hypothalamus and did so with considerable success although we did not achieve the very severe depletions which some investigators [2] have obtained by local injections of 6-OHDA into the tegmental area.

It was reported earlier [1] that electrolytic lesions in the dorsal tegmental area resulted in mild hyperphagia and obesity and these authors proposed that an interruption of noradrenergic projections to the hypothalamus might be responsible for the effects of their lesions because local injections of 6-OHDA which preferentially (although not exclusively) destroy catecholaminergic neurons had similar effects. More recently, the effects of tegmental 6-OHDA injections on food and water intake have been replicated [2] and the resulting syndrome differentiated from the hyperphagia and obesity that is seen after medial hypothalamic lesions. It is, however, not clear that the effectiveness of these injections is specifically related to their depleting action on hypothalamic NE. It was recently reported [39] that electrolytic lesions in the locus coeruleus which depleted hypothalamic norepinephrine significantly (although not to the same extent as some of the 6-OHDA treatments) failed to produce hyperphagia. We [23] have similarly found that some tegmental lesions which depleted hypothalamic NE failed to increase food intake. Other tegmental lesions which had comparable effects on hypothalamic NE produced hyperphagia but attempts to establish a correlation between the magnitude of the hyperphagia and the extent of the hypothalamic NE depletion was not successful. Recent data [31] support the hypotheses that the effects of electrolytic or chemical lesions in the dorsal tegmentum may be independent of their effects on hypothalamic NE. In a direct comparison of

electrolytic and 6-OHDA induced lesions, these workers found significant obesity only after electrolytic lesions which produced much smaller depletions of hypothalamic NE than the injections of 6-OHDA. It should be noted, however, that the chemical lesions used in this experiment were not as effective in depleting hypothalamic NE as those used in studies that produced hyperphagia after 6-OHDA [1,2]. The possibility thus remains that behaviorally effective tegmental lesions may severely deplete specific regions of the hypothalamus (without necessarily producing very large overall depletions) whereas behaviorally ineffective lesions might spare significant aspects of feeding-related areas. It is interesting to note, in this connection, that medial hypothalamic lesions that produce hyperphagia have been reported [2] to have little or no effect on the NE content of the remaining hypothalamic tissue.

The only significant effect of the tegmental knife cuts that were used in the present experiments on food intake was a marked inhibition of feeding responses to 2-deoxy-d-glucose. This deficit was particularly striking because the animals ate essentially normal quantities of food in response to another experimental treatment (insulin) that results in glucoprivic emergencies. Deficits in responding to 2-DG in animals that display normal sensitivity to insulin have been seen in hyperphagic as well as normophagic rats with slightly more lateral tegmental knife cuts [23] and after lesions or knife cuts involving the zona incerta and subthalamic area [52]. A similar dissociation of responsiveness to the two types of glucoprivic challenges has been reported after subdiaphragmatic vagotomy [8,43], although the eating response to 2DG was not as completely eliminated as it appeared to be in the present experiment and in earlier studies of CNS lesions. It is interesting to note that vagtomy apparently does not attenuate the feeding response to intracranial injections of 2DG [25,43] suggesting that there may be distinct peripheral and central receptors for this particular type of glucoprivic emergency. Vagal afferents may normally carry information from peripheral receptors which supplements or even supercedes signals from central glucoreceptors.

Impaired or absent feeding responses to systemic injections of 2DG have been reported after a number of electrolytic, surgical, or chemical brain lesions [7, 21, 25, 55, 56] which share a common characteristic, close proximity to ascending noradrenergic or adrenergic projections. Although the coincidence is striking, there is, as yet, no compelling evidence of a causal relationship between the NE depleting effects of our cuts and their effectiveness in blocking the feeding response to 2DG.

Several investigators [9,32] have reported that some lesions in the midbrain tegmentum result in transient hyperdipsia, and it has been suggested [39] that this may specifically reflect an interruption of ascending NE projections from the locus coeruleus. We did not observe significant alterations in ad libitum water intake in our rats with coronal cuts through the tegmentum, possibly because our cuts were somewhat lateral to the region that has been implicated in earlier experiments (see [23] for a detailed anatomical analysis). MB cuts also did not modify the quantity of water consumed in response to osmotic or hypovolemic challenges but our analysis revealed a striking correlation between the effects of the cuts on hypothalamic NE and the quantity of water consumed in response to an osmotic challenge. The drinking response to cellular thirst stimuli was also positively correlated in one other experimental group (rats with AV cuts) which did not sustain significant NE depletions. Comparable relationships were also indicated for rats with PH cuts and the control animals but the correlations did not reach our stringent statistical criterion. These observations are in good agreement with earlier reports of deficits in responding to cellular thirst stimuli after 6-OHDA injections which depleted hypothalamic norepinephrine without significantly lowering striatal dopamine [46].

Specific deficits in the behavioral response to osmotic challenges have been reported after lesions in the zona incerta [51], in the lateral preoptic area [6,40] and after knife cuts ventral to the striatum (present experiments). We have suggested (above) that the effects of all of these lesions may be due to an interruption of dopaminergic projections to the ventral striatum. The effectiveness of the coronal cuts caudal to the origin of this projection system suggests that noradrenergic pathways may also play a role in the regulation of drinking responses to cellular dehydration.

There is some evidence that the influence of this noradrenergic system may be indirect. Central injections of beta-adrenergic compounds have been reported to decrease urine sodium as well as urine volume [10], whereas alpha-adrenergic compounds decrease renin release [41] and increase urine sodium without changing urine volume [10]. Decrease beta-adrenergic activity thus could reduce the drinking response to osmotic stimuli simply by increasing sodium clearance. Reduced beta-adrenergic activity should, by the same mechanism, enhance sodium appetite. This pattern of effects is precisely what we have recently observed in animals which sustained NE depleting knife cuts. The concentration of hypothalamic NE was positively correlated with the response to cellular dehydration (as in the present experiments) but negatively correlated with the intake of hypertonic saline induced by extracellular dehydration (unpublished observations).

The results of our experiments indicate that ingestive behaviors may be altered by a variety of central knife cuts. Despite some similarities in the initial postoperative deficits (eg. aphagia and adipsia), chronic changes in the regulatory behavior of rats receiving disimilar cuts do not coincide. This suggests that the duration of aphagia and adipsia does not depend upon damage to common neural substrates for ingestive regulation. Further, while biochemical assay may provide insight as to the etiology of behavioral dysfunction after monoamine manipulations by lesions and cuts, some caution is indicated. These manipulations may substantially alter the relationship between a behavioral measure and a particular neurochemical system. In our study the correlations observed for rats with knife cuts were not identical with the correlations observed for controls. While the number and variety of correlations that we observed suggest that the role of the monoamines in regulatory behavior is not a simple one, their effects are pervasive, but not indiscriminant. The robust correlations that we have reported should serve as guides for further exploration of these effects.

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