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Behavioral and Biochemical Effects of Knife Cuts that Preferentially Interrupt Principal Afferent and Efferent Connections of the Striatum in the Rat[1]

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KELLY, J., G. F. ALHEID, L. MCDERMOTT, A. HALARIS AND S. P. GROSSMAN. *Behavioral and biochemical effects of knife cuts that preferentially interrupt principal afferent and efferent connections of the striatum in the rat.* PHARMAC. BIOCHEM. BEHAV. 6(1) 31–45, 1977. – Knife cuts were made that preferentially interrupted (a) the nigrostriatal pathway; (b) pallidofugal projections to the lower brainstem; (c) caudate-pallidal interconnections; and (d) fibers entering or leaving the striatum ventrally. The effects of these cuts on conditioned (shuttle box) avoidance, passive avoidance, swimming escape, sucrose-rewarded alley running, locomotor activity, and various measures of sensory-motor function were examined. The norepinephrine, dopamine and serotonin content of the striatum, residual forebrain and hypothalamus were determined following the completion of behavioral testing. The pattern of results suggests that striatal functions which are significantly influenced by several afferent and efferent connections are essential for the acquisition and, perhaps, execution of complex behavior in appetitive as well as aversive test paradigms. A special role for the dopaminergic afferents to the striatum was not established in these tests.

Striatal connections Avoidance behavior Runway behavior Swimming behavior
Dopamine Norepinephrine Serotonin

A NUMBER of investigators have presented experimental evidence for the hypothesis that central catecholaminergic pathways play an important role in the organization of avoidance behaviors. This conclusion is supported by the results of investigations using electrolytic lesions [10, 15, 23, 34, 37]; surgical knife cuts [20]; intercranial injections of neurotoxins such as 6-hydroxydopamine (6-OHDA) [7, 8, 9, 14, 26, 27, 28, 39, 53, 60] or other pharmacological treatments [11, 35, 40, 49, 50].

The relative importance of noradrenergic (NE) and dopaminergic (DA) pathways has been the subject of considerable debate. It has been suggested that the release of norepinephrine is an essential aspect of all learned behavior [21] and this intriguing suggestion has been supported [2] by experiments showing that destruction of the locus coeruleus (which gives rise to a significant portion of the ascending NE projections) all but eliminated learning in a simple maze situation. In the case of avoidance learning, the bulk of the evidence appears to favor the alternative hypothesis that dopaminergic pathways may be specifically involved in this behavior.

Some of the earlier pharmacological investigations, [49, 50] demonstrated that reserpine-induced deficits in avoidance behavior were reversed by the catecholamine precursor dihydroxyphenylalanine (DOPA). Alpha-methyl-p-tyrosine (alpha MPT), which inhibits catecholamine synthesis at the rate limiting tyrosine hydroxylase level, similarly interferes with avoidance behavior [43,44] and this effect is also reversed by l-DOPA [36]. These results can be interpreted in terms of a drug action on NE systems [1] but the results of more recent experiments favor explanations involving dopamine more specifically.

Neill and Grossman [37] observed avoidance deficits in rats with electrolytic lesions in the caudate nucleus (which has the highest concentration of dopamine in the brain) and impaired avoidance learning has been reported [34] in rats with damage to the nucleus of origin of the dopaminergic nigrostriatal pathway as well as lesions in its target area in the caudate nucleus. Neill *et al.* [41] have reported impaired avoidance behavior following intrastriatal administrations of 6-OHDA (which destroys catecholaminergic nerve terminals preferentially) and noted that the behavioral effects were correlated with depletions of forebrain DA but not forebrain NE. Cooper *et al.* [7] used two intracisternal injections of 6-OHDA in combination with systemic desimipramine or single injections of 6-OHDA in combination with alpha-MPT or reserpine to selectively deplete DA, and found severe deficits in avoidance be-

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havior. Zis *et al.* [60] demonstrated impaired avoidance behavior following intraventricular injections of 6-OHDA and a marked improvement after l-DOPA. Lenard and Beer [27] similarly reversed a 6-OHDA induced avoidance deficit with systemic injections of l-DOPA or apomorphine or with intraventricular injections of dopamine. These investigators also reported improved avoidance behavior after intraventricular injection of NE or systemic injections of the noradrenergic receptor stimulant conidine but concluded that dopaminergic rather than noradrenergic pathways were essential for avoidance behavior because the dopamine blocker spiroperidol prevented the restorative effects of all noradrenergic as well as dopaminergic agonists.

In view of an extensive and reasonably consistent literature which implicates striatal mechanisms in avoidance behavior [15, 23, 34, 37, 41], it is widely accepted that drug actions on dopaminergic components of this region (i.e., the nigrostriatal afferents) may be responsible for the effects of CA depleting or blocking compounds. It should be noted, however, that the possible influence of other dopaminergic projections to the mesolimbic forebrain and temporal region have not yet been specifically studied. The role of the many non-catecholaminergic afferent and efferent connections of the striatum in avoidance behavior is poorly understood at this time. Neill and Grossman [37] demonstrated that lesions in either the dorsal or the ventral portions of the caudate nucleus produced avoidance deficits and that a selective blockade of the cholinergic components of the dorsal area duplicated the effects of the lesions whereas a blockade of the cholinergic components of the ventral portion of the nucleus had opposite, facilitatory effects. This suggests that cholinergic as well as dopaminergic components of the region may influence avoidance behavior but the specific nature of their interaction is, as yet, unknown.

The anatomy of the complex cortical and brainstem connections of the striatum is reasonably well known for many species including the rat [24] but their funtional significance is not well established. The striatum subserves important motor functions (although many reports of motor effects of electrical stimulation of the region probably reflect an activation of fibers of passage [13,25]. Sizeable lesions in the striatum of the rat nonetheless do not result in incapacitating motor dysfunctions in our experience and a number of complex, integrative functions are suggested by the results of various experimental investigations. Posttrial electrical or chemical stimulation of the region has been reported to produce severe deficits on subsequent recall tests in simple passive avoidance as well as multiple-trial learning situations [12, 18, 42, 59, 61], and has apparently nonspecific inhibitory effects on cortical functions which are reflected in overt behavior [6]. Lesions in the striatum also produce sensory deficits [28] and it has been suggested that the sensory-neglect seen in rats with lateral hypothalamic lesions may be the result of an interruption of nigrostriatal projections [32]. Stricker and Zigmond [54] have recently proposed that the striatum, particularly the nigrostriatal projection to the structure, may be essential for arousal responses to sensory input because a 6-OHDA induced depletion of brain DA is typically accompanied by severe arousal deficits.

The present series of experiments was designed to investigate the behavioral influence of some of the principal afferent and efferent connections of the striatum by means of surgical knife cuts which produce little damage to cellular components of the area of intervention but interrupt all fibers of passage. Earlier experiments [20] had indicated that a transection of laterally coursing interconnections between the lower brainstem and the striatum results in a severe impairment in all complex learned behaviors. The present experiments were intended to complement and extend these observations.

GENERAL METHOD

Animals

Adult male albino rats of the Sprague-Dawley strain (Holzman, Madison, Wisc.) weighing 350–450 g at the time of surgery were used. The animals were maintained on ad lib food (Teklad 6% fat diet) and water while housed in individual steel cages. The temperature of the vivarium was maintained at 21°–24°C. A 12-hour light-dark cycle (0700–1900 hr light) was employed. All of the animals were aphagic and adipsic for various durations after surgery. Unless voluntary ingestive behavior appeared within 48 hours after surgery, the animals were fed intragastrically several times a day, using a liquid diet which consisted of evaporated milk, 50% sucrose wt./vol. in tap water, eggs, and liquid multiple vitamins. Tube feeding was continued until voluntary food and water intake reappeared. After the recovery of voluntary intake, most animals were subjected to a battery of tests designed to establish their ability to respond adequately to nutritional (i.e., glucoprivic) or hydrational (i.e., cellular or extracellular dehydration) challenges. The results of these experiments will be reported elsewhere. The tests of instrumental learning as well as most of the tests of sensory and motor ability which are the subject of the present report were conducted after the completion of the tests for food and water intake. The surgery-test intervals are specified in the methods sections of specific experiments below.

Surgery

Knife cuts were performed under Nembutal anesthesia using an encephalotome similar to that previously described [48]. Four bilaterally symmetric cuts were made:

(1) A cut in a parasagittal plane along the lateral border of the hypothalamus (PH) was produced by lowering the guide shaft, constructed of a 27 gauge hypodermic needle to the De Groot [16] coordinates A.P. = 6.0; H = −0.5; L = ±2.0. A 150 micron diameter wire knife was then extended from the slightly bent tip such that the knife extended caudally at 90° to the guide shaft for 2.0 mm. The entire instrument was then lowered to H = −3.0, the wire retracted into the shaft, and removed from the animal's brain.

(2) A cut lateral to the internal capsule and medial to the globus pallidus (MP) which was executed by lowering a knife to the coordinates A.P. = 7.3; H = +1.5; L = ± 1.8. The wire knife was extended from the shaft tip for 3.0 mm at a 50° angle to the parasagittal plane. With the knife extended at 90° to the guide shaft the apparatus was lowered to H = −1.0, the wire was retracted and the instrument removed.

(3) A cut ventral to the globus pallidus (VP) was produced by lowering the tip of the guide cannula to the coordinates A.P. = 7.0; H = −0.5; L = ± 2.0 at an angle of

30° to the horizontal plane. The cannula entered the cranium contralateral to the side of the cut and passed through the septum and the contralateral caudate nucleus. The wire knife was extended caudally at 90° to the guide shaft for 2.2 mm and the assembly was lowered for 3.0 mm through the entrance angle to complete the transection. The wire knife was retracted and the assembly withdrawn.

(4) A cut dorsal to the globus pallidus (DP), undercutting portions of the caudate nucleus was produced by lowering the tip of the encephalotome through an angle of 45° to the vertical plane and slanting dorsoventrally to the coordinates A.P. = 7.5; H = +2.8; L = ± 1.8. This entrance route traversed the cortex just dorsal to the septum. The wire was extended caudally for 3.0 mm at 110° to the guide shaft. The assembly was lowered through the entrance angle for a 3.0 mm distance. The knife was retracted into the shaft and the entire instrument withdrawn.

Hsitological Procedure

Following behavioral testing the animals were scheduled in a balanced fashion (based on the duration of aphagia) for either histological or biochemical analysis. Animals scheduled for histology were killed with an overdose of Nembutal and perfused intracardially with isotonic saline followed by a 10% formol-saline solution. Following fixation in Formalin, their brains were sectioned on a freezing microtome. Fifty micron sections were made and every fifth one in the area of the knife cut was saved. These sections were mounted on glass slides and stained with cresyl violet.

Statistical Analysis

A student's *t*-test [58] was used for all activity and sensory-motor tests as well as for the conditioned avoidance procedure. Runway performance (Experiment 2), passive avoidance (Experiment 3), and swimming performance (Experiment 4) were analyzed by analysis of variance for unequal group n's (unweighted means solution, [58]). Analysis of sucrose intake of individual groups vs. their baseline water intakes utilized the Sandler's A test for correlated samples [47].

Biochemistry

Rats were sacrificed by decapitation, the brains quickly removed and dissected on ice. Brain regions were weighed and stored in liquid nitrogen until assayed. NE, DA and 5-HT were determined in pooled striata from the right and left hemisphere. The same amines were determined in the remaining telencephalon in about half of the animals. In hypothalamus only NE and 5-HT were measured. Brain regions were homogenized in 15 ml ice cold 0.4 N perchloric acid (PCA) with 0.25 ml 4% disodium (ethylenedinitrilo) tetraacetate (EDTA) 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 (HCl). 5-HT was reacted with concentrated HCl and the catecholamines were oxidized according to Barchas *et al.* [3].

Brain regions were dissected according to the following procedures: After the brain was removed from the calvarium, the olfactory bulbs were removed and discarded. Coronal cuts were then made at the rostral and caudal edges of the olfactory tubercles. The left and right striata were then removed from the remaining section by trimming away the cortex along the corpus callosum, removing the amygdala by a horizontal cut central to the striata and removing the septum by cutting along the lateral ventricles. The parts surrounding the striatum (including the frontal lobes) were combined with the remaining cortex when telencephalic amines were measured. The hypothalamus was dissected by cutting just caudal to the mammillary bodies to remove the midbrain, and by cutting horizontally at about the dorsal edge of the fornix (anteriorly) to remove the thalamus.

ANATOMICAL AND BIOCHEMICAL OBSERVATIONS

(a) Anatomical

The location and extent of the knife cuts was determined in selected animals from each group. Others were retained for additional behavioral testing and/or brain monomaine assays (reported below).

Parasagittal hypothalamic (PH) cuts (Fig. 1). The majority (8 of 11) of the brains of this group which were selected for histological examination had bilaterally symmetric cuts along the medial border of the internal capsule which extended from the caudal edge of the optic chiasm to the level of the subthalamic nucleus and from the base of the brain to the center of the zona incerta. In most animals, the cut conformed closely to the changing shape of the internal capsule, because the flexible wire knife was deflected, to some extent, by the dense fiber bundles that characterize this structure. The remaining three animals sustained cuts which were similar in their general dimension but had slightly asymmetric medio-lateral coordinates (one of the cuts invaded the internal capsule while the contralateral cut was displaced slightly towards the midline). There were no systematic differences in performance on any of our tests between animals with strictly symmetric and slightly asymmetric cuts.

These parasagittal hypothalamic cuts were intended to preferentially interrupt the ascending dopaminergic nigrostriatal projections, but also involved noradrenergic projections to the caudate nucleus, portions of the ventral amygdalofugal pathway, and, possibly, portions of ascending cholinergic projections [52]. Most pallidofugal projections were spared by these cuts since in rats they leave the globus pallidus medially and enter the internal capsule enroute to the thalamus and lower brainstem [24]. The reciprocal connections between the globus pallidus and the subthalamic region and entopeduncular nuclei were also largely intact.

Medial pallidal (MP) cuts (Fig. 2). All but two of the animals of this group which were selected for histological analysis had bilaterally symmetric cuts which separated the globus pallidus (GP) from the internal capsule. The cuts followed the medial border of the globus pallidus starting at the level of the anterior commisure and extending caudally to the level of the ventromedial nucleus of the hypothalamus. Horizontally these cuts extended from the ventral border of the GP to a line only a few tenths of a millimeter below its dorsal border. These cuts severed most of the descending pallidal connections and interrupted cortical and brainstem projections to the caudate nucleus which pass through the globus pallidus, but not the serotonergic pathways which ascend primarily in the region

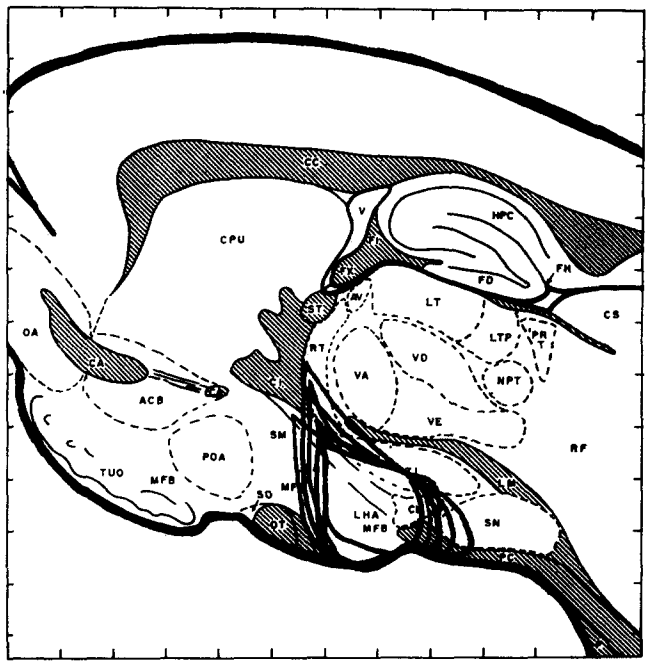

FIG. 1. Superimposed outlines of representative parasagittal knife cuts at the lateral edge of the lateral hypothalamus (PH) (DeGroot atlas, 1963).

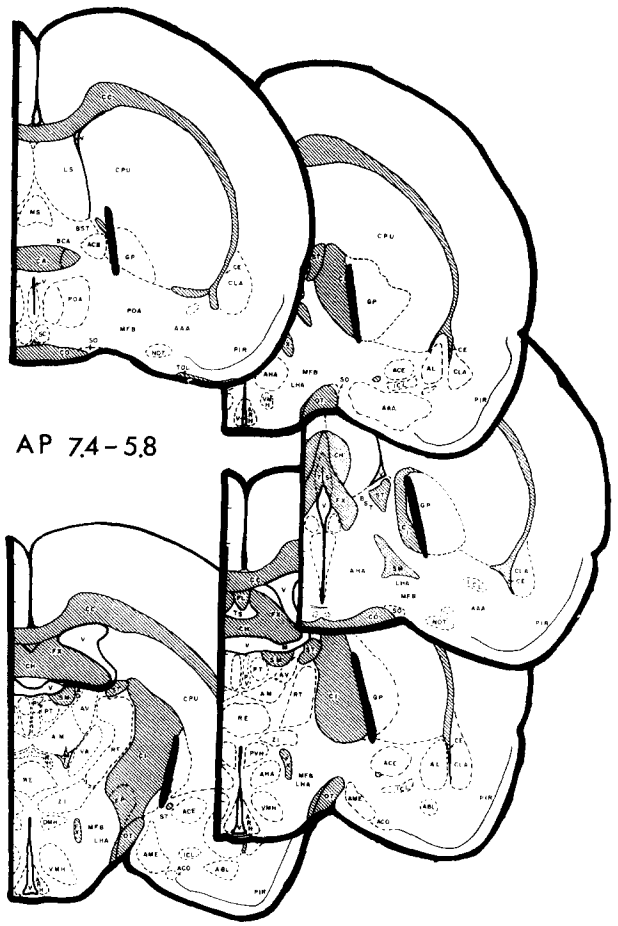

FIG. 2. Schematic representation of knife cuts medial to the globus pallidus (MP) (DeGroot atlas, 1963).

just ventral to the internal capsule [31]. The noradrenergic projections to the caudate nucleus were also largely intact.

In the two animals which sustained cuts that were not perfectly bilateral, only the anterior portion of one of the cuts was displaced (laterally in one instance and medially in the second). The remainder of these cuts (as well as the entire contralateral cuts) were as described above. The behavioral data from these two animals could not be distinguished from those of rats with perfectly bilateral cuts.

Ventral pallidal (VP) cuts (Fig. 3). The four animals of this group which were selected for histological study had bilaterally symmetric cuts below the globus pallidus and striatum except that in one animal one of the cuts extended 0.4 mm farther anteriorly than intended. These cuts extended from the medial edge of the internal capsule into the anterior amygdaloid region and dorsal amygdala. The posterior portion of the cuts passed through the internal capsule and portions of the entopeduncular nucleus. These cuts were designed to preferentially interrupt the ansa peduncularis of Meynert and dopaminergic projections to the nucleus accumbens. As executed, they reached farther into the internal capsule than intended and interrupted some DA projections to the striatum as well.

Dorsal pallidal (DP) cuts (Fig. 4). The four animals of this group which were selected for histological study had bilaterally symmetric cuts except that in one animal the cut on the left side of the brain began 0.5 mm farther anterior than the cut on the contralateral side. The cuts were designed to selectively interrupt a significant portion of the connections between the caudate nucleus and the globus pallidus but also severed cortico-fugal and -petal connections of the striatum. The cuts followed the dorsolateral border of the medial portion of the globus pallidus but departed from it laterally near its anterior pole and medially in the posterior portion of the nucleus.

(b) Biochemical

The effects of the various knife cuts on the concentrations of monoamines in the hypothalamus, striatum, and telencephalon are summarized in Table 1. All of our cuts reduced the dopamine concentration of the striatum but the effect was small after dorsal pallidal cuts and somewhat variable after ventral pallidal cuts. (The variability in the VP group may be due to slight differences in the caudal extent of the cuts which determine the degree of damge to the internal capsule.) All cuts except those dorsal to the globus pallidus also reduced striatal norepinephrine reliably. Striatal 5HT concentrations were not significantly affected in any of our groups.

The telencephalic concentrations of all three monoamines were reliably reduced by the parasagittal cuts. Small but statistically reliable depletions of telencephalic NE and 5HT were also seen after cuts ventral to the globus pallidus but not after cuts medial or dorsal to that structure. Telencenphalic DA levels were depleted significantly after cuts medial to the globus pallidus.

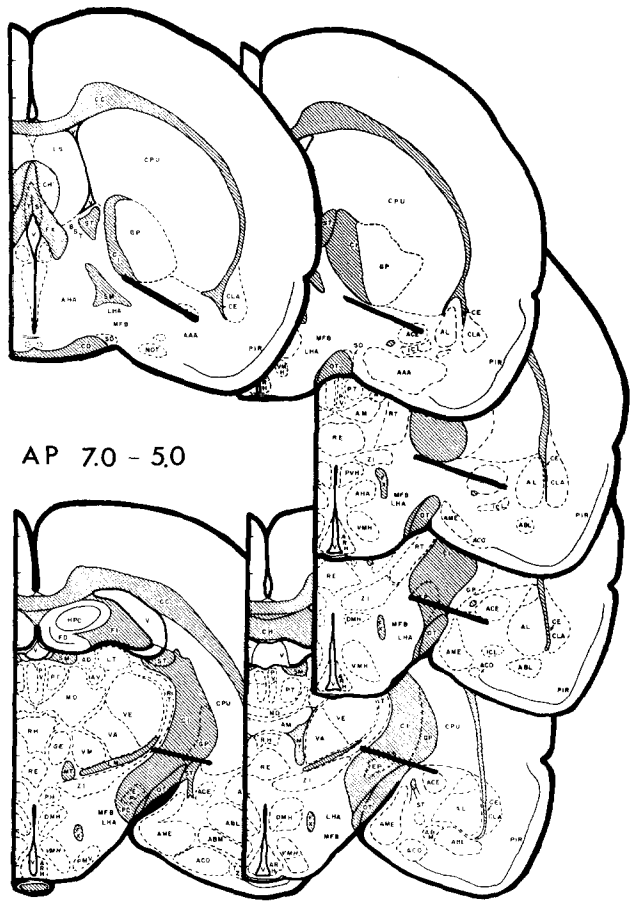

FIG. 3. Schematic representation of knife cuts ventral to the globus pallidus (VP) (DeGroot atlas, 1963).

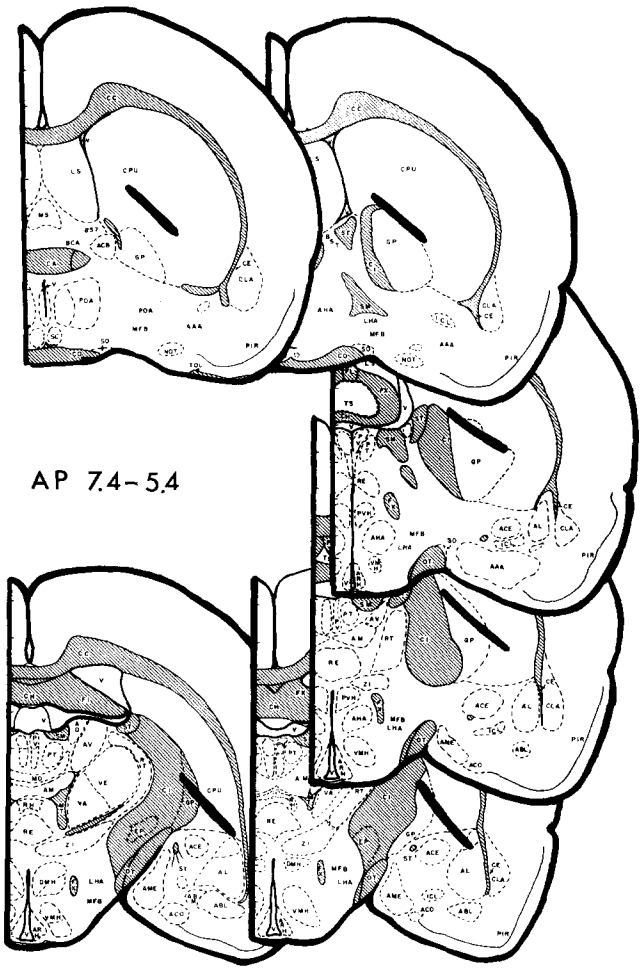

FIG. 4. Schematic representation of knife cuts dorsal to the globus pallidus (DP) (DeGroot atlas, 1963).

None of our cuts produced significant NE or 5HT depletions in the hypothalamus. The animals which sustained cuts lateral to the hypothalamus or cuts ventral to the globus pallidus had significantly higher concentrations of one or both of these amines in hypothalamic tissue. It is possible that these significant increases may reflect nothing more than the occasional large variations one expects when a number of differences are statistically evaluated. However, the fact that increases were seen only in hypothalamic tissues suggests that compensatory collateral sprouting of amine terminals may occur when the axons of monoaminergic nerve terminals are transected further rostrally.

BEHAVIORAL EXPERIMENTS 1: AVOIDANCE ACQUISITION AND PERFORMANCE, LOCOMOTOR ACTIVITY, AND SENSORY-MOTOR FUNCTIONS

The first group of experiments was designed to investigate the effects of the knife cuts described above on the acquisition and performance of a two-way shuttle box avoidance response and to determine the possible influence of gross sensory or motor dysfunctions.

METHOD

Animals

Twenty-five rats were trained to avoid painful footshock in a shuttle box approximately one week prior to surgery. These animals were assigned to five groups of equal size (four experimental groups and one control) in such a way that their preoperative avoidance performance was as comparable as could be arranged. An additional 30 rats were randomly assigned to additional experimental and control groups which were subjected to surgery 3–5 weeks prior to the beginning of training in the shuttle box. The preoperatively trained animals were retested 3–5 weeks after surgery.

Apparatus

Two 53 × 20 × 23 cm high shuttle boxes, housed in sound-attenuating enclosures, were used. The boxes were constructed of clear Plexiglas except for the end panels which were covered with aluminum in contact with the last steel rod of the floor. The floor of the apparatus was constructed of 0.5 mm stainless steel rods separated by 2.0 cm. The rods were connected to a source of constant current which delivered a 100 micro A constant current that was pulsed by a solid state device at the rate of 1/sec with an "on" time of 0.5 sec [5]. The location of the animal in the apparatus was monitored by means of photocells and infrared light sources mounted in the walls

TABLE 1

MEAN MONOAMINE LEVELS (± SE) IN SELECTED BRAIN TISSUES FOLLOWING TRANSECTIONS (NG/G WET TISSUE WEIGHT)

	Caudate			Hypothalamus		Forebrain		
	DA	NE	5HT	NE	5HT	DA	NE	5HT
Control	9475	409	418	1949	1221	610	492	666
± S.E.	±275	±18	±56	±88	±101	±13	±13	±11
n =	(23)	(10)	(10)	(23)	(16)	(5)	(5)	(5)
PH	2460*	219*	283	1739	1554‡	262†	354‡	474*
± S.E.	±532	±15	±46	±73	±67	±50	±34	±55
n =	(9)	(9)	(9)	(9)	(9)	(4)	(4)	(4)
MP	4422†	307†	398	2041	1357	372†	418	616
± S.E.	±542	±18	±51	±82	±112	±41	±32	±49
n =	(6)	(6)	(6)	(6)	(6)	(3)	(3)	(3)
DP	8006	427	452	2110	1279	205	463	739
± S.E.	±839	±39	±79	±89	±56	±152	±24	±73
n =	(6)	(6)	(6)	(6)	(6)	(3)	(3)	(3)
VP	4187*	275*	315	2442†	1630†	500	389†	617‡
± S.E.	±798	±23	±43	±106	±56	±49	±17	±15
n =	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(5)

*Diff. controls $p<0.001$.
†Diff. controls $p<0.01$.
‡Diff. controls $p<0.05$.

of each box at its center and 10 cm to either side of the center. Escape and avoidance responses were recorded by automated equipment.

Procedure

Avoidance behavior. In the shuttle box, each animal was permitted a brief period of exploration. On each subsequent avoidance trial, the half of the apparatus that was occupied by the rat was illuminated by an overhead light. Seven seconds later, the grid floor in the illuminated section of the apparatus was connected to the constant current source through a solid-state device that assured that each bar was hot with respect to all other bars at all times. Running into the dark portion of the apparatus constituted the avoidance (or escape) response which terminated the CS/UCS combination. Successive CS and UCS presentations were scheduled 21 sec apart. Intertrial crossings were not punished. All animals were given 100 massed trials in this fashion. Those that failed to reach a criterion of eight avoidance responses on 10 consecutive trials were given a second 100 trial training session 3–4 days later.

Tilt box activity. Five to ten days after the completion of avoidance training all animals were placed in tilt cages. Eight tilt cages were maintained in a sound attenuating room on the same 12 hr light dark cycle as the home colony. The cages were constructed of dark green plexiglass walls with a clear Plexiglas top. The floor was made of wire mesh and was suspended on a rod in the middle of the cage bottom such that the animal tilted the floor to the side on which it was situated. A microswitch at one end of the floor was connected to a counter which monitored the number of crossings the animal made. Readings were taken every six hours for 24 hr. Ad lib food was available from a basket and tap water from a bottle that were both situated in the middle of the front wall.

Open field activity. Locomotor activity in a novel open field was observed 120 days after surgery for 2 min in a 2 × 2 ft. compartment with a floor that was divided into 6 in. squares. The number of squares entered was recorded. An entry was scored when the animal crossed with two paws into a square. This measure was obtained during the light part of the light/dark cycle.

Proprioceptive stepping. Reflex limb use was tested 120 days postoperatively by holding the rat upright but at an angle to a table surface. The limb proximal to the surface was then allowed to support the weight of the rat and the rat was moved laterally. Normal rats flex this limb and reposition it under the new center of gravity, thus resulting in a stepping reflex as lateral movement is continued.

Horizontal stabilization. Rats were placed on a wire platform which was gradually tilted so that the rat had to resist the pull of gravity. Normal rats grasp the rungs of the wire platform and extend the down-hill hind- and forelimbs to maintain a nearly horizontal position. This test was administered 120 days after surgery.

Step down latency. Animals were placed on a 8 × 12 × 8 cm high platform. The time required for the animal to step down from this platform onto a table surface was recorded. A step-down response was scored when two paws touched the table. The maximum time allowed was 60 sec. This was tested 120 days after surgery.

Forelimb strength. This was evaluated by grasping the rat by either forepaw and recording the latency of compensatory movements (the rat grasps the experimenter's hand and pulls itself up). Both limbs were tested. The maximum time allotted per forepaw was 60 sec. Tests were administered 120 days postoperatively.

Visual placing. The rat was held by its hindquarters with its head extended downward. It was then brought close to the edge of the table. Normal rats extend their forepaws to

grasp the edge of the table. The presence or absence of this response was recorded. Visual placing was tested 120 days after surgery.

RESULTS

The avoidance behavior of postoperatively trained rats is compared with the performance of preoperatively trained rats in Fig. 5. Rats with parasagittal hypothalamic cuts ($p<0.01$), ventral pallidal cuts ($p<0.025$), or medial pallidal cuts ($p<0.01$) showed severe acquisition deficits when an attempt was made to train them 3–5 weeks after surgery. There were no significant ($p<0.05$) differences in the rate of acquisition of these three experimental groups. The fourth experimental group (rats with cuts dorsal to the GP) learned the response as rapidly as the controls.

When tested for retention of a preoperatively learned avoidance response only rats with cuts ventral to the globus pallidus performed reliably poorer ($p<0.05$) than the controls. The ineffectiveness of most of our cuts with respect to recall performance is particularly striking in rats with parasagittal hypothalamic and medial pallidal cuts which performed significantly better ($p<0.01$ and 0.025 respectively) on the recall test than animals with comparable cuts did when trained de novo after surgery.

Table 2 summarizes the tilt box activity of all experimental and control groups, recorded 5–10 days after the completion of the postoperative avoidance test. None of the experimental groups displayed significant hypoactivity which might have interfered with behavior in the shuttle box. Two of the experimental groups were significantly more active than controls. One of these groups (the animals with ventral pallidal cuts) performed poorly in the avoidance situation during initial training and during the postoperative recall test. The second of the hyperactive groups (rats with cuts dorsal to the GP) performed well during both avoidance tests, suggesting that activity may not have been a determining factor in the avoidance tests. Our second index of locomotor activity, the open field test, failed to disclose reliable differences between any of our experimental and control groups 120 days after surgery (See Table 3).

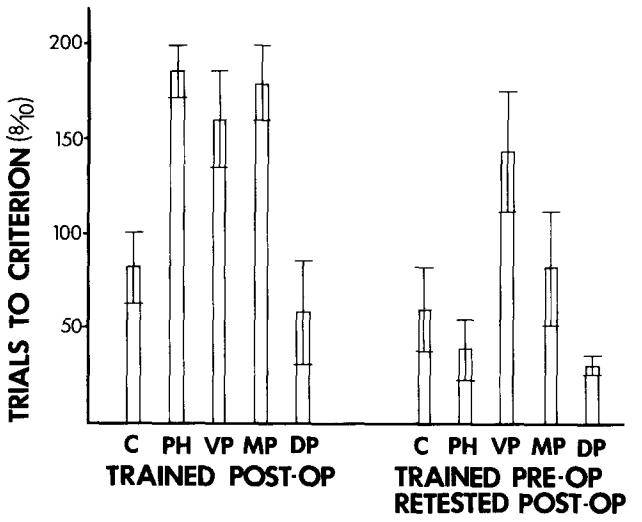

FIG. 5. Conditioned Shuttle-Box Avoidance. Mean trials to criterion for experimental and control groups (see text for abbreviations) which were trained 3–5 weeks post-operatively (left) or trained prior to surgery and retested post-operatively.

Our tests of proprioceptive stepping, horizontal stabilization, forelimb strength, visual placing, and step down latency also failed to show persisting deficits 120 days after surgery. It is, unfortunately, not clear whether these functions were entirely intact during the time when the avoidance tests were conducted. We have some evidence from animals with comparable cuts that visual placing, in particular, is deficient a minimum of 40 days after surgery in about 80% of animals with cuts ventral to the globus pallidus (which showed the most severe performance deficits in the avoidance apparatus) and in 90% of the animals with medial pallidal cuts (which performed well on the recall test but were deficient in acquiring the avoidance response de novo).

TABLE 2

MEAN ACTIVITY COUNTS (± SE) OBTAINED IN A TILT CAGE DURING A CONSECUTIVE 24 HR PERIOD

Group	n	1300-1900	1900-0100	0100-0700	0700-1300	24 Hr Total
NC	8	89.10 (±9.9)	85.75 (±10.7)	63.63 (±14.9)	19.75 (±4.3)	258.2 (±15.8)
PH	10	64.80 (±11.0)	101.80 (±17.50)	68.20 (±6.4)	27.10 (±5.4)	261.90 (±31.6)
MP	9	105.4 (±5.5)	136.6 (±37.9)	89.66 (±30.5)	38.55 (±9.8)	370.20 (±83.1)
VP	8	110.7 (±17.7)	151.70* (±21.70)	93.40 (±24.8)	67.70* (±13.6)	423.48* (±45.7)
DP	9	125.00 (±26.4)	185.2* (±23.5)	94.00 (±17.7)	51.56* (±2.5)	455.76* (±51.6)

*Diff. controls $p<0.01$.

TABLE 3

MEAN OPEN FIELD ACTIVITY COUNTS (± SE), n*

Group	NC	PH	MP	VP	DP
	26.83	34.0	14.86	23.67	16.67
	(6.44)	(8.80)	(4.91)	5.83	(7.15)
n	6	5	7	6	6

*(None of the differences between groups were statistically reliable)

DISCUSSION

The results of this experiment agree well with earlier reports of avoidance deficits after surgically, electrolytically, or chemically induced disruptions of striatal functions [14, 20, 37, 39].

Our parasagittal hypothalamic cuts severely disrupted the acquisition of avoidance responses as previously reported [20] but had little deleterious effects on performance on postoperative recall tests which had also shown marked effects of the larger cuts used by Kent and Grossman [20]. The selective effects of our shorter cuts on postoperative acquisition appear to be more nearly comparable to the effects observed after injections of 6-OHDA into the substantia nigra [14] which, like our cuts, produced severe but not total depletions of striatal dopamine. The acquisition deficit does not appear to be due to simple sensory or motor deficits since our rats with parasagittal cuts performed a preoperatively learned avoidance response as well as unoperated controls. They also showed no gross sensory or motor disturbances on any of our specific tests.

Cuts medial to the globus pallidus produced avoidance deficits that appeared to be similar to those seen in rats with parasagittal hypothalamic cuts (i.e., a marked impairment of initial acquisition but essentially normal performance of preoperatively learned avoidance behavior). This is particularly interesting because the cuts medial to the GP produced much smaller depletions of dopamine from the striatum as well as the remaining forebrain, than the parasagittal cuts along the lateral border of the hypothalamus.

The avoidance behavior of animals with cuts ventral to the globus pallidus was most severely affected. Their postoperative acquisition performance was comparable to that of animals with parasagittal hypothalamic and medial pallidal cuts. However, the VP group was the only one to show a severe impairment in preoperatively acquired avoidance behavior. The reasons for this were not immediately apparent. As a group, these animals displayed some hyperactivity in the tilt boxes, but so did rats with cuts dorsal to the GP which performed extremely well when trained or tested postoperatively in the avoidance situation. Some animals with ventral pallidal cuts displayed evidence of visual placing difficulties when tested shortly after surgery but an even greater proportion of animals with cuts medial to the globus pallidus (which performed well on the postoperative recall test) were deficient in this test. The effects of the ventral pallidal cuts on striatal catecholamine concentrations were variable. As a group, the depletions were not as large as those produced by parasagittal hypothalamic cuts which had no effect on the performance of preoperatively learned avoidance behaviors.

Dorsal pallidal cuts which interrupted a large proportion of the interconnections between the GP and the caudate nucleus as well as cortico-fugal projections did not interfere with the acquisition or performance of avoidance behavior in any of our tests. This observation does not contradict the hypothesis that dopaminergic components of the striatum in particulr may be related to avoidance behavior since these cuts failed to produce significant dopamine depletions in the striatum. It appears that the nigrostriatal projections do not diffusely project through the globus pallidus in the rat but may follow a more circuitous route around or through more lateral or caudal portions of the GP.

BEHAVIORAL EXPERIMENTS 2: ACQUISITION OF A SUCROSE REINFORCED RUNNING RESPONSE

The second experiment was designed to examine a critical prediction from the hypothesis that the deficits seen in three of our experimental groups in the preceding portion of the investigation might be peculiar to avoidance behavior. For this purpose, we designed a novel apparatus which consisted of an automated runway with drinking cups at both ends. The operant response required to obtain a highly preferred 10% sucrose solution was shuttling back and forth between the two drinking cups. The topography of this behavior is reasonably similar to that required in the shuttle box.

Severe impairments in both the acquisition and performance of food- or brain stimulation-rewarded alley running have been reported after large parasagittal cuts along the lateral border of the diencephalon [20]. Food- or water-rewarded approach behavior as well as more complex food-rewarded operant responses have also been reported to be impaired after intraventricular or intranigral injections of 6-OHDA [4, 14, 33], or intrastriatal injections of anticholinergic compounds [38].

METHOD

Animals

All of the rats in the avoidance test described above were used. Additional animals received comparable surgical treatments to increase the subject pool for the present experiment to: parasagittal hypothalamic n = 13; medial pallidal n = 10; dorsal pallidal n = 10; ventral pallidal n = 9; and control n = 12.

Apparatus

Three similar alleys were used. Each measured 18 × 81 × 18 cm high and was constructed of wood except for the front panel which was made of translucent Plexiglas. At each end of the runway, a drinking cup was mounted in the center of the endwall, 5 cm above the floor. A Sylvania 24 PSB light bulb was mounted 8 cm above the cup. Illumination of the light indicated that the cup was filled with 0.1 ml of a 10% sucrose/water solution (wt/vol).

Procedure

Approximately 60 days after surgery, all animals were offered a 1.0% sucrose solution (wt/vol in water) in the home cage during a 24-hr period when no other food was available. Intake during this period was compared to a

similar 24-hr measure when only tap water was available. This test was designed to determine the animals' ability to detect the mild sugar solution, and drink it in preference to tap water.

On the day before training began, each animal was permitted to explore the runway for 10 min. During this test, the drinking cups contained only tap water. On the next day the cup on one end of the runway was filled with 0.1 ml of a 10% sucrose solution and the light above it was illuminated. As soon as the animal touched the cup, a response was automatically recorded, the light above the cup was turned off, the cup at the other end of the runway was filled, and the light above it illuminated. The rat could obtain sucrose rewards ad lib by shuttling back and forth between the two ends of the apparatus for 10 min. Each animal was given a total of twelve sessions (2 per day for the first 5 days, and 1 per day on Days 6 and 7). All test sessions were given during the dark portion of the animals' light/dark cycle. During the first ten sessions regular laboratory food and tap water were available ad lib in the home cages. Following the tenth session all animals were food deprived until the following test (approx. 24 hr). Food was again available ad lib after Trial 11, and all rats were given a final runway test on the following day.

RESULTS

The control animals rapidly learned the simple shuttling response required to obtain the sucrose solution reward in the alley. Their performance improved throughout the first ten sessions and reached asymptotic levels only when the animals could consume 0.1 ml of sucrose and run down a nearly 3 foot long alley in only 6–9 sec. None of the experimental groups quite matched this performance (See Fig. 6).

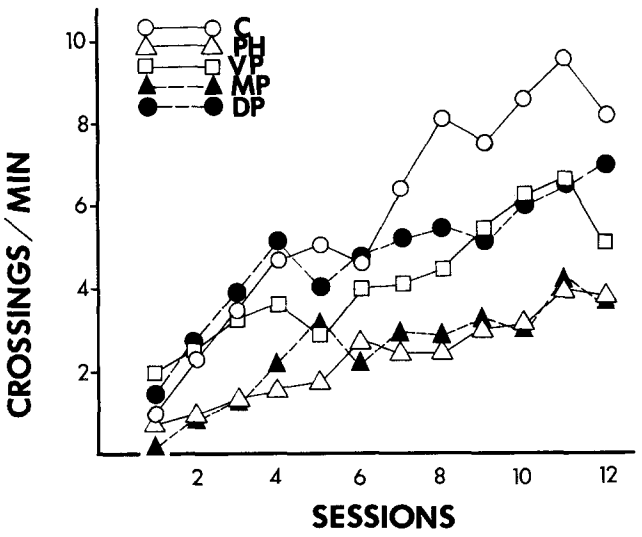

FIG. 6. Sucrose-Rewarded Running. Mean number of crossings per min in the shuttle runway.

An analysis of variance indicated a significant treatment (i.e., knife cut) effect ($p<0.01$) as well as a significant trials by groups interaction ($p<0.01$) which suggested different rates of acquisition for the experimental and control groups. Individual group comparisons indicated further that the overall performance of rats with dorsal pallidal (DP) cuts did not differ reliably from that of the controls whereas all other experimental groups performed reliably poorer (PH $p<0.01$; MP $p<0.01$; VP $p<0.05$). A separate analysis of the first (Sessions 1–6) and last (Sessions 7–12) half of the training period indicated that the rats with cuts dorsal or ventral to the GP acquired the running response as rapidly as the controls ($p>0.05$) but could not match their terminal performance ($p<0.05$). The performances of rats with parasagittal hypothalamic or medial pallidal cuts were significantly ($p<0.05$) inferior to that of the control group throughout the experiment.

Food deprivation (Session 11) increased running speed slightly in nearly all groups. However, this effect was not statistically reliable ($p<0.05$), indicating that the strong sucrose solution provided optimal incentive even in the absence of food deprivation.

DISCUSSION

The results of these experiments agree with earlier reports [14, 20, 33, 38] that striatal dysfunctions interfere with appetitively as well as aversively controlled operant responding. However, a comparison of the pattern of effects seen in this and the preceding experiment suggest that different components of the striatum may contribute to the organization of appetitively and aversively controlled behaviors.

A rather general deficit is indicated in the case of animals with parasagittal hypothalamic or medial pallidal cuts which learned both avoidance and sucrose-rewarded running poorly. These animsls clearly preferred a weak sucrose solution to tap water but seem unable or unwilling to initiate or execute a simple running response to obtain an even sweeter one. The results of the preceding experiment as well as a more detailed account of the motor capabilities of rats with larger parasagittal hypothalamic cuts [20], indicate that simple sensory or motor disturbances are not responsible for these effects.

Rats with ventral pallidal cuts displayed a pattern of effects which suggests a more selective impairment. Although these animals performed much worse than rats with parasagittal hypothalamic or medial pallidal cuts in the post-operative retest of preoperatively learned avoidance behavior (and as poorly in post-operative avoidance learning tests), their performance of the sucrose-rewarded running response was clearly superior.

The rats with parasagittal hypothalamic or medial pallidal cuts drank less of the 1% sucrose solution in the home cage (See Table 4) and also ran slower in the runway. However, there was only a weak correlation between home cage intake and initial running speed in the runway ($p<0.05$ for the combined experimental groups) and none between home cage consumption and individual rates of acquisition. Sucrose preference thus does not seem to be an important determinant of the differential running speeds seen amongst our experimental groups.

BEHAVIORAL EXPERIMENTS 3: PASSIVE AVOIDANCE

Experimental treatments that increase or decrease locomotor activity or reactivity to sensory input can have quite different effects on avoidance behaviors, depending on the nature of the contingencies. Shuttle box avoidance behavior

TABLE 4

MEAN INTAKE (±SE) (ML) OF TAP WATER AND A 1.0% SUCROSE SOLUTION DURING SEPARATE 24 HOUR PERIODS WHEN FOOD WAS ABSENT

Group	n	Water	Sucrose
NC	12	29.7 (4.3)	84.5 (5.0)
PH	13	9.1 (1.1)†	43.4 (5.2)†
MP	10	6.7 (1.1)†	30.2 (5.2)†
VP	9	12.5 (2.8)†	67.2 (12.7)
DP	10	10.8 (1.9)†	63.9 (6.7)*

*Diff. controls $p<0.05$.
†Diff. controls $p<0.01$.

may be facilitated by an increase in the animal's tendency to become active in response to a change in its environment whereas most so-called passive avoidance paradigms which require the withholding of a pre-potent response tend to show opposite, deleterious effects.

Although the pattern of effects seen in the first group of experiments does not indicate that activity changes played a major role in the avoidance decrements produced by most of our cuts, it appeared worthwhile to pursue the matter further since a number of investigators have reported differential effects on active and passive avoidance behavior of various treatments that deplete central CA stores. Cooper *et al.* [7], for instance, reported that intracisternal injections of 6-OHDA severely impaired active avoidance behavior but had little or no effect on a passive avoidance response. Smith *et al.* [53] similarly reported that rats which had received 6-OHDA injections directly into the hypothalamic region that is traversed by the medial forebrain bundle performed an active avoidance response poorly but showed no passive avoidance deficit. Other investigators who have used surgical procedures that interrupt the nigrostriatal projections extensively have typically reported deleterious effects on both active and passive avoidance behavior. Kent and Grossman [20], for instance, reported severe deficits in both paradigms following long parasagittal knife cuts along the lateral border of the hypothalamus and a similar pattern of effects has been reported after electrolytic lesions of the substantia nigra or the caudate nucleus [34].

METHOD

Animals

Experimentally naive rats which had been subjected to the surgical treatments described under GENERAL METHOD were used. Fifty-one animals were tested (control, n = 8; PH, n = 12; MP, n = 10; VP, n = 5; DP, n = 16).

Apparatus

A 46 × 46 × 64 cm high translucent Plexiglas box with a floor made of 0.5 cm stainless steel rods, spaced 2.0 cm apart, was used for the passive avoidance test. The rods of the floor were connected to a constant current source which assured that each rod was hot with respect to all other rods when the experimental conditions required it [5]. A 13 × 13 × 8 cm high wooden platform was placed into the middle of the Plexiglas box.

A test of shock sensitivity was conducted in 35 × 26 × 22 cm high translucent Plexiglas boxes with floors made of 0.5 cm stainless steel rods placed 2.0 cm apart. The rods were connected to a constant current source similar to that used in the passive avoidance test.

Procedure

Approximately 120 days after surgery, the animals were placed onto the small wooden platform of the passive avoidance apparatus. When an animal stepped down from the platform, a latency was recorded, the wooden platform removed and the shocker was turned on for 5 sec. The current level was set at 100 micro A for all animals. If the animal remained on the platform for 120 sec (i.e., perfect avoidance), it was pushed off and shocked in the same way. This procedure provided equal shock experience for all animals across all trials. The test was repeated 24, 48, and 72 hours after the initial exposure.

A few days after the completion of the passive avoidance test, the animal's shock sensitivity was investigated by determining the threshold for flinch responses to footshock. For these tests, the animals were placed into the apparatus, and given 0.5 sec. bursts of grid shock 60 sec. apart, beginning with 2.0 micro A and ascending to 200 micro A (or beginning at 200 micro A and descending to 2 micro A). Each animal was tested twice with the ascending and the descending shock intensities and the threshold was defined as the median of the four tests.

RESULTS

The data from the passive avoidance test are shown in Fig. 7. A two-way analysis of variance and appropriate group comparisons indicated that the rats with parasagittal hypothalamic ($p<0.01$); ventral pallidal ($p<0.05$); or dorsal pallidal ($p<0.01$) cuts acquired the passive avoidance response significantly slower than the controls or rats with medial pallidal cuts which did not perform reliably different controls.

The test for shock sensitivity did not reveal statistically reliable differences between any of the groups tested. It may be noteworthy, however, that all of the experimental groups had slightly lower thresholds than the controls (flinch threshold means were: controls–29 micro A; parasagittal hypothalamic cuts–18 micro A; medial pallidal cuts–11 micro A; dorsal pallidal cuts–19 micro A; and ventral pallidal cuts–11 micro A). These results suggest that differential shock sensitivity is probably not a significant factor in the performance impairments seen in this as well as earlier experiments of the current series.

DISCUSSION

Our observation that rats with parasagittal cuts along the lateral border of the hypothalamus acquire a passive avoidance response poorly if at all although their detection threshold for footshock appears normal replicates earlier observations of the effects of more extensive cuts [20] and is congruent with the report [34] that damage to the nuclei of origin or termination of the nigrostriatal pathway produces a comparable impairment.

The passive avoidance test revealed an unexpected and potentially instructive difference between the animals with

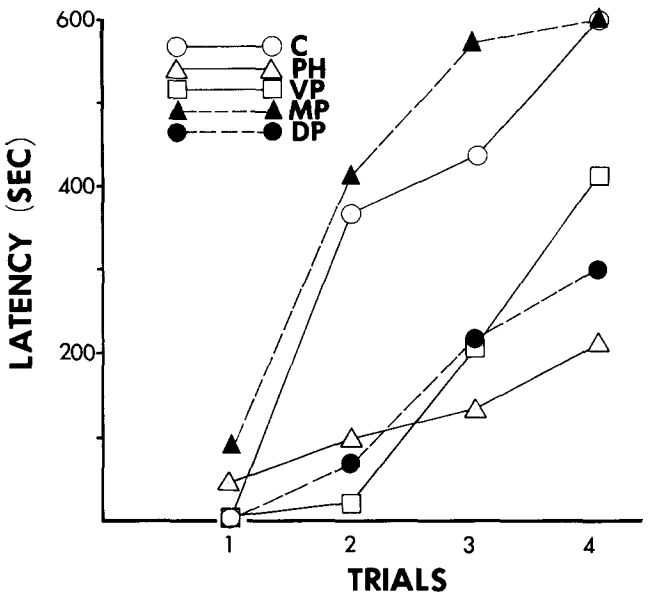

FIG. 7. Step-Down Passive Avoidance. Mean latency to step down onto an electrified grid.

parasagittal hypothalamic cuts (that were deficient in this as well as all previous tests of learned behavior) and the animals with medial pallidal cuts (that had been similarly impaired in all previous tests but performed as well as controls in the passive avoidance tests). Our tests of locomotor activity (see Experiment 1) indicate that the difference in passive avoidance behavior between these two groups does not reflect differential activity levels. It is interesting to note, in this context, that the rats with medial pallidal cuts retained considerably more DA as well as NE in the striatum and also showed smaller depletions of these amines from forebrain than our animals with parasagittal hypothalamic cuts.

The passive avoidance test also succeeded in demonstrating an impairment in the one experimental group which had performed without difficulty in all previous tests of learned behavior. Rats with cuts dorsal to the globus pallidus learned and performed active avoidance responses in the shuttle box and sucrose-reward running well but performed poorly in the passive avoidance test. It is tempting to suggest that this cut which interrupted the principal efferents from the caudate nucleus to the globus pallidus but did not significantly alter brain CA concentrations may specifically interfere with functions that are responsible for response suppression. There are numerous reports of impaired behavioral suppression in different test paradigms, including passive avoidance [34]; DRL contingencies [41]; alternation [17]; and discrimination reversal [22] after striatal lesions. Our results suggest that a specific efferent pathway may be responsible for these effects. It is, however, not clear, to what extent the slight hyperactivity which was seen in our rats with dorsal pallidal cuts (Experiment 1) as well as striatal lesions [57] may influence these apparent incidents of impaired response inhibition.

Ventral pallidal cuts produced a severe impairment in passive avoidance learning which provides further evidence for our suggestion that the deficits seen in these animals may be more specifically related to avoidance behavior than may be the case in animals with parasagittal hypothalamic cuts or cuts dorsal or medial to the globus pallidus.

BEHAVIORAL EXPERIMENTS 4: SWIMMING ESCAPE

A number investigators [30, 45, 46, 56] have reported that chemical or electrolytic lesions which involve the nigrostriatal projection system severely impair swimming in the rat. Stricker and Zigmond [54] have recently suggested that this, as well as other behavioral dysfunctions that characterize rats which have little or no striatal dopamine may be the result of a deficit in general arousal because their performance can be dramatically improved when cold rather than thermoneutral water is used in the swimming test. Our rats do not show the marked arousal impairments typical of rats with lateral hypothalamic lesions or interventricular 6-OHDA treatments but it appeared important to investigate our animals' ability to swim and to examine the influence of water temperature on this behavior.

METHOD

Animals

One hundred and twenty three rats were used, 94 of which sustained knife cut surgery as described under GENERAL METHOD above. Sixty-two were tested in thermoneutral water (38° C ± 0.5° C) (Control, n = 14; PH, n = 16, MP, n = 10; VP, n = 9; DP, n = 13) and 61 were tested in cold water (20° C ± 0.5° C) (Control, n = 15; PH, n = 14; MP, n = 10; VP, n = 9; DP, n = 13).

Apparatus

Swimming escape was observed in a 92 x 51 x 46 cm deep tank with a 20 cm diameter island at one end. The island extended 2 cm above the water line which was 18 cm below the upper edge of the tank. The island was placed at least 15 cm from the nearest tank wall.

Procedure

At the beginning of each trial, the rat was placed into the 28 cm deep water of the tank at the end opposite to that which contained the island. A stop watch was activated and the latency of a complete escape response (i.e., all four limbs on the island) was recorded. During the trial, the animals' ability to swim was rated using a modification of a rating system developed by Shapiro [51] to describe stages of neonatal development of this behavior. The following categories were used: (1) hindlimb use only with extensor rigidity of forelimbs (most mature); (2) use of hindlimbs but occasional use of forelimbs; (3) use of forelimbs and hindlimbs approximately equally; (4) head frequently under water (least mature).

RESULTS

Escape Latencies

A three-way analysis of variance indicated a significant effect of knife cuts ($p<0.01$); trials ($p<0.01$) and water temperature ($p<0.05$) (see Fig. 8).

Rats with ventral pallidal (VP) cuts showed the most marked performance differences in the two test situations. In warm water, the escape latencies of these animals did not decrease over trials and they performed consistently poorer

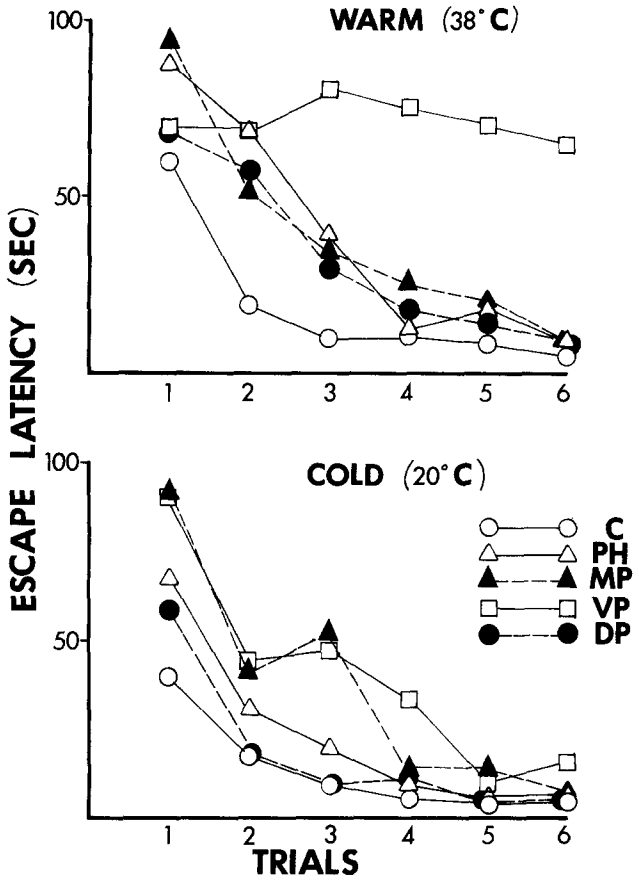

FIG. 8. Swimming Escape. Mean latency to escape from thermoneutral (above) and cold water (below).

($p<0.001$) than the controls throughout the experiment. In cold water, these animals also performed poorly during the early trials and improved significantly slower than the controls ($p<0.01$) but their asymptotic performance levels were not reliably different from those of the control or other experimental groups. The overall performance of these animals was significantly ($p<0.001$) better in cold than in approximately thermoneutral water.

Rats with dorsal pallidal (DP) cuts performed as well as the controls in cold water. In more nearly thermoneutral water, these animals performed poorly on the early trials ($p<0.01$) but reached asymptotic performance levels which were not reliably different from those of the controls. The overall performance of these animals was significantly ($p<0.01$) better in cold than in warm water.

Rats with medial pallidal (MP) cuts did not escape as quickly as the controls from either the warm or the cold water ($p<0.01$) during the first four trials but reached comparable ($p>0.05$) asymptotic performance levels. Their overall performance in warm and cold water did not differ significantly. Rats with parasagittal hypothalamic (PH) cuts were significantly slower than controls in warm or cold water ($p<0.01$) during early trials. However, their asymptotic scores did not differ from those of the controls. The overall performance of rats with PH cuts was better in cold water when compared with that in warm ($p<0.01$).

Quality of Swimming

Infant rats swim poorly, using forelimbs and hindlimbs equally, and succeeding only intermittently to maintain their heads above water. As the animals mature, competent behavior gradually emerges, until, in the adult rat, well-integrated swimming responses are seen which involve smooth paddling with the hindlimbs while the forelimbs are extended rigidly. We rated the competence of the swimming behavior in our experimental and control animals and found that our knife cuts interfered with the development of the adult swimming pattern (see Table 5). Even after eight days of training, none of the experimental groups achieved the consistent behavioral profile seen as early as Day 1 or 2 in the control animals ($p<0.01$). It is interesting to note that the severity of the impairment was not correlated with the latency scores reported above. Rats with ventral pallidal (VP) cuts showed no improvement in latency to escape from warm water but swam as well or better than the other experimental groups which escaped much more rapidly. Moreover, the VP animals (as well as rats with dorsal pallidal cuts) scored slightly (but not significantly) better in warm water from which they escaped only slowly than in the cold water which provided a much more effective stimulus for escape. This provides an interesting contrast to the pattern observed in control, animals which acquired competent adult swimming patterns more rapidly in the cold water tests ($p<0.001$). These observations suggest that the latency of the escape response may be largely independent of motor dysfunctions that might interfere with swimming.

TABLE 5

MEAN TRIALS TO ACQUIRE ADULT SWIMMING POSTURE ON TWO SUCCESSIVE TRIALS

		NC	PH	MP	VP	DP
Warm	$\bar{X}$	2.07	3.88*	5.2*	4.7*	3.92*
	± SE	± 0.24	± 0.46	± 0.81	± 0.76	± 0.60
	(n)	(14)	(16)	(10)	(9)	(13)
Cold	$\bar{X}$	1.2	3.79*	4.5*	5.9*	4.46*
	± SE	± 0.14	± 0.41	± 0.90	± 0.76	± 0.68
	(n)	(15)	(14)	(10)	(9)	(13)

*Diff. controls $p<0.01$.

DISCUSSION

A number of investigators have reported severely impaired swimming escape after hypothalamic lesions [30, 45, 46]. Because intranigral injections of 6-OHDA also have this effect [56], it is widely held that this effect of hypothalamic lesions may be due to an interruption of the nigrostriatal pathway. Our results support the conclusion that an interference with striatal functions impairs swimming escape but suggest that dopaminergic mechanisms may not play as important a role as has been assumed. Cuts below the ventral surface of the striatum, which interrupt the ansa peduncularis, dopaminergic projections to the nucleus accumbens, and other ventrally coursing connections of the striatum had by far the most severe effect on swimming escape in our tests even though

their effects on striatal dopamine were much less than in animals with parasagittal hypothalamic cuts. The latter produced the most severe and consistent depletion of striatal DA but had only slight effects on escape from warm or cold water and did not prevent the acquisition of competent swimming escape behavior. Rats with medial pallidal cuts (which produced much less of a depletion of DA in the striatum than the parasagittal cuts) performed about as poorly in the warm water test but somewhat better in the cold water experiment.

The competent escape from cold water of rats with parasagittal hypothalamic cuts is particularly interesting when viewed in the context of the earlier experiments which consistently showed that this cut severely interfered with the acquisition of active as well as passive avoidance responses. The fact that these animals performed better in cold water supports the suggestion [30], that an interruption of the nigrostriatal system may interfere with sensory-activation mechanisms necessary for the organization of complex, goal-oriented behavior. However, our animals with parasagittal (or other) cuts did not show the gross arousal deficits that have been reported in rats after dopamine-depleting intraventricular 6-OHDA injections [54] and we do not believe that a general arousal failure is part of the etiology of the many behavioral deficits which we have observed in these animals.

GENERAL DISCUSSION

The results of the present experiments support the general conclusion that the striatum plays an important role in the organization of avoidance behaviors. The hypothesis that dopaminergic projections to the striatum may specifically subserve avoidance behavior and related functions did not receive consistent verification. Surgical interruption of various afferent and efferent connections of the striatum severely impaired shuttle box avoidance, swimming escape, and passive avoidance behavior but an appetitively controlled behavior was similarly affected. All of our cuts which produced significant striatal CA depletions interfered with shuttle box avoidance acquisition but there was no indication of a correlation between the magnitude of the DA or NE depletions and the severity of the behavioral deficit. Indeed, the only cut which reliably interfered with preoperatively learned avoidance behavior (the cut below the striatum) produced CA depletions that were smaller on the average than those seen in rats with parasagittal cuts which had no effect on performance in this test. Rats with cuts below the striatum displayed by far the most severe impairments in the swimming escape test, whereas rats with PH cuts (which produced the largest depletions of striatal catecholamines) acquired this behavior almost normally in cold water and showed only a transient impairment in thermoneutral water.

Pharmacological interventions that deplete striatal dopamine have been reported to interfere with active avoidance acquisition without affecting so-called passive avoidance behavior [7,53]. Our results indicate that cuts which produce marked striatal DA depletions impair passive as well as active avoidance learning. However, there was, once again, no indication of a correlation between the magnitude of the behavioral and biochemical effects of our cuts. That striatal pathways which do not depend on catecholamine transmitters contribute importantly to the organization of these behaviors is further indicated by the fact that cuts above the globus pallidus which did not significantly interfere with striatal CA content resulted in a deficit in this (but no other avoidance) test.

It has been suggested that chemical and surgical destruction of the dopaminergic afferents to the striatum may interfere with endogenous arousal or arousal responses to environmental stimuli [30,54]. Our animals do not show the gross arousal deficits seen in 6-OHDA treated rats or in animals with large lateral hypothalamic lesions and we have seen no evidence of hypoactivity in any of our tests. The differential effects of our cuts on escape from thermoneutral or cold water suggest, however, that at least one of the behavioral dysfunctions can be partially overcome by an increase in arousal (or, in the specific motivational substrata of the behavior).

The results of our tests indicate that not only the dopaminergic afferents to the striatum but other afferent as well as efferent connections of this structure may be essential for the normal acquisition of complex, appetitively as well as aversively controlled behaviors. Medial pallidal (MP) cuts which interfered with the principal efferent connections of the striatum produced effects on shuttle box avoidance, swimming escape, and sucrose rewarded alley running which were similar to those seen in rats with parasagittal hypothalamic cuts even though the MP cuts had much less effects on the striatal concentrations of catecholamines. Ventral pallidal cuts, which interrupted still a third set of afferent and efferent connections and produced relatively moderate effects on striatal DA had even more severe effects in the shuttle box and the swimming escape test.

It appears from this pattern of effects that any major interference with striatal functions (including pharmacological or surgical interventions that result in DA depletions) may produce impairments in a function (or functions) which appears to be essential for the acquisition of novel complex behaviors. The function in question does not appear to be as crucial for the execution of previously learned behaviors since most rats eventually reached performance levels which were indistinguishable from those achieved earlier by control animals. However, behavior is particularly labile during initial acquisition and the acquisition/performance differences seen in the present experiments may merely reflect this well known fact. The severe impairments seen in rats with ventral pallidal cuts on our shuttle-box avoidance recall test as well as earlier observations of apparently irreparable acquisition and performance losses in rats with larger parasagittal cuts [20] indicate that some striatal functions may be essential for the execution of all complex behavior.

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