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Avoidance, Operant and Locomotor Behavior in Rats With Neostriatal Injections of Kainic Acid

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SANBERG, P. R., M. PISA AND H. C. FIBIGER. *Avoidance, operant and locomotor behavior in rats with neostriatal injections of kainic acid.* PHARMAC. BIOCHEM. BEHAV. **10**(1) 137–144, 1979.—Compared with saline injected controls, rats with bilateral injections of kainic acid (KA) in the dorsal neostriatum showed increased locomotor response to d-amphetamine, increased resistance to extinction and impaired acquisition and retention of passive avoidance. The KA injection resulted in loss of local neurons in the dorsal neostriatum, with no appreciable damage either to dopaminergic terminals or to extrinsic myelinated axons, thus supporting both the selective neurotoxic action of KA on neuronal perikarya and the proposed similarity of KA-induced neostriatal lesions with those found in the caudate-putamen of patients with Huntington's disease. Although loss of hippocampal neurons was occasionally observed, the behavioral results could not be wholly attributed to hippocampal damage, since rats with no demonstrable extrastriatal lesions were not less impaired than those with hippocampal damage. An altered arousal reaction to stressful situations might account for the learning and memory impairments of the KA neostriatal rats.

Kainic acid Neostriatal lesions Avoidance behavior Operant behavior Locomotor activity d-Amphetamine

KAINIC ACID (KA), a rigid analogue of the putative excitatory transmitter glutamate, has been recently shown to have potent neurodegenerative effects [39]. Although its mechanism of action is not yet well understood, an irreversible ionic shift resulting from chronic membrane depolarization has been proposed to account for its neurotoxic effects [40].

Injections of KA into the neostriatum result in degeneration of local intrinsic neurons, leaving apparently intact both axons and terminals of extrinsic neurons [9, 10, 11, 27, 28, 31, 48, 49]. The resulting biochemical and histological picture appears to be strikingly analogous to that found in the caudate-putamen of patients with Huntington's disease (HD) [1, 6, 11, 14, 21, 23, 33, 42].

The selective neurodegenerative effects of KA invite the preferential use of this new lesioning tool in behavioral studies of neostriatal function vis a vis traditional electrolytic or thermocoagulative methods of lesions, which unavoidably result in damage to cortical afferent and efferent fibers transversing the neostriatum. Furthermore, to the extent that KA neostriatal lesions provide an adequate model of the lesions found in patients with HD, they appear well suited for behavioral and pharmacological analyses of the effects of neostriatal degeneration and its attendant biochemical alterations in HD [11, 26, 27, 28, 44, 45].

Emotional instability, inability to maintain a steady train of thought, lack of concentration on the task at hand, and choreatic movements are among the chief symptoms of HD [5, 6, 7, 11, 14].

Although the dyskinesias have been commonly attributed to neostriatal pathology, and the psychiatric symptoms to concomitant cortical atrophia [2, 6, 41], the animal literature strongly suggests an involvement of the neostriatum in tasks of learning and memory [13, 19, 34, 43, 44, 51, 54].

The present study represents an extension of a previous investigation in which KA induced neostriatal lesions were shown to result in impairments of acquisition and retention of a passive avoidance task [44]. In the latter study, 1 μl of a 6 nmoles/μl solution of KA was bilaterally injected in the dorsal neostriatum. Measures of choline acetyltransferase and glutamic acid decarboxylase activity indicated that the injections had indeed resulted in loss of cholinergic and GABAergic neostriatal interneurons. No histological verification of the lesions was available, however. Also, recent investigations indicate that at the doses used in that study, KA may affect extrastriatal neurons [10,55].

In the present work relatively low doses of KA acid were used, and the specificity and extent of the lesions were assessed both biochemically and histologically. In order to provide a more detailed analysis of factors that might account for the impairment in passive avoidance behavior, learning and extinction of an appetitive operant response were also investigated to assess whether neostriatal lesions also affect performance in positively reinforced tasks. Additionally the role of the neostriatum in motor control was investigated by assessing the effects of neostriatal lesions on spontaneous locomotor activity and on locomotor response to d-amphetamine administration.

METHOD

Animals

Twenty-one male Wistar albino rats weighing 300–320 g at the time of surgery were used. They were housed in groups of six before surgery and in individual stainless steel cages afterwards, with free access to water and Purina Rat Chow food. The colony room had a temperature of 22–25°C, humidity of 45–55%, and a 12 hr light-dark cycle.

Surgery

Seven days after their arrival in the laboratory, the rats were randomly assigned to either a control (n=10) or a kainic-acid lesioned (KAL) group (n=11). The rats were anesthetized with sodium pentobarbital (50 mg/kg), and positioned on a Kopf stereotaxic instrument with the incisor bar adjusted at 4.2 mm below the interaural line. Two holes were drilled in the skull, and 3 nmoles of kainic acid dissolved in 0.5 μl of a phosphate buffered isotonic saline solution, pH 7.2, were bilaterally injected over a 3-min period at the following coordinates: 9.6 mm rostral and 4.5 mm dorsal to the intraural line, 2.8 mm lateral to the sagittal suture. In pilot experiments these coordinates were shown to correspond approximately to A=8.4, H=0.8, and L=2.2 of König and Klippel atlas [22]. After the injection the 34 gauge cannula was left in place for 5 min to allow for diffusion of the solution from the tip. The control rats were bilaterally injected with 0.5 μl of the vehicle solution.

Postoperatively the KAL rats showed aphagia, adipsia, and little or no grooming. To promote recovery, they were tube-fed with 10 ml of Soyalac® twice daily, until they resumed feeding and drinking, which took about 1–3 days. The control rats were similarly handled but were not tube fed. The animals were given a three-week period of recovery before starting the behavioral tests.

Apparatus

Locomotor activity. Six photoactometer cages (BRS Foringer No. PAC-001) 61 cm in dia. with black walls 43 cm high and grid floors were used. The interior of the cages was crossed by six infrared photocell beams, interruption of which incremented electromechanical counters. An automatic printout counter (BRS Foringer No. POS-112) recorded counts cumulated over periods of 10 min. The cages were illuminated by 4×100 W bulbs located 3.6 m above.

Appetitive barpressing. Four standard BRS Foringer Skinner boxes enclosed in sound proof chambers and fitted each with a lever and a dispenser of food pellets were used. Digibits modules were assembled in a logical circuit controlling the reinforcement schedule, with 45-mg Noyes pellets being used as reinforcers. Bar presses were recorded on conventional electromechanical counters.

Passive avoidance. A 27×27×30 cm box with Plexiglas walls, grid floor, and a 7.5×26.7 cm wooden platform shelf located to the side and hinged on a microswitch 9.4 cm above the floor, was used. On release of the microswitch, scrambled DC current electrified the stainless steel rods of the grid, which were spaced 1.5 cm apart.

The same box, with the platform blocked off by a sheet of cardboard, was also used for both shock threshold and freezing tests.

Procedure

Locomotor activity. The rats were individually placed in the photoactometers at either 10 am or 1 pm and their activity recorded for six periods of 10 min each. They were then injected with 1 mg/kg of d-amphetamine IP and immediately replaced in the photoactometers for another twelve 10-min periods. Two-way analyses of variance, with Lesion and Periods as Factors, were separately conducted on the pre- and the postinjection activity scores.

Acquisition and extinction of barpressing. A week after the test of locomotor activity the food diet of the rats was restricted to about 15 g of Purina Chow daily, until they reached 90% of their free-feeding weights, which took about a week. The rats were thereafter maintained at these reduced weights by appropriately adjusting their daily amount of food, to which the rats had access for about 1 hr after training. The animals were first given 12 acquisition sessions of 30 min each under a continuous reinforcement schedule (CRF). To promote learning, at the onset of Session 1 ten 45-mg Noyes pellets were attached on the bar with cellophane tape and another ten pellets were placed in the food magazine. At the onset of Session 2 five pellets were freely available on the bar. In the following ten sessions only pellets contingent on bar pressing were available. On Sessions 13–17 reinforcement was discontinued. Each of these extinction sessions lasted until the rats ceased to respond for three consecutive minutes. Both latency and number of responses to the extinction criterion were recorded. Two-way analyses of variance, with Lesion and Sessions as main Factors, were conducted on the responses during acquisition and on both the responses and the latencies during extinction. One lesioned rat was excluded from the analysis of the locomotor and CRF testing because of methodological and control problems in running groups of unequal size.

Passive avoidance. At the end of the barpressing experiment all rats were given free access to food for two weeks. At the onset of the acquisition session a small amount of electrode paste was applied to the paws of each rat. The rats were then placed on the platform. Upon stepping on the grid they received a 2 mA footshock, lasting until they returned to the platform. Latency to the first step down, latency to an avoidance criterion of three consecutive minutes spent on the platform, and number of descents to criterion were recorded. One day following the acquisition sessions, the rats were placed on the platform, and their latencies to step down, measured to a maximum of 3 min, were recorded.

Three days after the retention test, footshock detection thresholds were determined. Prior to being placed on the grid floor, electrode paste was applied to the paws of each rat. The animal was allowed to habituate to the apparatus for 1 min and then presented with a series of inescapable 0.5 sec footshocks of ascending intensities (0.25 mA–3.0 mA). An intershock interval of 15 sec was used. Threshold intensities of flinch, jump, and vocalization were determined by the occurrence of the appropriate behavior in at least three out of five presentations at that intensity.

After five days the freezing reaction to footshock was determined. The rat was exposed to five 0.5-sec, 2 mA inescapable footshocks at intervals of at least 30 sec. Both latency of the first movement (except eyeblink) and number of fecal boli were recorded.

The passive avoidance experiments were run blind insofar as the investigator did not know the identity of the animals. Two-tailed t statistic was used to evaluate the re-

sults, except for the avoidance retention data, which were analyzed using Mann-Whitney U statistic [50].

Histology

Two control and three KAL rats were given an overdose of sodium pentobarbital and perfused intracardially with isotonic saline solution followed by 10% Formol saline. Sections were cut from frozen tissue at 50 μ and every third section was saved and stained with cresyl violet.

Biochemistry

Eight control and eight KAL rats were sacrificed by cervical fracture. The activities of choline acetyltransferase (CAT), glutamic acid decarboxylase (GAD), and tyrosine hydroxylase (TOH), were assayed in samples of the dorsal neostriatum, ventral neostriatum, nucleus accumbens, and cortex of four control and four KAL rats, using the methods of McCaman and Dewhurst [29], Chalmers *et al.* [8] and McGeer *et al.* [32], respectively. The remaining four control and four KAL rats were used to assay noradrenaline (NA) levels in the combined samples of neocortex and hippocampus according to the method of McGeer and McGeer [30].

RESULTS

Histology

A representative neostriatal lesion is shown in Fig. 1. In all three brains sampled for histology the ventricles were enlarged and the neostriatum appeared shrunken bilaterally. The rostral aspect of the neostriatum revealed marked, bilateral loss of neuronal perikarya and dense glial infiltration in the space surrounding the fascicles of the internal capsule. The fascicles appeared to be more packed than in normal tissue, but their size and stain density was not appreciably altered. In two brains the area showing neuronal loss had a diameter of about 0.8 mm. In the third rat the lesion was larger, extending from A 9.0 to A 6.5. In all brains the ventral neostriatum did not show appreciable damage, however.

Additional damage included a slight decrease of neuronal density in the layers V and VI of the neocortex above the injection site, in all three brains. Also, in the brain of the rat with relatively large neostriatal lesions a decrease in the number of pyramidal cells was observed in the CA3 field of the anterior dorsal hippocampus and in the CA1 field of the posterior dorsal hippocampus. The hippocampal neuronal loss was mostly unilateral. No other damage to brain areas outside the neostriatum could be detected.

Biochemistry

The results are shown in Table 1. There were no significant differences between control and KAL rats in activities of CAT, GAD, or TOH in either the cortex or the nucleus accumbens. Also, the animals of the two groups did not significantly differ in NA levels in the cortical-hippocampal regions. These results indicate that the injections of kainic acid did not damage cholinergic and GABAergic neurons of the neocortex and the nucleus accumbens, or noradrenergic afferent terminals to the cortex and the hippocampus.

Clear differences between groups were found, however, in the activities of neostriatal enzymes. Specifically, both CAT and GAD activities in the dorsal neostriatum were significantly lower in the KAL than in the control rats, $t=2.47$ and 3.57, respectively, $df=14$, p's<0.005. However, the rats of the two groups did not significantly differ either in GAD activity in the ventral neostriatum, $t<1$, or in TOH activity, both in the dorsal neostriatum, $t=1.56$, $df=14$, and in the ventral neostriatum, $t=1.57$, $df=14$.

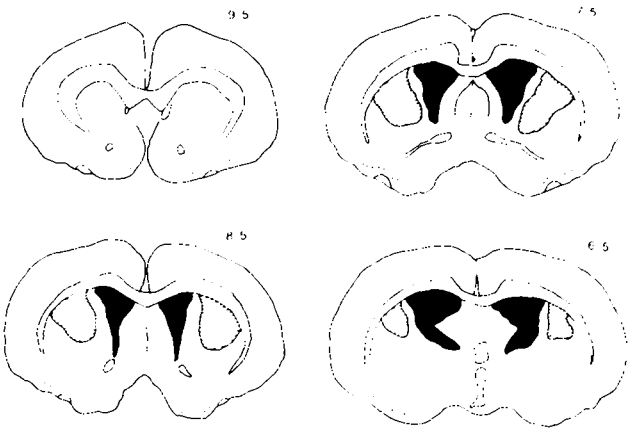

FIG. 1. Area of neostriatal neuronal loss in a rat treated with intrastriatal injections of three nmoles of kainic acid. Numbers correspond to frontal planes of König and Klippel atlas [22].

Behavior

Locomotor activity. The results are shown in Fig. 2. Before d-amphetamine administration there was no significant effect of lesion on locomotor activity, $F<1$. The significant effect of periods, $F(5,90)=26.3$, $p<0.001$, reflected the progressive decrease of activity of the rats of both groups. After administration of d-amphetamine, however, the KAL rats revealed a significantly greater increase in activity than the controls, $F(1,18)=13.04$, $p<0.005$.

Appetitive barpressing. Although the average response rate of the KAL rats during acquisition was slightly lower than that of the controls (Fig. 3), neither the effect of lesion, $F(1,8)=2.55$, nor the interaction of lesion with sessions, $F(11,98)=1.03$, reached significant levels. The reliable effect of sessions, $F(11,98)=34.2$, $p<0.001$, reflected the improvement in performance of the rats of both groups. By mistake, the animals were given ad lib food on the day before Session 10. This accident accounts for the drop in performance on that session.

During extinction (Fig. 4) the KAL rats performed more responses and took longer to reach the extinction criterion than the controls. Analysis of variance of the responses revealed significant effects of lesion, $F(1,18)=5.05$, $p<0.05$, and sessions, $F(4,72)=11.21$, $p<0.01$, and a significant interaction effect, $F(4,72)=3.54$, $p<0.05$. Tests of simple main effects [53], showed that the KAL rats responded significantly more than the controls in both the first session, $F(1,18)=13.3$, $p<0.01$, and the second session, $F(1,18)=6.3$, p's<0.05, but not in the subsequent sessions, p's>0.05.

Analysis of variance of the latencies also revealed significant effects of lesions, $F(1,18)=10.41$, $p<0.01$, and sessions, $F(4,72)=4.36$, $p<0.01$, with no significant interaction effect, $F=1$. Tests of simple main effects revealed that the KAL rats took significantly longer than the controls to reach criterion in both the first and the second session, F's$(1,18)=7.95$ and

TABLE 1

ENZYME ACTIVITIES AND NORADRENALINE LEVELS IN VARIOUS BRAIN AREAS OF KAINIC ACID NEOSTRIATAL LESIONED RATS*

Area	CAT		GAD		TOH	
Cortex						
Controls	15.2 ± 1.95		79.5 ± 2.18		0.12 ± 0.07	
Lesioned	15.4 ± 3.32	(101%)	78.6 ± 3.46	(99%)	0.13 ± 0.05	(108%)
Accumbens						
Controls	47.3 ± 6.57		136.8 ± 5.23		9.66 ± 0.99	
Lesioned	40.4 ± 2.85	(86%)	147.4 ± 8.14	(108%)	9.85 ± 0.44	(102%)
Neostriatal Regions						
Dorsal						
Controls	72.8 ± 7.98		57.7 ± 4.47		9.47 ± 0.31	
Lesioned	43.3 ± 8.85	(60%)†	37.7 ± 3.36	(65%)‡	10.56 ± 0.63	(112%)
Ventral						
Controls	66.6 ± 3.42		74.2 ± 4.09		9.50 ± 0.34	
Lesioned	44.7 ± 5.58	(67%)‡	68.9 ± 6.33	(93%)	8.80 ± 0.28	(93%)
Hippocampal and Cortical Noradrenaline						
Controls	0.37 ± 0.01					
Lesioned	0.34 ± 0.02	(92%)				

*Choline acetyltransferase (CAT), glutamic acid decarboxylase (GAD), and tyrosine hydroxylase (TOH) activities are expressed as nanomoles per mg protein per hr in control and kainic acid treated rats (N=4 per group). Noradrenaline values are expressed as μg per wet weight of tissue (N=4 per group). Data represent means + standard error of the mean. Figures in parentheses are percentages of control values.

†Significantly different from controls, $p<0.03$ (two-tailed test).

‡Significantly different from controls, $p<0.005$ (two-tailed test).

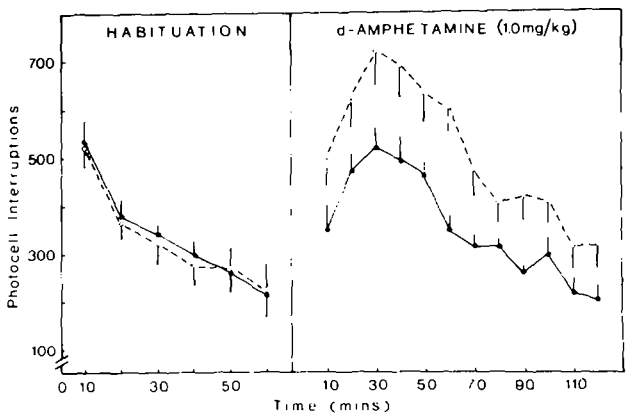

FIG. 2. Mean locomotor activity and standard error of the mean of the rats in each group before (left panel) and after (right panel) administration of d-amphetamine (1 mg/kg). Filled circles=control rats; open circles=rats with intrastriatal injections of kainic acid.

5.51, respectively, p's<0.05, but not in the subsequent sessions, p's>0.05.

Passive avoidance. The acquisition data are shown in Table 2. There were no significant differences between groups in latency to the first step down, $t<1$. After footshock the KAL rats showed a significant impairment in terms of both number of step down responses and latencies to criterion, t's=3.64 and 4.62, respectively, $df=19$, p's<0.005.

The KAL rats were also impaired in the retention test (Table 2) as indicated by their significantly shorter latency to step off the platform compared with that of the controls, $U=25.5$, n1/n2=10/11, $p<0.05$.

There were no significant differences between groups in detection thresholds of flinch, jump, and vocalization, t's<1 (Table 3). Also, there were no significant differences between groups in number of boli defecated after the 2 mA footshock, $t<1$ (Fig. 5). However, the KAL rats showed a significantly shorter immobility reaction than the controls, $t(19)=3.03$, $p<0.01$.

DISCUSSION

Confirming the results of previous studies [27,28] both the histological and the biochemical data indicated a loss of neostriatal neurons following injections of KA in the dorsal neostriatum. An interesting finding was the decrease of CAT but not of GAD activity in the ventral neostriatum. One possible explanation of this result is that cholinergic neurons of the ventral neostriatum are more sensitive to the neurotoxic action of KA than GABAergic neurons. However, the histology showed no evidence of neuronal loss in the ventral neostriatum. It is therefore more likely that the selective decrease of ventral neostriatal CAT activity resulted from anterograde degeneration of cholinergic interneurons presumably projecting from the dorsal to the ventral neostriatum.

TABLE 2

EFFECT OF BILATERAL KAINIC ACID LESIONS OF THE NEOSTRIATUM ON ACQUISITION AND RETENTION OF PASSIVE AVOIDANCE*

Group	Initial Step-down Latency	Time to Criterion (sec)	Number of descents to Criterion	24-hr Retention: Step-down latency (sec)
Control (N=10)	3.58 ± 1.01	298.70 ± 28.73	3.10 ± 0.23	148.20 ± 16.67
Kainic acid Neostriatal (N=11)	3.78 ± 1.40	502.64 ± 42.84‡	6.09 ± 0.58§	83.50 ± 23.14†

* Data represent means ± standard error of the mean.
† Significantly different from controls, $p<0.05$ (two-tailed test).
‡ $p<0.005$ (two-tailed test).
§ $p<0.0005$ (two-tailed test).

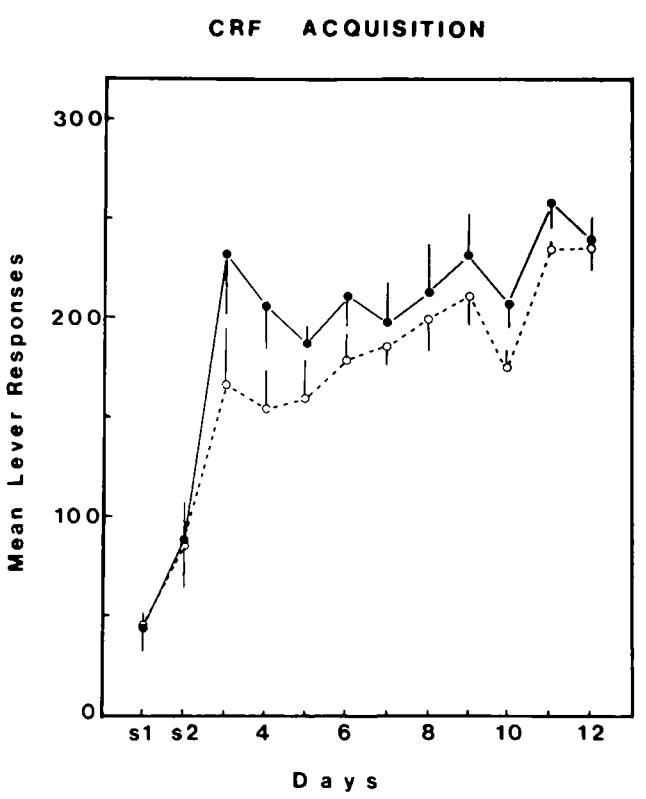

FIG. 3. Mean responses and standard error of the mean during acquisition of continuously reinforced bar pressing. Filled circles=control rats; open circles=rats with intrastriatal injections of kainic acid; s1 and s2=sessions in which shaping procedures were used.

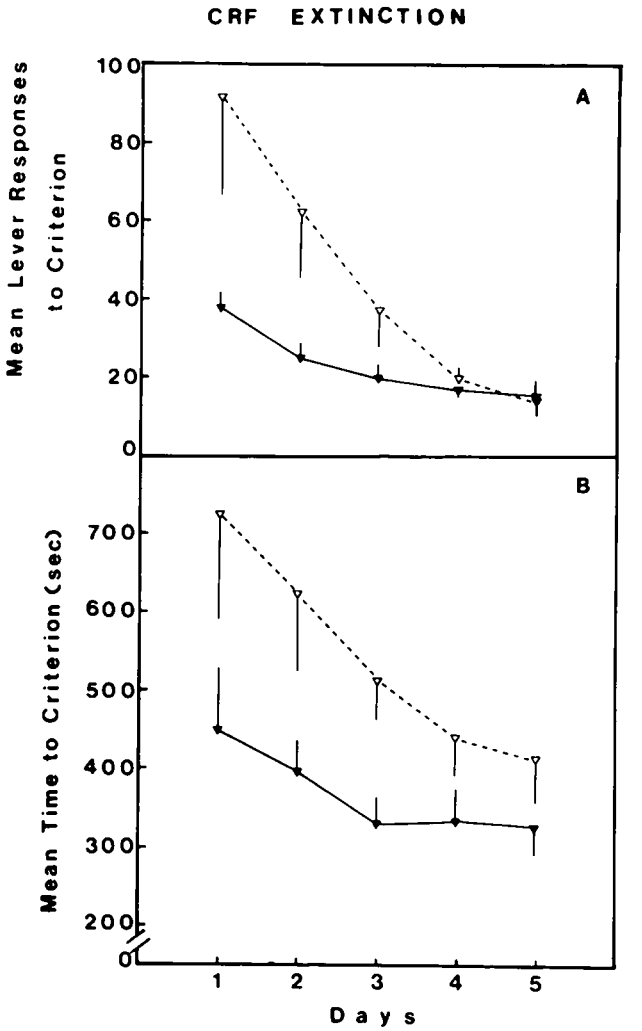

FIG. 4. Mean responses and standard error of the mean (upper panel), and mean latency to criterion and standard error of the mean latency (lower panel) during extinction of bar pressing. Filled triangles=control rats; open triangles=rats with intrastriatal injections of kainic acid.

According to one group of investigators neostriatal injections of KA result in specific loss of neostriatal perikarya, with no demyelinization of fibers of passage, and no loss of extrastriatal neurons, at least in a range of doses of KA including that used in the present study [10]. These investigators observed neuronal loss both in the hippocampal CA3–CA4 fields and in the neocortex overlying the neostriatal injection site only with doses of 2–5 μg of KA. Other

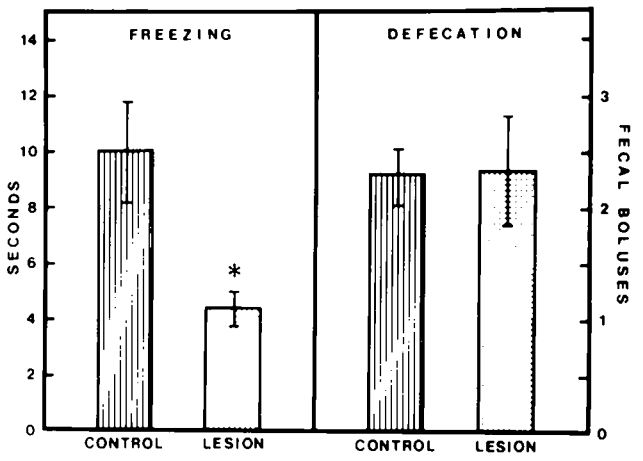

FIG. 5. Freezing time and number of fecal boli after a 2 mA footshock in control rats and in rats with intrastriatal injections of kainic acid. Data represent means of five trials. Bars represent standard errors of the means. *Significantly different from controls, $p<0.01$.

TABLE 3

EFFECT OF BILATERAL KAINIC ACID LESIONS OF THE NEOSTRIATUM ON SHOCK THRESHOLDS OF FLINCH, JUMP AND VOCALIZATION*

Group	Thresholds (mA) Flinch	Jump	Vocalization
Control (N=10)	0.95 ± 0.09	1.80 ± 0.11	1.70 ± 0.17
Kainic acid Neostriatal (N=11)	0.86 ± 0.07	1.86 ± 0.15	1.73 ± 0.24

*Data represent means ± standard error of the mean.

investigators have reported more extensive damage with intrastriatal injections of 2.5 μg of KA, including nonspecific necrosis in the neostriatum and neocortex, demyelinization of fibers of passage, necrosis and neuronal degeneration in the amygdala, pyriform cortex, and entorhinal cortex, and selective neuronal loss in the CA3–CA4 hippocampal fields [55].

With injections of 3 nmoles, i.e., 0.63 μg, of KA we did not observe necrotic phenomena at the injection site. The architecture of the myelinated fiber bundles passing through the lesioned area appeared intact. Also the normal levels of TOH activity in both the dorsal and the ventral neostriatum of the experimental rats indicated sparing of the dopaminergic terminals of nigrostriatal fibers. The normal levels of NA in the cortex suggest on the other hand that KA spared noradrenergic fibers in transit through the neostriatum [24]. However, it is not possible to exclude the occurrence of some fiber demyelinization especially near the injection site, or an alteration of impulse transmission in fiber bundles that were apparently intact on morphological inspection.

Some extrastriatal damage was present in the brains of the experimental rats used for histology. Thus, despite the fact that KA injections did not substantially modify CAT and GAD activity in cortical samples, the histology showed a slight neuronal rarefaction in layers V and VI of the neocortex overlying the injection site. Furthermore, one brain also showed neuronal loss in the hippocampus. It therefore appears that even with the relatively low doses used in the present study damage may occur to extrastriatal neurons that are especially sensitive to the action of KA. Both smaller doses and slower rates of injection of KA should probably be used in the attempt to obtain lesions that are more selectively confined to the neostriatum.

We replicated the results of previous studies [27, 28, 44, 45] showing that KA-induced lesions of the dorsal neostriatum do not alter daytime locomotor activity, at least if measured in photoactometers, but greatly enhance the locomotor response to d-amphetamine. Similar results were originally obtained using electrolytic lesions of the neostriatum [38]. The increased response to d-amphetamine of rats with dorsal neostriatal lesions has been considered analogous to the exacerbation of choreic movements induced by d-amphetamine in HD patients [20,21] and has been tentatively attributed to interruption of a striatonigral projection normally inhibiting the locomotor-inducing activity of mesolimbic dopaminergic neurons [27,28]. Because of its robustness, this pharmacological effect may be used as a preliminary check of the lesioning effectiveness of KA striatal injections before using the animals in time consuming behavioral studies.

The KA neostriatal lesions did not interfere with either rate of acquisition or asymptotic performance of lever-pressing for continuous reinforcement. However, the lesions increased resistance to extinction. Similar results have been reported using thermocoagulative lesions of the caudate [47]. In the latter study it was found that dorsolateral frontal ablations did not alter resistance to extinction, suggesting that damage to cortical connections in transit through the internal capsule were not responsible for the perseverative responding of the caudate lesioned animals. The present findings support this view, by showing an increased resistance to extinction after KA neostriatal lesions that apparently spare fibers of the internal capsule.

The results of the passive avoidance experiment, showing an impairment in both acquisition and retention of the punishment contingency after dorsal neostriatal lesions, confirm and extend those of a previous study [44] in which larger doses of KA were used for the neostriatal injections. Impairments in passive avoidance and increased resistance to extinction may result from lesions of extrastriatal structures, including the dorsal noradrenergic bundle [12,25] and the hippocampus [4,46]. Since the KAL rats showed normal levels of cortical norepinephrine it is not likely that their behavioral impairments resulted from damage to forebrain noradrenergic fibers.

Hippocampal damage may have contributed to the altered performance of some experimental rats. However, the two rats without hippocampal damage showed similar impairments to those of the rat with demonstrable hippocampal lesions, indicating that a selective loss of dorsal caudate neurons was at least in part responsible for the observed behavioral deficits.

An account of the impairments in passive avoidance in terms of decreased footshock sensitivity is unlikely, since the experimental rats did not substantially differ from the controls in shock thresholds of both flinch-jump and vocalization. A more plausible explanation might be that dorsal

neostriatal lesions interfere with associative and memory processes [19, 34, 43, 44, 51, 54]. The results of the lever pressing experiment, however, indicated that these lesions did not have any significant effect on learning of an appetitive instrumental response, thus arguing against the hypothesis of a generalized associative impairment. Also, the finding that the rats with neostriatal lesions showed a much longer step down latency during retention than before any footshock experience suggests that their amnesia for the punishment contingency was at least incomplete.

An alternative account of both the increased resistance to extinction and the impairment in suppression of punished response might be an interference of dorsal neostriatal lesions with inhibitory control of voluntary movements [13, 17, 36, 37, 47]. The finding that the rats with lesions showed a shorter immobility reaction to footshock than normal rats might be taken in support of this hypothesis.

Other results appear to be in conflict with this hypothesis, however. Thus there were no significant differences between control and experimental rats in either spontaneous locomotor activity in the photoactometers or in preshock step down latency. There is, however, evidence that electrolytic lesions of the caudate in rats result in locomotor hyper activity after food deprivation, at night, or in brightly illuminated environments, i.e., in conditions presumably involving high levels of arousal [18,38]. The findings that KA-induced dorsal neostriatal lesions result in locomotor hyperactivity at night [26] and an increased locomotor response to d-amphetamine also support the view of a role of the dorsal neostriatum in inhibition of arousal reactions.

An exaggerated arousal reaction either to lack of expected reinforcement or to occurrence of aversive stimuli might therefore account at least in part for the abnormally high levels of responding of the experimental rats after extinction and punishment, respectively. Such analysis of the effects of dorsal neostriatal lesions in rats would be consistent in turn both with the view that altered arousal levels probably contribute to the cognitive and motor disorders of patients with HD [3, 6, 15, 16, 35] and with the finding that baclofen, an inhibitor of dopaminergic mesolimbic neurons [52] improves the motor symptoms of patients with HD [1]. Further studies are warranted to assess whether this agent can also improve the performance of both HD patients and animals with neostriatal lesions in tasks of learning and memory.

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