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Deficits Induced by Quinolinic Acid Lesion to the Striatum in a Position Discrimination and Reversal Task Are Ameliorated by Permanent and Temporary Lesion to the Globus Pallidus: A Potential Novel Treatment in a Rat Model of Huntington's Disease

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Abstract: Symptoms in the early stages of Huntington's disease (HD) are assumed to reflect basal ganglia circuit dysfunction secondary to degeneration of striatal projections to the external segment of the globus pallidus (GPe). The hypothesis that GPe lesion would ameliorate HD symptoms by "normalizing" the circuit's functioning was tested in a rat model of this disease. The performance of rats sustaining quinolinic acid lesion to the striatum (a rat model of HD) in a position discrimination and reversal task was compared with the performance of rats sustaining in addition a bilateral excitotoxic lesion to the globus pallidus (GP) carried out simultaneously with the striatal lesion (Experiment 1) or 1 month after the striatal lesion (Experiment 2), as well as a unilateral temporary lesion of the GP (Experiment 3). The striatal lesion-induced deficit in the task was effectively reversed by a bilateral excitotoxic GP lesion carried out simultaneously or 1 month after the striatal lesion, as well as by a temporary unilateral GP inactivation. Given that a similar dysfunction of basal ganglia circuitry is thought to subserve the behavioral alterations seen in quinolinic acid lesioned rats and some of the symptoms in HD, these results raise the possibility that lesion or inactivation of the GPe may alleviate some of HD symptoms. © 2003 Movement Disorder Society

Key words: striatum; globus pallidus; basal ganglia-thalamocortical circuitry; Huntington's disease (HD); rat

Huntington's disease (HD), one of the CAG trinucleotide-repeat diseases,[1] is a progressive neurodegenerative disorder of mid-life onset, characterized clinically by progressive involuntary choreiform movements, cognitive decline, and personality changes.[2–5] Brain imaging and neuropathological studies have revealed that in the early stages of the disease the striatum is most severely affected, although other brain regions, including the cortex, may show some pathological changes.[4,6–14] In the striatum, the early stages of the disease are marked by a selective loss of striatal neurons projecting to the external segment of the globus pallidus (GPe) and the substantia nigra pars reticulata, whereas neurons projecting to the internal segment of the globus pallidus are lost only in later stages.[6,15–20] Because the structures affected in HD are linked anatomically and functionally within several circuits connecting the basal ganglia, thalamus and cortex,[2,21–28] it has been proposed that HD symptoms reflect a dysfunction of basal ganglia-thalamocortical circuitry.[5,22,29–31] According to the leading model of HD, launched by Penney and Young,[2,4] in the early stages of HD, loss of striatal projections to GPe results in overactivity of GPe, which in turn results in the disruption of basal ganglia output to the thalamus.[2,4,32–35] A detailed application of the model to HD may be found in the work by Joel.[36]

Although the anatomo-functional model of basal ganglia circuitry on which this account is based has been

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challenged,[37–39] the model has been utilized successfully to account for the pathophysiology and treatment of several basal ganglia-related disorders,[2,4,40] as well as for the development of novel treatments.[41] A central assumption of this model is that complex behavioral pathologies resulting from damage to one of the circuit's components reflect dysfunction of the circuit as a whole, and can therefore be alleviated by manipulations of a different component of the circuit. Based on this assumption, we have suggested that in HD, lesion of the presumably overactive GPe should normalize the functioning of basal ganglia-thalamocortical circuitry, thus ameliorating some of the symptoms of this disease.[27,36,42]

The present study tested in rats whether a lesion to the globus pallidus (GP, the rat analogue of the primate GPe) would alleviate a behavioral deficit induced by a quinolinic acid (QA) striatal lesion, using a position discrimination and reversal task known to be sensitive to striatal damage.[43–47] Striatal QA lesion is a leading rat model of HD, because the pattern of neuronal loss in the striatum is considered to mimic the cellular pathology seen in HD.[48–51] The possibility that such lesions also duplicate the selective degeneration of striatal projection neurons in early HD has been raised based on findings that striatal terminals in GP are more affected by QA striatal injection than are striatal terminals in the entopeduncular nucleus (the rat analogue of the primate internal segment of the globus pallidus).[50] This observation, however, was not paralleled by findings of greater degeneration of striatal neurons projecting to GP compared with those projecting to the entopeduncular nucleus.[50] In addition, because in rats many of the striato-entopeduncular projections are collaterals of striato-pallidal projections,[52] the projections to both structures are likely to be affected similarly by the toxin. It therefore remains unclear whether the QA-lesioned striatum models the striatum of early or late HD. Because in both cases striatal projections to GP would be affected, however, the QA lesion can be used to test the hypothesis that lesion of the GP can ameliorate behavioral deficits induced by damage to these projections.

We assessed the potentially ameliorating effects of three types of lesion to the GP, namely, a bilateral excitotoxic lesion carried out simultaneously with (Experiment 1) or 1 month after the striatal lesion (Experiment 2), and a unilateral temporary inactivation induced by intrapallidal injection of the $GABA_A$ agonist muscimol (Experiment 3). Muscimol was used because it has been shown to be a reliable agent for temporarily inactivating several brain structures including the amygdala[53,54] and the hippocampus[55–57] in rats, and the globus pallidus in primates.[58,59]

MATERIALS AND METHODS

Materials

Male Wistar rats (Tel-Aviv University, Sackler Faculty of Medicine, Israel) approximately 4 months old, weighing 310–400 g before surgery, were housed under reversed cycle lighting (lights on 1900–0700) with food and water freely available. All experimental protocols were carried out according to the guidelines of the Institutional Animal Care and Use Committee of Tel Aviv University.

Surgery

Rats received 3 mg/kg diazepam, and 20 minutes later were anesthetized with Avertin (10.0 ml/kg). Lesions were made by bilateral infusion of QA (Sigma Chemical, Rehovot, Israel; dissolved in 1 M NaOH and diluted with phosphate-buffered saline [PBS] to a final pH of 7.4) through 31-gauge cannulae at a constant rate over 3 minutes, at the following coordinates (according to the atlas of Paxinos and Watson[60]): striatal lesion, 1 μl of 150 (Experiment 1) or 120 (Experiment 2 and 3) nmol/μl QA at 1.0 mm anterior to bregma (A–P), 2.5 mm lateral to the midline (M-L), and 4.3 mm ventral to dura (D-V); GP lesion, 0.3 μl of 120 nmol/μl QA at −0.5 mm A–P, 2.6 mm M-L, and 5.5 mm D-V. For a delayed GP lesion (Experiment 2), bregma was marked using a driller at the time of striatal surgery to be clearly seen a month later during GP lesioning. In the sham operation, rats underwent the same surgical procedure as striatal rats but vehicle was used instead of QA. The cannulae were left in place for additional 5 minutes, to reduce upward diffusion of the solution. For the cannulae implantation, a 23-gauge guide cannula was lowered vertically into the brain and anchored to the skull, with its tip aimed at coordinates −0.5 mm A–P, 2.6 mm M-L, and 3.5 mm D-V. To maintain cannula patency, a stylet (30-gauge wire) was placed in the cannula and removed just before infusion of drugs. Behavioral testing began 5 (Experiment 1 and 2) or 3 (Experiment 3) weeks after surgery.

Injection Procedure

Rats were restrained gently while the stylet was removed, the injection needle (30-gauge) was inserted into the guide cannula to protrude 2 mm below its tip, and 0.5 μl of either vehicle (PBS) or muscimol (0.1 μg/μl) were delivered slowly at a constant rate over 1 minute. The needle was removed slowly 1 minute after the injection and replaced by the stylet. Unoperated and striatal rats that did not receive intrapallidal infusion were restrained for an equivalent period of time. Behavioral testing started 5 minutes after drug injection.

Histology

After completion of behavioral testing, rats were overdosed with Nembutal and perfused intracardially with 100 ml 0.1 M PBS at pH 7.4, followed by 150 ml 4% paraformaldehyde solution in PBS. Their brains were removed from their skulls and postfixed for 2 hours in the same fixative and then stored at 4°C in 30% sucrose in PBS. For histological examination every second 40-μm frozen coronal section was mounted and stained with cresyl violet. Verification of lesion and cannula placement used the atlas of Paxinos and Watson.[60] Histological analysis was carried out blind to the behavioral results.

Apparatus

The position discrimination and reversal task was conducted in a water T-maze (width, 15.5 cm; height of walls above the water, 11 cm; length of stem, 70 cm; length of cross piece, 121 cm). Two guillotine doors were located 1 cm from the beginning of each of the arms. A hidden transparent plastic platform (15.5 × 15.5 cm) was located 1 cm below the water at the end of one of the arms.

Procedure

Initial Position Discrimination.

On Day 1, each rat was trained to swim to the platform, which was located consistently in one of the arms (left and right sides counterbalanced within animals and within groups), until it reached a criterion of 5 consecutive correct trials. At the start of each trial, the rat was placed in the starting box, facing the wall opposite the cross piece, and allowed to swim and choose between the two arms. Once it had entered an arm, the guillotine door blocking that arm was lowered preventing the rat from retracing. If the rat chose the correct arm it was allowed to remain on the platform for 5 seconds after which it was removed from the maze to a holding cage for the 10-second intertrial interval. If the wrong arm was chosen, the rat was confined to the arm for approximately 5 seconds and then removed from the maze to a holding cage for the duration of the intertrial interval. A rat that did not enter an arm within 100 seconds in 4 consecutive trials was excluded from the experiment.

Position Discrimination and Reversal.

In Experiments 1 and 2, in which the effects of a permanent GP lesion were assessed, rats underwent 4 days of position discrimination and reversal (Days 2–5). In Experiment 3, in which the effects of a temporary GP lesion were assessed, rats were given 1 day of position discrimination and reversal (Day 2). On each day, each rat was first retrained until criterion on the position discrimination on which it was trained last on the previous day (i.e., on Day 2 rats were retrained on the initial discrimination, whereas on Days 3–5 they were retrained on the reversal of the previous day). The rat was then trained until criterion on the reversal of this discrimination, i.e., the platform was located in the opposite arm. Other than that, training continued exactly as in Day 1. The arm chosen on each trial was recorded by the experimenter (who was not blind to the lesion the rats received). In Experiments 1 and 2, the number of trials to reach criterion on the 5 discriminations (Days 1–5) and on the 4 reversals (Days 2–5) were calculated for each rat. In Experiment 3, the number of trials to reach criterion on the discrimination and the reversal of Day 2 were calculated for each rat. The results were analyzed using an analysis of variance (ANOVA) with a main factor of lesion and a repeated measurements factor of stage (discrimination, reversal) on the mean number of trials to criterion per stage.

RESULTS

Anatomical

The striatal lesions obtained in the three experiments were very similar, except that in Experiment 1 (values in brackets below) they tended to be somewhat larger than in Experiments 2 and 3. In most animals, the striatal lesions extended from 1.7 (1.7) mm anterior to bregma to 1.3 (1.5) mm posterior to bregma (A–P), from 1.8 (1.5) mm to 4.7 (4.0) mm lateral to the midline (M-L), and from 3.0 (3.3) to 7.2 (7.4) mm ventral from dura (D-V). Maximal damage was between 1.3 to −0.4 (1.4 to −0.8) mm A–P, 2.1 to 4.1 (1.9 to 3.9) mm M-L, and 3.6 to 6.4 (3.6 to 6.7) mm D-V (Fig. 1A, 2B). The pallidal lesions obtained in both experiments were also similar. In most animals, the lesions extended from −0.26 to −1.6 mm A–P, from 1.5 to 4.5 mm M-L, and from 4.8 to 7.7 mm D-V. Maximal damage was between −0.3 to −1.3 mm A–P, 1.9 to 3.9 mm M-L, and 5 to 7 mm D-V (Fig. 1B, 2C). In all the rats in the intra-pallidal infusion experiment, cannulae tips were located in the GP (Fig. 2D).

Behavioral

Experiment 1: Effects of a GP Lesion Carried Out Simultaneously With the Striatal Lesion.

Forty-nine rats were allocated randomly to the 4 groups (striatal, pallidal, combined, and sham). Three rats (two striatal, one combined) that did not enter an arm within 100 sec in 4 consecutive trials were excluded from the experiment. Two rats (one pallidal and one

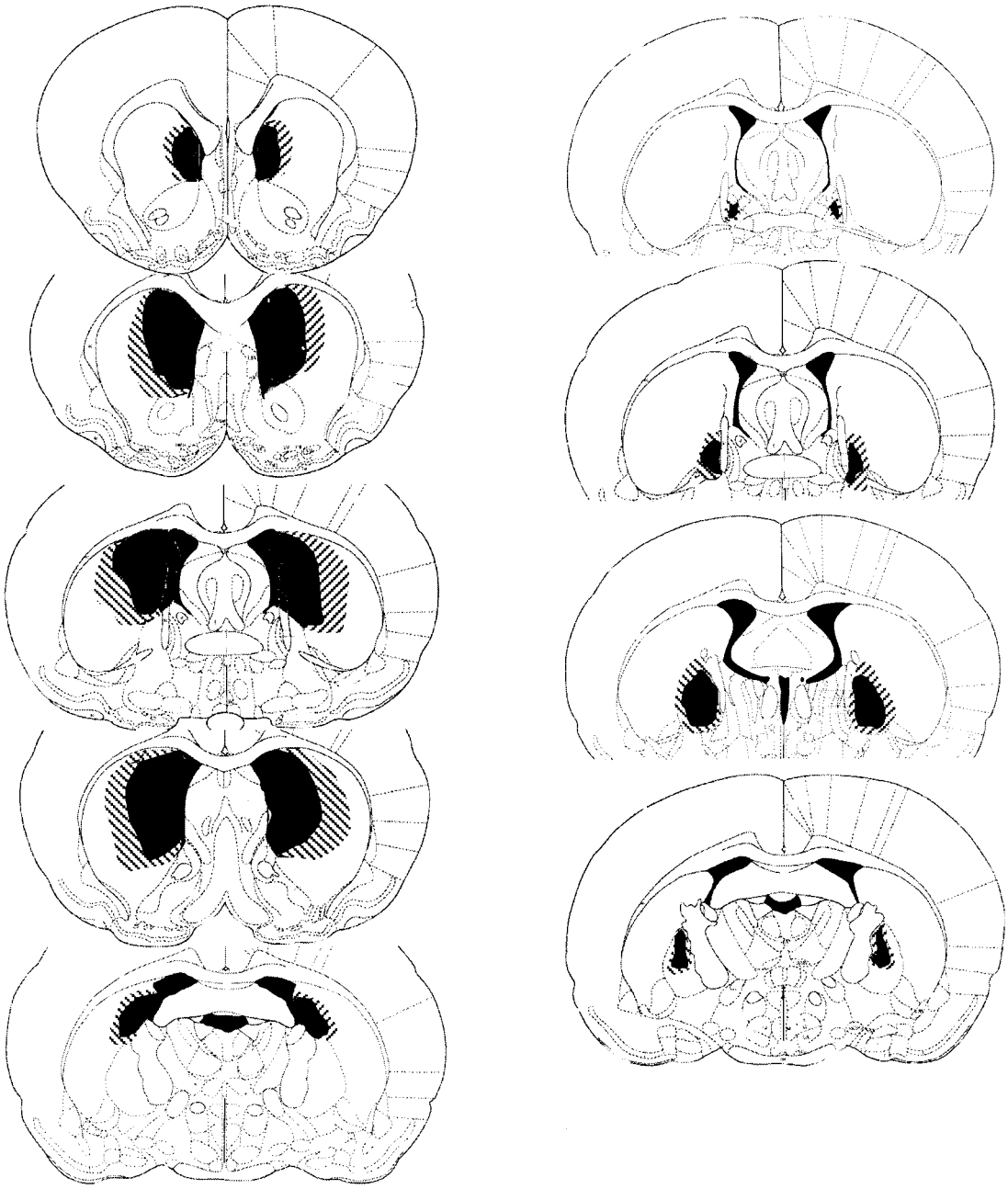

FIG. 1. A series of coronal sections illustrating (**A**) the striatal (Experiments 1–3), and (**B**) the pallidal (Experiments 1 and 2) lesions in successive brain sections representing the minimal (black) and the maximal (hatched) extent of the damage, in common for all rats in the group.

combined), in which the pallidal lesion caused damage to the internal capsule, were excluded from the final analysis. Thus, the final analysis included 12 striatal, 9 pallidal, 12 combined, and 11 sham rats.

Figure 3 presents the mean and the standard error of the mean (SEM) number of trials to criterion on the discriminations (Days 1–5) and reversals (Days 2–5) of the sham, striatal, pallidal, and combined groups. As can

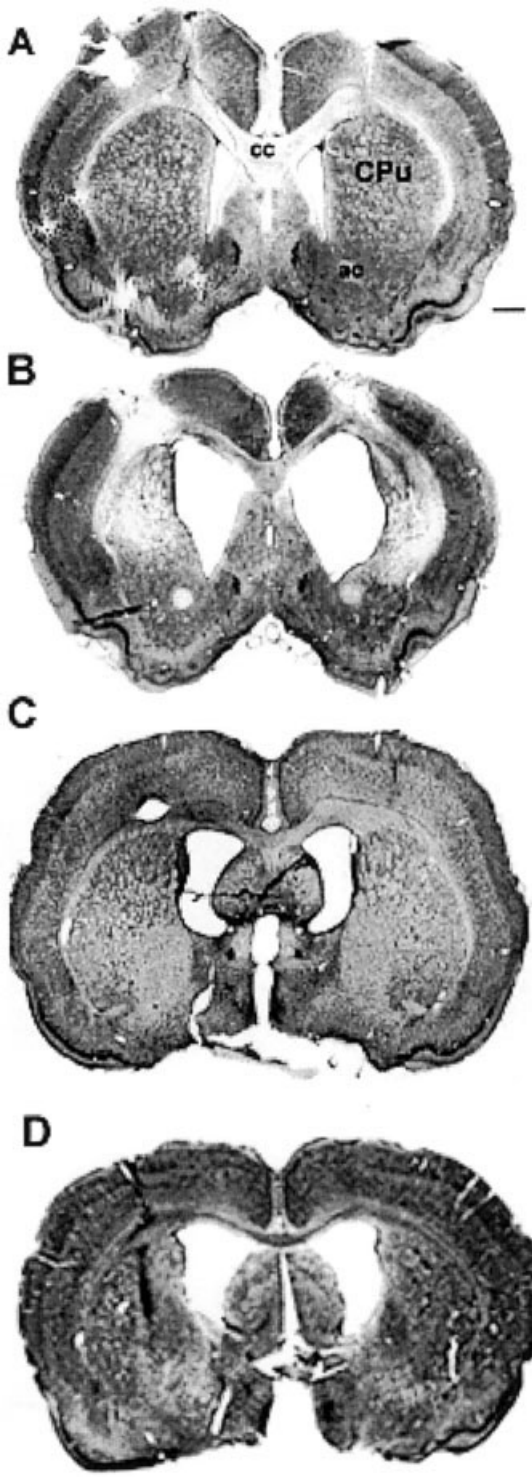

FIG. 2. A photomicrograph of (**A**) the striatum of a sham-operated rat, (**B**) a representative striatal lesion (Experiments 1–3), (**C**) a representative pallidal lesion (Experiments 1 and 2), and (**D**) a representative cannula placement in the GP (Experiment 3).

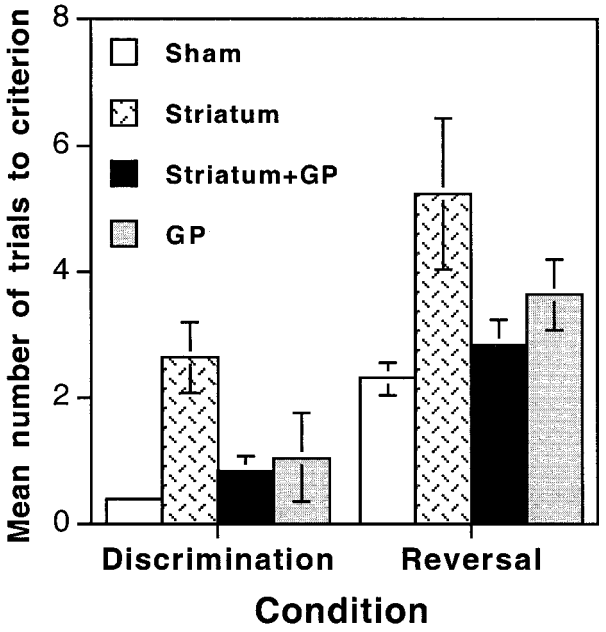

FIG. 3. Mean and the standard error of the mean number of trials to reach criterion on the discriminations (Days 1–5) and reversals (Days 2–5) of the sham, striatal, pallidal, and simultaneously combined (striatal and pallidal) groups (Experiment 1).

be seen, rats sustaining a bilateral striatal lesion required more trials to reach criterion on the discriminations and on the reversals compared with rats sustaining a sham lesion. This deficit was not seen in rats that sustained a simultaneous bilateral pallidal lesion in addition to the striatal lesion, so that these rats performed similarly to sham rats. Pallidal lesion on its own had no effect on either the discriminations or the reversals. An ANOVA with a main factor of lesion and a repeated measurements factor of stage yielded significant effects of lesion $F(3,40) = 6.40$, $P < 0.01$ and stage $F(1,40) = 107.22$, $P < 0.0001$.

Experiment 2: Effects of a GP Lesion Carried Out 1 Month After the Striatal Lesion.

Twenty-seven rats were allocated randomly to 3 groups (striatal, delayed–combined, and sham; pallidal lesion alone was not tested because in Experiment 1 rats with such a lesion did not differ from sham rats). One rat, in which the striatal damage was minimal, was excluded from the final analysis. Thus, the final analysis included 8 striatal, 7 delayed–combined and 11 sham rats.

Figure 4 presents the mean number and SEM of trials to criterion on the discriminations (Days 1–5) and reversals (Days 2–5) of the sham, striatal, and delayed–combined groups. As can be seen, striatal rats needed more trials to reach criterion on the discriminations and rever-

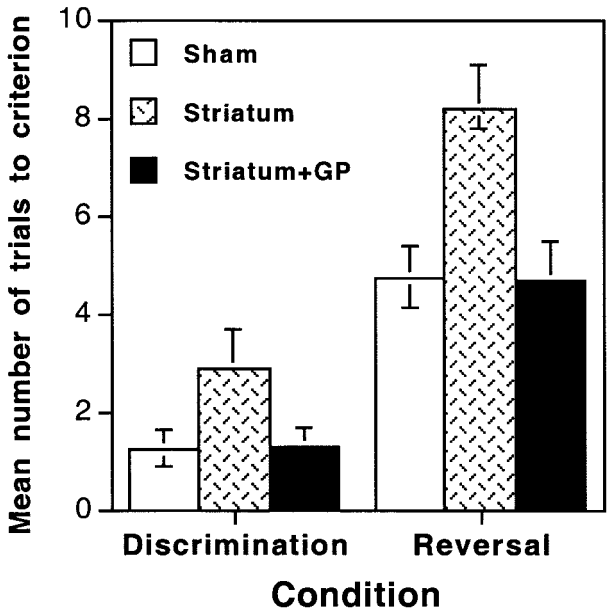

FIG. 4. Mean and SEM number of trials to reach criterion on the discriminations (Days 1–5) and reversals (Days 2–5) of the sham, striatal, and delayed combined (striatal and pallidal) groups (Experiment 2).

sals compared with sham rats, whereas rats sustaining in addition a delayed lesion to the GP performed similarly to sham rats. An ANOVA with a main factor of lesion and a repeated measurements factor of stage yielded significant effects of lesion $F(2,23) = 6.84$, $P < 0.01$, and stage $F(1,23) = 88.44$, $P2 < 0.0001$, as well as a significant lesion × stage interaction $F(2,22) = 4.56$, $P < 0.05$.

Experiment 3: Effects of Temporary Inactivation of the GP.

Thirty-one rats were allocated randomly to the 4 groups (unoperated, striatal, striatal and intrapallidal infusion of PBS, striatal and intrapallidal infusion of muscimol). One rat with an infection in the cannula region and very extensive damage to tissue around the cannula track was excluded from the final analysis. Thus, the final analysis included 6 unoperated, 10 striatal, 6 striatal + PBS-in-GP, and 8 striatal + muscimol-in-GP rats.

Figure 5 presents the mean and SEM number of trials to criterion on the discrimination and reversal of the unoperated, striatal, striatal + PBS-in-GP, and striatal + muscimol-in-GP groups. As found in the first two experiments, rats with striatal lesion were impaired in both the discrimination and in the reversal compared with unoperated controls. No such impairment was exhibited by striatal lesioned rats that received intra-pallidal infusion of muscimol, whereas striatal rats that received intra-pallidal infusion of PBS were as impaired as striatal rats. An ANOVA with a main factor of lesion and a repeated measurements factor of stage yielded a nearly significant effect of lesion $F(3,26) = 2.57$, $P\ 2 = 0.076$, and a significant effect of stage $F(1,26) = 47.30$, $P < 0.0001$.

DISCUSSION

Rats sustaining a QA lesion to the striatum were impaired severely in a position discrimination and reversal task, consistent with previous reports in the literature[43–47] (but see Oliveira and colleagues[61]). The novel finding of this study is that the behavioral deficit induced by the striatal lesion was reversed effectively by a lesion to the GP. This ameliorating effect was obtained after a bilateral excitotoxic GP lesion carried out simultaneously or 1 month after the striatal lesion, as well as after a temporary unilateral GP inactivation. Thus, whereas striatal rats showed poorer discrimination and reversal learning compared with sham rats, rats sustaining a combined striatal and pallidal lesion (simultaneous, delayed, or temporary) did not differ from sham rats. Importantly, the pallidal lesion on its own did not impair rats' performance in the task. This implies that the reversal of the striatal lesion-induced deficit by the pallidal lesion cannot be interpreted as reflecting a simple additive effect of the two lesions.

We have shown previously that a bilateral electrolytic lesion to the GP ameliorates the deleterious effects of a

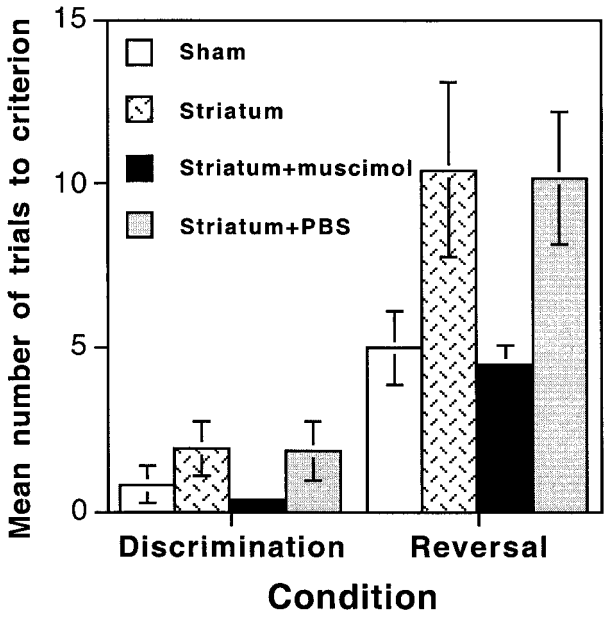

FIG. 5. Mean and SEM number of trials to reach criterion on the discrimination and reversal of Day 2 of the sham, striatal, striatal and intra-pallidal PBS, striatal and intra-pallidal muscimol groups (Experiment 3).

QA striatal lesion on several behavioral measures.[42] The present results extend these findings and indicate that the ameliorating effect of the pallidal lesion is due to damage to cell bodies of the GP rather than to fibers of passage. Moreover, the finding that the striatal lesion-induced behavioral deficit was reversed by a permanent as well as by a temporary GP lesion sustained at a considerable time interval after the striatal lesion, indicates that the effect of the GP lesion was not due to its effects at the time of damage to the striatum, but rather to GP lesion-induced alterations of some long-term effects of the striatal lesion.

Our hypothesis was derived from the leading model of the pathological mechanism underlying HD, which postulates that selective degeneration of striatal projections to the GPe (GP in rats) leads to overactivity of the GPe projections to the subthalamic nucleus. Although the effectiveness of the GP lesion demonstrated here may provide partial support for this possibility, there is only limited evidence that QA lesions in rats lead to preferential damage to striatal projections to GP. Likewise, whereas according to the above model of HD, the present results may be interpreted as reflecting disruption of GP projections to the subthalamic nucleus, other alterations in basal ganglia circuitry that could result from a pallidal lesion could have contributed to the observed ameliorating effect. Specifically, the pallidal lesion could have disrupted pallidal projections to the entopeduncular nucleus, substantia nigra, and striatum[62–64] as well as to the reticular nucleus of the thalamus,[65] and disruption of each of these projections can disrupt the functioning of basal ganglia-thalamocortical circuitry. In addition, because in rats many of the striato-entopeduncular and striato-nigral projections are collaterals of striato-pallidal projections,[52] disruption of the latter could have led to disruption of the former, again leading to alterations in the functioning of basal ganglia circuitry. It therefore remains unclear at present what mechanisms underpin the capacity of the GP lesion to reverse the behavioral deficit of the striatal lesion.

Whatever the mechanisms underlying the beneficial effects of GP lesion, the finding that delayed damage to the GP can reverse a behavioral deficit resulting from damage to the striatum, strongly supports the view that the components of an anatomically defined basal ganglia-thalamocortical circuit act in tandem to produce behavioral output. To date, most of the support for the notion that disrupted functioning of basal ganglia circuitry after damage to a station of the circuit can be counteracted by manipulating other stations within the circuit, has come from the demonstration that in Parkinson's disease patients and in parkinsonian non-human primates, a lesion to the internal segment of the GP or to the subthalamic nucleus alleviates symptoms resulting from degeneration of dopaminergic neurons.[41,66] The present findings further reinforce this notion, and provide the first demonstration that an excitotoxic lesion to the pallidal component can ameliorate behavioral deficits resulting from a lesion to the striatal component of the basal ganglia.

Although our findings do not reveal the nature of the dysfunction in basal ganglia circuitry after the striatal lesion or the changes in this circuitry after the combined striatal and pallidal lesion, they may provide a basis for developing a new treatment for HD. Thus, it may be suggested that lesion of the GPe could ameliorate some of HD symptoms, similarly to the ameliorating effects of lesions to the internal segment of the GP in Parkinson's disease.[66] In this context, the demonstration in rats that GP lesion or inactivation can ameliorate the deleterious behavioral effects of a pre-existing striatal lesion is of particular importance, because in HD patients, the striatal lesion is likely to be present at the time of GP manipulation. Our finding that an ameliorating effect could also be obtained with a unilateral inactivation of GP is particularly encouraging because it suggests that a relatively safe and limited manipulation could be efficacious.

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