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Effects of Dorsal Noradrenergic Bundle Lesions on Recovery After Sensorimotor Cortex Injury

LARRY B. GOLDSTEIN*† AND SARAH BULLMAN†

*Department of Medicine (Division of Neurology), Center for Health Policy Research and Education, Duke University, Durham, NC 27710
†Department of Veterans Affairs Medical Center, Durham, NC 27705

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GOLDSTEIN, L. B. AND S. BULLMAN. *Effects of dorsal noradrenergic bundle lesions on recovery after sensorimotor cortex injury.* PHARMACOL BIOCHEM BEHAV **58**(4) 1151–1157, 1997.—Several lines of evidence suggest that the recovery of the ability of rats to traverse a narrow beam after unilateral injury to the sensorimotor cortex is noradrenergically mediated. We tested the hypotheses that the influence of norepinephrine on beam-walking recovery occurs, at least partially, through effects in the contralateral and/or ipsilateral cerebral cortex. Rats had either a selective left or right 6-hydroxydopamine lesion or sham lesion of the dorsal noradrenergic bundle (DNB) 2 weeks before suction-ablation or sham injury of the right sensorimotor cortex. The rats' abilities to perform the beam-walking task were measured over the 10 days following cortex surgery. DNB lesions did not affect the initial severity of the beam-walking deficit and had no effect on the performance of the task in rats with sham cortex injuries. Lesions of the contralateral but not ipsilateral DNB significantly impaired recovery. Further, in cortically lesioned rats with contralateral DNB lesions, norepinephrine content in the cerebral cortex opposite to the sensorimotor cortex lesion was significantly correlated with recovery. These data suggest that the effect of norepinephrine on recovery of beam-walking ability may be partially exerted in the cerebral cortex contralateral to the injury. © 1997 Elsevier Science Inc.

Cortex Recovery Motor function Dorsal noradrenergic bundle Norepinephrine Stroke Trauma Rat

RECENT clinical studies in human stroke patients suggest that motor recovery after hemispheric stroke may be enhanced by the administration of *d*-amphetamine (14,53). However, the mechanism of this amphetamine effect is uncertain. The recovery of the ability to traverse a narrow elevated beam has been used to measure motor recovery after a unilateral sensorimotor cortex injury in the rat and provides an animal model of recovery after injury to the cerebral cortex (18,25). Several lines of evidence now suggest that this recovery is, at least in part, noradrenergically mediated. Pharmacological experiments have shown that centrally acting α_2-adrenergic receptor antagonists increase the rate of recovery of beam-walking performance (20,21,23,31,50) whereas the administration of an α_2-adrenergic receptor agonist (21,28) is harmful. Although selective α_1-adrenergic receptor agonists have no effect on beam-walking recovery (21), selective α_1-adrenergic receptor antagonists are detrimental (21,50). Furthermore, pretreatment with a neurotoxin that depletes central norepinephrine (DSP-4) impairs (3,26) and intraventricular infusions of norepinephrine facilitate (4) beam-walking recovery after a sensorimotor cortex lesion.

The results of these pharmacological studies are supported by experiments in which selective lesions were placed in the pontine nucleus locus coeruleus (LC), the major source of central noradrenergic projection fibers (42,52). Bilateral LC lesions 2 weeks prior to a right sensorimotor cortex lesion resulted in poorer recoveries when compared to rats that had sham LC lesions (7,22). Unilateral LC lesions, either ipsilateral or contralateral to a sensorimotor cortex lesion, also affect beam-walking recovery (7,22).

Because LC neurons are highly collateralized (13,39,44), LC lesioning experiments cannot be used to determine whether noradrenergic regulation of beam-walking recovery after unilateral sensorimotor cortex injury is exerted at the level of the ipsilateral or contralateral cerebral cortex, the ipsilateral or contralateral cerebellum, or other brain structures. However, a major role for the cerebellum has been hypothesized (5–9,17). Supporting this hypothesis, cerebellar infusions

Requests for reprints should be addressed to Larry B. Goldstein, M.D., Box 3651, Duke University Medical Center, Durham, NC 27710.

of norepinephrine were found to facilitate recovery (6,9). However, these experiments do not exclude a possible role of the contralateral or ipsilateral cerebral hemispheres in noradrenergically mediated recovery. LC neurons project to the cerebral cortex and subcortical structures via the dorsal noradrenergic bundle (DNB), which can be selectively lesioned by local infusion of the neurotoxin 6-hydroxydopamine (6-OHDA) (16,43). We studied the effects on beam-walking recovery of selective lesions of noradrenergic projection fibers to the cerebral cortex contralateral and ipsilateral to a subsequent unilateral sensorimotor cortex lesion. If the effects of norepinephrine are partially mediated in these brain regions, then selective lesions of these noradrenergic projection fibers would be expected to impair recovery.

METHOD

Animals

Male Sprague–Dawley rats (n = 39) weighing 250–350 g were obtained from Charles River Breeding Laboratories, Inc. (Raleigh, NC) and housed in a vivarium with a 12 L:12 D cycle and controlled temperature and humidity. Food (Purina Rat Chow) and water were provided ad lib.

Apparatus

The behavioral testing apparatus consisted of a goal box located at one end of a 2.5 × 122 cm elevated wooden beam. A switch-activated source of bright light and white noise were located at the start-end of the beam and served as avoidance/activating stimuli (25).

Surgery and Behavioral Procedures

Rats were acclimated to the housing facility for 1 week prior to the start of the experiments. Groups of rats then underwent either unilateral left (Experiment 1) or unilateral right (Experiment 2) selective lesions of the DNB by local infusion of 6-OHDA or the corresponding sham DNB lesions. The rats were first anesthetized with pentobarbital sodium (50 mg/kg, IP; additional doses were given as necessary to maintain anesthesia) and then placed in a small animal stereotaxic frame (David Kopf Instruments). To block monoamine oxidase, pargyline HCl (50 mg/kg, IP) was administered 10–30 min prior to local administration of 8 μg of 6-OHDA base dissolved in 3 μl of 0.9% NaCl, 0.1% ascorbic acid, pH 5.5. The 6-OHDA solution was infused over 5–10 min for DNB lesions; vehicle was infused without 6-OHDA in sham-operates (stereotaxic coordinates from the interaural line; AP −9 mm, X +/−1 mm, Y −6 mm). The rats were then permitted to recover for 10 days. This time period was chosen because depletion of both norepinephrine and dopamine-β-hydroxylase (DBH) activity reach their nadirs approximately 2 weeks after LC lesions (46).

The rats were then trained at the beam-walking task. For each training or testing trial, the rat was placed at the start-end of the beam opposite to the goal box. If the animal did not begin to traverse the beam after ten seconds, the light and noise stimuli were activated and continued until the rat's nose entered the goal box or for a total of 80 s, at which time the trial was terminated. On the first day of training, each rat was given a series of three approximate trials. Motor performance was rated on a seven-point scale as described in the legend for Fig. 1. Subsequent training consisted of one trial on the beam each day until the rat achieved the maximum possible score.

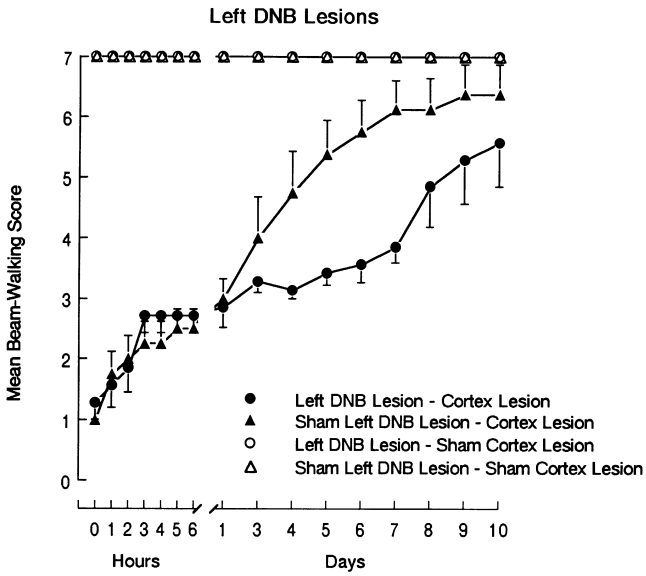

FIG. 1. Effects of prior left DNB lesions on beam-walking scores after a subsequent right sensorimotor cortex lesion. Time in "Hours" and "Days" refers to time after the first postoperative beam-walking trial. The first trial, "0" hours, was given 24 h following cortex lesion or sham cortex surgery (2 weeks after DNB or sham DNB lesion). The symbols represent the mean (±SEM) beam-walking scores for each trial. Motor performance was rated on a seven-point scale as previously described (18,25,29): 1, the rat is unable to place the affected hindpaw on the horizontal surface of the beam; 2, the rat places the affected hindpaw on the horizontal surface of the beam and maintains balance for at least 5 s; 3, the rat traverses the beam while dragging the affected hindpaw; 4, the rat traverses the beam and at least once places the affected hindpaw on the horizontal surface of the beam; 5, the rat crosses the beam and places the affected hindlimb on the horizontal surface of the beam to aid less than half its steps; 6, the rat uses the affected hindpaw to aid more than half its steps and; 7, the rat traverses the beam with no more than two footslips.

Following training (2 weeks after DNB or sham DNB lesions), rats were anesthetized for cortex lesion surgery (pentobarbital sodium 50 mg/kg, IP; additional doses were administered as necessary to maintain anesthesia). The rats then underwent a right-sided craniotomy extending from 2 mm rostral to 2 mm caudal to the coronal suture and from 1 mm lateral of the sagittal suture to the temporal ridge. The cortex underlying the craniotomy site was removed by gentle suction through a fine glass Pasteur pipette until the underlying white matter was visualized. We have previously found that this method results in lesions of uniform size and depth (29). Control rats underwent the identical surgical procedure, but craniotomy was not performed. Thus, there were four groups of rats in Experiment 1 (left DNB lesion—Cortex lesion, n = 7; left sham DNB lesion—cortex lesion, n = 8; left DNB lesion—sham cortex lesion, n = 3; and left sham DNB lesion—sham cortex lesion, n = 2) and four groups of rats in Experiment 2 (right DNB lesion—cortex lesion, n = 7; right sham DNB lesion—cortex lesion, n = 7; right DNB lesion—sham cortex lesion, n = 2; and right sham DNB lesion—sham cortex lesion, n = 3).

Beginning 24 h after cortex lesion surgery, the rats were tested on the beam at 1-h intervals for 6 h and then over the subsequent 10 days (Fig. 1; "Hours" and "Days" refers to time after the first post-cortex lesion or sham cortex lesion beam-

walking trial). This testing schedule was selected to facilitate comparisons with our previous work (18,27,29). The rats were not stimulated in any way during a trial other than with light-noise activation as described above.

Lesion Extent

The day following completion of the behavioral measurements, rats were anesthetized with pentobarbital sodium, sacrificed by decapitation, and the brains were dissected and immediately placed on ice. Lesion sizes (areas) and maximum medial extents (closest approximation of the lesion to the interhemispheric fissure) were later measured from the digitized images (24). The right and left cerebral cortex and the right and left cerebellar hemispheres were dissected and stored at −70°C for later determination of norepinephrine content. The brainstem was dissected and immersed in 10% formalin for 6–8 h at 4°C and stored in phosphate-buffered saline (PBS, pH 7.4) at 4°C for histology as described below. Thus, it was possible to measure the extent of the sensorimotor cortex lesion, determine the norepinephrine content in the cerebral cortices and cerebellar hemispheres, and obtain histological assessments of the LC in each rat.

Histology

For histology, the stored brainstem blocks were cryoprotected by immersion in a solution of 25% sucrose in PBS buffer at 4°C and serial 16 μm coronal sections were then cut on a cryostat. Alternate sections were stained with cresyl violet and for DBH immunocytochemistry. For cresyl violet stain, the tissue was mounted, immersed in cresyl violet stain, rinsed in water, and then dehydrated by passing through graded ethanol and xylene. For DBH immunostaining (34), the tissue was first fixed in 50% methanol, 1% H_2O_2 in PBS for 10 min. Sections were washed in PBS × 3.5 min and then incubated for 30 min in a solution containing 2% normal goat serum, 2 mg/ml BSA, 0.02% azyde in PBS. Incubation with the primary antibody was carried out for 3–5 days at 4°C or overnight at room temperature. Control sections were run without inclusion of the primary antibody. The tissue was then washed in PBS and incubated for 4–6 h with the secondary antibody (goat biotinylated antirabbit IgG), again washed in PBS, and then incubated with ABC elite reagent for 30 min at room temperature. The tissue was then washed in PBS and Tris buffer and visualized by incubating in 1 mg/ml diaminobenzidine (DAB), 1 μl H_2O_2 2ml Tris for 2 min.

In preliminary experiments, we found that the total of counts obtained through six preselected levels of the LC (−1.8 to −2.8 mm from bregma at 0.2 mm intervals) was highly correlated with the total LC cell count. At each preselected level, only DBH-positive LC neurons with a defined nucleus are counted. "Countable" neurons were then recorded with camera lucida drawings of the LC from each of the selected sections.

Neurochemistry

The norepinephrine contents of the frozen right and left cerebral corticies and right and left cerebellar hemispheres were determined by high-pressure liquid chromatography with electrochemical detection (HPLC-ED, Bioanalytic System, West Lafayette, IN) according to methods previously described (26). Briefly, the samples were weighed and homogenized in 10 vol of ice-cold buffer [0.1 M monobasic sodium phosphate, 1 mM disodium ethylenediamine tetra-acetate (EDTA) and 1 mM sodium octane sulfonic acid, adjusted to pH 4.0 with a saturated citric acid solution, then mixed with acetonitrile (9:1 v/v)], which contained the internal standard, 3,4-dihydroxybenzylamine (DHBA). Following centrifugation (15,000 × *g* for 45 min), the pellets were discarded and the supernatants combined with 1 ml of 3 M Tris buffer (pH 8.6) containing 2% EDTA and activated alumina. The samples were then vigorously shaken. The alumina was allowed to settle to the bottom of the tube and then washed once with Tris buffer and twice with distilled water. Norepinephrine was eluted from the alumina with homogenization buffer. The samples were then passed through a reversed phase HPLC column at a flow rate of 1.5 ml/min and the current measured using an applied voltage of 0.70 volts. All samples were corrected for the recovery of DHBA.

Statistical Analysis

Because an ordinal scale was employed to measure beam-walking recovery, the trapezoidal rule (2) was used to calculate the areas under the curves formed when each rat's beam-walking scores were plotted against time (i.e., area under the time–effect curve) and provided a summary measure of each rat's recovery (25). The resulting summary data were analyzed by ANOVA. The Fisher LSD test was subsequently applied to determine the significance of differences between groups. For ordinal data, the Kruskal–Wallis test was used to determine the significance of differences among more than two groups, and the Dunn Procedure (45) was used for post hoc pairwise comparisons. Cortex lesion size data were analyzed by unpaired *t*-tests for two group comparisons. Paired *t*-tests were used to compare LC cell counts between the 6-OHDA lesioned and sham-lesioned sides in rats with unilateral DNB lesions. The norepinephrine content in the cerebral cortices were compared with two-way (DNB lesion vs. sham DNB lesion and cortex lesion vs. sham cortex lesion), repeated measures (left vs. right hemisphere) ANOVA (data for sham DNB- sham cortex-lesioned rats were pooled). The Fisher LSD test was used for post hoc pairwise comparisons. The norepinephrine content of the cerebellar hemispheres ipsilateral and contralateral to the side of the DNB or sham DNB lesions were compared with paired *t*-tests.

RESULTS

DNB lesions did not affect the abilities of rats to learn the beam-walking task. Regardless of treatment group, all rats trained to criterion over 2–3 days.

Experiment 1

The effects of unilateral left DNB lesions on beam-walking recovery after a subsequent right sensorimotor cortex lesion are given in Fig. 1. Cortex lesions significantly impaired beam-walking ability on the first postoperative trial (hour "0," Kruskal–Wallis $H = 16.9$, $p < 0.001$). There was no effect of prior DNB lesions on beam-walking performance in rats with sham cortex lesions (Fig. 1, Hour "0," left DNB lesion—sham cortex lesion vs. sham DNB lesion—sham cortex lesion; Dunn procedure, $p > 0.05$) and no significant difference in initial beam-walking scores between cortex-lesioned rats with or without prior DNB lesions (Fig. 1, Hour "0," left DNB lesion—cortex lesion vs. sham DNB lesion—cortex lesion; Dunn procedure, $p > 0.05$). However, cortex-lesioned rats with prior left DNB lesions had significantly impaired recoveries (areas under the time–effect curves) compared to cortex-le-

TABLE 1
EXTENT OF CORTEX LESION

Group	Area (mm^2)	p	Medial Extent (mm)	p
Left DNB Lesion	32.1 ± 6.4	0.69	0.79 ± 0.3	0.40
Sham Left DNB Lesion	36.0 ± 7.0		1.32 ± 0.5	
Right DNB Lesion	33.8 ± 3.0	0.87	0.50 ± 0.3	0.75
Sham Right DNB Lesion	32.9 ± 4.7		0.66 ± 0.4	

sioned rats with sham DNB lesions [ANOVA, $F(3, 16) = 11.6$, $p < 0.001$; left DNB lesion—cortex lesion vs. sham DNB lesion—cortex lesion, Fisher LSD, $p < 0.02$].

Table 1 gives the mean extents of the cortex lesions between cortex-lesioned rats with and without left DNB lesions. There were no significant difference between the groups. Table 2 gives mean LC cell counts by experimental group. There were no significant differences in cell counts between the LCs ipsilateral and contralateral to the DNB lesion in any of the groups (because of tissue damage, not all preselected sections were available for every rat). Figure 2 (top panel) gives the norepinephrine contents of the cerebral cortex in each group. Two-way repeated measures ANOVA indicated a significant effect of DNB lesion [ANOVA, $F(1, 19) = 9.1$, $p = 0.001$], a significant interaction between DNB lesion and hemisphere [ANOVA, $F(1, 19) = 14.3$, $p = 0.001$], but no effect of cortex lesion. The difference between left and right hemispheres is significant in both groups of rats with DNB lesions (Fisher LSD, $p < 0.005$, respectively). There was no effect of DNB lesions on NE content in the cerebellum (NE left cerebellum 168 ± 28, right cerebellum 162 ± 25 pg/mg, $p = 0.082$). Figure 3 gives the correlations between norepinephrine content in the left (top left panel) and right (top right panel) cerebral cortex and beam-walking recovery (area under the time–effect curve) for rats with left DNB or sham DNB lesions and cortex lesions. There was a significant correlation between norepinephrine content in the left but not right cerebral cortex and beam-walking recovery.

Experiment 2

The effects of unilateral right DNB lesions on beam-walking recovery after a subsequent right sensorimotor cortex lesion are given in Fig. 4. Cortex lesions significantly impaired beam-walking ability on the first postoperative trial (Hour "0," Kruskal–Wallis $H = 12.5$; $p < 0.001$). There was no effect

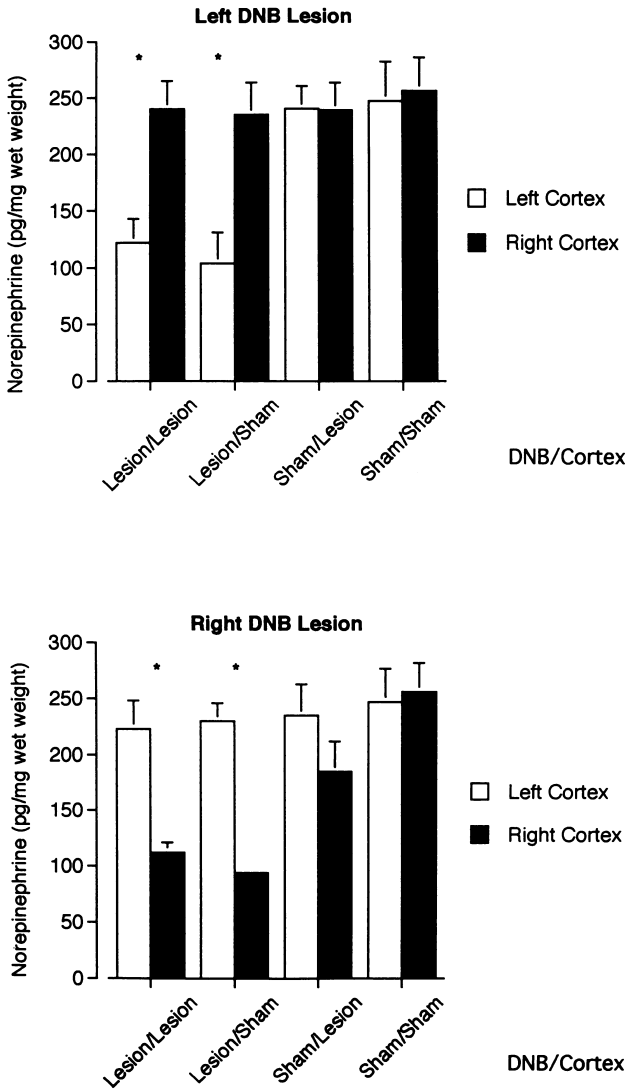

FIG. 2. Mean norepinephrine content in the left and right cerebral cortex in rats with a unilateral right sensorimotor cortex lesion or sham cortex lesion and a left 6-OHDA DNB lesion or sham DNB lesion (top panel) or a right 6-OHDA DNB or sham DNB lesion (bottom panel). *Post hoc Fisher LSD tests indicates that the differences between the left and right hemispheres in rats with DNB lesions are significant ($p < 0.005$).

TABLE 2
LC CELL COUNTS

DNB	Cortex	Left	Right	p
Left DNB				
Lesion	Lesion	258 ± 54	235 ± 43	0.30
Sham	Lesion	231 ± 20	223 ± 16	0.41
Lesion	Sham	191 ± 13	156 ± 18	0.10
Sham	Sham	284 ± 103	269 ± 118	0.50
Right DNB				
Lesion	Lesion	350 ± 47	339 ± 39	0.54
Sham	Lesion	162 ± 25	159 ± 25	0.66
Lesion	Sham	222 ± 81	204 ± 76	0.17
Sham	Sham	254 ± 73	236 ± 59	0.34

of prior right DNB lesions on beam-walking performance in rats with sham cortex lesions (Fig. 1, Hour "0," right DNB lesion—sham cortex lesion vs. sham DNB lesion—sham cortex lesion; Dunn procedure, $p > 0.05$) and no significant difference in initial beam-walking scores between cortex-lesioned rats with or without prior right DNB lesions (Fig. 1, Hour "0," right DNB lesion—cortex lesion vs. sham DNB lesion—cortex lesion; Dunn procedure, $p > 0.05$). There was no effect of prior right DNB lesions on bean walking recovery (areas under the time–effect curves) after a subsequent right sensorimotor cortex lesion [ANOVA, $F(3, 15) = 11.0$, $p < 0.001$; right DNB lesion—cortex lesion vs. sham DNB lesion—cortex lesion, Fisher LSD, $p = 0.8$].

Table 1 gives the mean extents of the cortex lesions between cortex-lesioned rats with and without left DNB lesions.

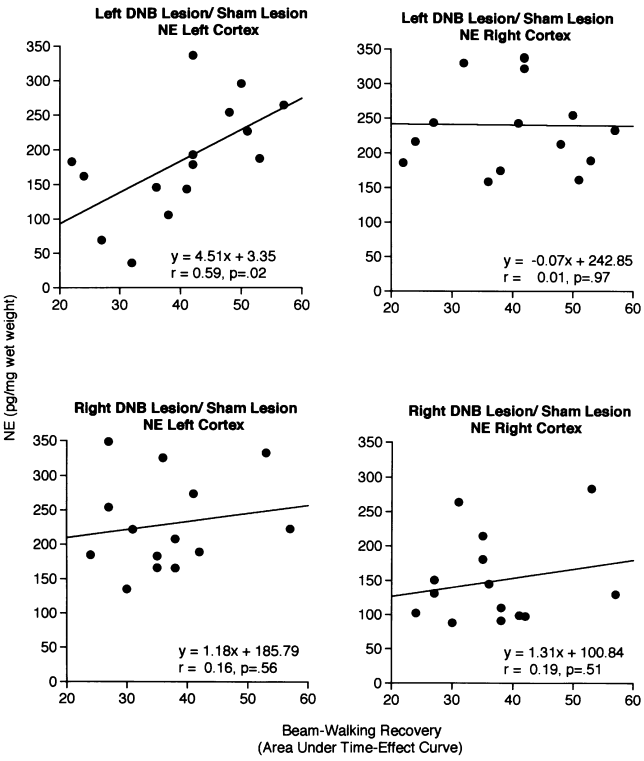

FIG. 3. Correlations between beam-walking recovery (area under the time–effect curve) in rats with unilateral right sensorimotor cortex lesions and norepinephrine content in the left (top left panel) and right (top right panel) cerebral cortex in rats with left DNB lesions and norepinephrine content in the left (bottom left panel) and right (bottom right panel) cerebral cortex in rats with right DNB lesions. Norepinephrine content in the contralateral but not ipsilateral cerebral cortex in rats with contalateral DNB/sham DNB lesions correlates with the rate of beam-walking recovery (top panels). There was no significant correlation between norepinephrine content in either cerebral hemisphere and beam-walking recovery in rats with ipsilateral DNB/sham DNB lesions (bottom panels).

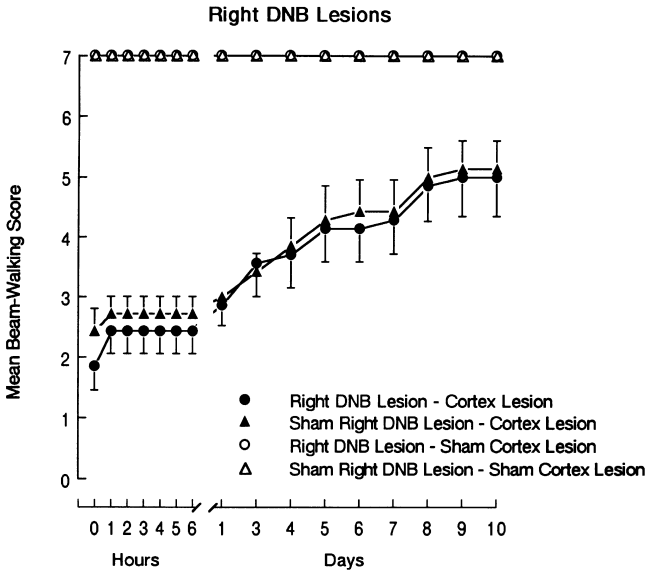

FIG. 4. Effects of prior unilateral right DNB lesion on beam-walking scores after a subsequent right sensorimotor cortex lesion. The first trial, "0" Hours, was given 24 h following cortex lesion or sham cortex surgery (2 weeks after DNB or sham DNB lesion). Time in "Hours" and "Days" refers to time after the first postoperative beam-walking trial. The symbols represent the mean (±SEM) beam-walking scores for each trial. The rating scale is defined in the legend for Fig. 1.

There were no significant difference between the groups. Table 2 gives mean LC cell counts by experimental group. There were no significant differences in cell counts between the LCs ipsilateral and contralateral to the DNB lesion in any of the groups (because of tissue damage, not all preselected sections were available for every rat). Figure 2 (bottom panel) gives the norepinephrine contents of the cerebral cortex in each group. Two-way repeated measures ANOVA indicated a significant effect of DNB lesion [ANOVA, $F(1, 17) = 6.1$, $p = 0.02$], a significant interaction between DNB lesion and hemisphere [ANOVA, $F(1, 17) = 10.0$, $p = 0.006$], but no effect of cortex lesion. The difference between left and right hemispheres is significant in both groups of rats with DNB lesions (Fisher LSD, $p < 0.009$, respectively). There was no effect of DNB lesions on NE content in the cerebellum in rats with DNB lesions (norepinephrine left cerebellum 131 ± 26, right cerebellum 147 ± 35 pg/mg, $p = 0.68$). Figure 3 gives the correlations between norepinephrine content in the left (bottom left panel) and right (bottom right panel) cerebral cortex and beam-walking recovery (area under the time–effect curve) for rats with right DNB or sham DNB lesions and cortex lesions. There was not a significant correlation between norepinephrine content in either cerebral cortex and beam-walking recovery.

DISCUSSION

The main findings of the present experiments are that a prior selective lesion of noradrenergic projection fibers to the cerebral cortex contralateral but not ipsilateral to a subsequent sensorimotor cortex lesion impairs the recovery of locomotor ability as measured with the beam-walking paradigm. Further, the norepinephrine content in the contralateral but not ipsilateral cerebral cortex in rats with contalateral DNB/sham DNB lesions correlates with the rate of beam-walking recovery (Experiment 1, Fig. 3, top panels). There is no significant correlation between norepinephrine content in either cerebral hemisphere and beam-walking recovery in rats with ipsilateral DNB/sham DNB lesions (Experiment 2, Fig. 3, bottom panels). Although these latter results seem paradoxical, a correlation between norepinephrine content in the contralateral cerebral cortex and beam-walking recovery may not have been detectable in rats with ipsilateral DNB/sham DNB lesions because, as expected, norepinephrine content in the contralateral cerebral cortex varied over a relatively narrow range (Fig. 3, bottom left panel). Partial lesions of noradrenergic projection fibers may lead to an increased rate of firing of locus coeruleus neurons (11) and an increase in release of norepinephrine from remaining nerve terminals (1), possibly decreasing the impact of DNB lesions as measured by tissue norepinephrine content. However, there is no reason to suspect a differential effect following left or right-sided DNB lesions. There was no effect of the DNB lesions on ipsilateral compared to contralateral LC cell counts and the effect of the DNB lesions on norepinephrine content was limited to the ip-

silateral cerebral cortex. It should be noted that the absolute recoveries of sham DNB lesioned-cortex lesioned rats differed in the two experiments. Such variability between experiments is not uncommon, and reinforces the need to run groups of rats in parallel rather than sequentially in these types of experiments (25). In each experiment, there were no differences in the extents of the sensorimotor cortex lesions (24,29) and no differences in the initial beam-walking deficit among DNB-lesioned and sham DNB-lesioned rats with cortex lesions that might explain the present results. Taken together, these data suggest that the effect of norepinephrine on beam-walking recovery after a sensorimotor cortex lesion is mediated, at least in part, in the contralateral cerebral cortex. This finding is consistent with our previous experiments that demonstrated bilateral, unilateral left, and unilateral right LC lesions impair beam-walking recovery after a subsequent right sensorimotor cortex lesion (22). Each LC projects to the contralateral as well as the ipsilateral cerebral cortex (13,44). Therefore, a lesion of either LC might influence noradrenergic neurotransmission in both cerebral hemispheres.

The effect of norepinephrine on recovery of beam-walking ability after sensorimotor cortex injury has been hypothesized to be modulated, at least in part, by noradrenergic projections to the cerebellum (5–9,17). Supporting this hypothesis, rats with concomitant cerebellar lesions were found to have particularly impaired recoveries after sensorimotor cortex injury (5). In addition, cerebellar infusions of norepinephrine facilitate recovery (6,9), whereas infusion of an α_1-adrenergic receptor antagonist into the cerebellum contralateral to a cortex injury is detrimental (8). Although the present results suggest that the effects of norepinephrine may also be mediated in the contralateral cerebral hemisphere, they do not exclude the hypothesized role of noradrenergic projections to the cerebellum. Norepinephrine levels were measured at only a single, late time point in these experiments, and microdialysis studies indicate that norepinephrine release in the cerebellum is depressed soon after cortex injury (30,40).

The possibility that noradrenergically mediated motor recovery after an injury to the sensorimotor cortex is at least partially mediated in the contralateral cerebral cortex is consistent with several recent studies. Activation of the homotypic contralateral cerebral cortex by vibrissae stimulation 2 weeks after unilateral infarction of the barrel cortex is significantly increased after systemic administration of amphetamine (15), a drug shown to facilitate behavioral recovery after focal injury to the cerebral cortex in a variety of experimental models (18,19,25,32,33,47,51), including rat barrel cortex infarction (35). Electrophysiological studies have demonstrated an increase in neuronal excitability in the cerebral cortex contralateral to an ischemic lesion (54), an effect that could potentially be blocked by the inhibitory effects of norepinephrine (41,48). Anatomically, injury to the forelimb sensorimotor cortex in rats results in a transient, but significant increase in the thickness of the contralateral, homotypic cerebral cortex (36). Subsequent studies demonstrate a specific increase in dendritic arborizations of layer V pyramidal cells in the contralateral homotypic cortex that correlated with the behavioral experience of the animal (37,38). Furthermore, there are increases in synaptophysin immunoreactivity in the cerebral cortex contralateral to an ischemic injury suggesting synaptogenesis (49). Interestingly, positron emission tomography studies of humans who had recovered motor function after hemiplegic stroke have shown significant increases in regional cerebral blood flow induced by movement of the recovered limb in the sensorimotor cortex contralateral to the injury (12). Attempted speech in a partially recovered aphasic stroke patient resulted in activation of a right-lateralized region of cerebral cortex homologous to the left-lateralized area activated by normal subjects (10).

In summary, the present experiments provide additional support for the hypothesis that beam-walking recovery after a sensorimotor cortex lesion is, at least in part, noradrenergically mediated. This effect of norepinephrine may be partially exerted in the cerebral cortex contralateral to the injury.

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