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Unilateral, but not Bilateral, Locus Coeruleus Lesions Facilitate Recovery From Sensorimotor Cortex Injury

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BOYESON, M. G., K. A. KROBERT, C. M. GRADE AND P. J. SCHERER. *Unilateral, but not bilateral, locus coeruleus lesions facilitate recovery from sensorimotor cortex injury.* PHARMACOL BIOCHEM BEHAV **43**(3) 771-777, 1992.—This study investigates the role of the locus coeruleus in recovery from sensorimotor cortex injury. Unilateral locus coeruleus lesions given 2 weeks prior to unilateral sensorimotor cortex injury facilitate subsequent motor recovery compared to animals with only a sensorimotor cortex injury, while bilateral locus coeruleus lesions severely retard motor recovery. The results suggest that recovery of function from the cortical injury is facilitated as long as a sufficient amount of the noradrenergic system remains intact, perhaps to provide a basis for compensatory sprouting. The results also suggest that recovery does occur in the absence of the locus coeruleus, indicating that the noradrenergic system is not necessary for recovery to occur after the cortical injury.

Norepinephrine Locus coeruleus Brain injury Sensorimotor cortex Recovery of function

CURRENTLY, much interest has focused on the use of different pharmacological agents to facilitate recovery from brain injury (2,15) or prevent injury from becoming worse through inhibiting calcium loading into cells (11,33). In addition, some success has been achieved in preventing degeneration of neurons through the use of gangliosides and promoting new neural growth through manipulations of various growth factors (3). One of the most fruitful lines of investigation has been extensions from Feeney and collaborators (2,14,15) on the role of catecholamines in recovery from sensorimotor cortex (SMCX) injury. Such findings have been successfully extended to clinical applications (12,32) and offer a longer therapeutic window than possible excitotoxic inhibitory therapies. In the latter case, early intervention to prevent calcium loading after the insult is mandatory for effective therapeutic benefits (11,33).

Although the exact mechanisms of the catecholamine-induced recovery are unclear, previous research has indicated an important role for norepinephrine (NE) in facilitating recovery from SMCX injury in animals. NE agonists have shown therapeutic promise in facilitating recovery (1,5,8-16), while antagonists are disruptive (1,4,14,25,34). In addition, infusions of NE into either the ventricle (5) or cerebellum contralateral to a unilateral SMCX injury (8,9) have been reported to facilitate motor recovery. Because the major ascending NE innervation of forebrain and cerebellum arises from the locus coeruleus [LC;(29,30)], it is likely that the effects of NE on recovery are modulated through the LC system. Addressing the role of the NE system more directly, the present experiment reports the behavioral effects of either a unilateral or bilateral LC lesion given 2 weeks prior to a unilateral SMCX injury.

METHOD

Animals

Twenty male Sprague-Dawley rats weighing 300-324 g were handled on a daily basis (for approximately 30 s) for 1 week prior to the beam training period. They were individually housed, fed ad lib, and kept on 12 L : 12 D schedule (lights on at 0600 h). Behavioral assessments of beam walking took place between 1000-1400 h.

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Behavioral Analyses

A large, dark goal box (24.8 × 20.3 × 17.8 cm) was positioned at the end of the beam. Training on the beam-walk task began after a 1-week habituation period. On the first training day, the animal was given three trials. In trial one, the animal was placed just outside the goal box, in trial two, at the midpoint of the beam, and in trial three at the start position. Motivation for the animal to move consisted of a tail-flick combined with a hiss. Escape from this stimulation to a darkened box was easily learned by the animal. Those few animals that attempted to turn around on the beam were immediately faced in the appropriate direction at the point of occurrence. No motivational stimuli were given to moving animals. The net result of doing this tended to wash out motivational differences between groups (unresponsive animals were "motivated" more by the experimenter than responsive animals), and treatment effects were less variable and less ambiguous to interpret when they occurred in animals. Nevertheless, others have reported success with similar therapeutic regimens that do not employ this selective motivation [see (20)], indicating the robust nature of the treatments employing the beam walking assessment of sensorimotor dysfunction. Single trials were then conducted every other day, and animals were rated on a seven-point scale by two observers, one blind to treatment conditions. The rating scale is described in detail elsewhere (8). In brief, if an animal traversed the beam with no more than two hindlimb footslips, it was rated the maximum score of "7" on two successive trials (usually within four trials); no further training was conducted so that slower animals were able to attain the same presurgery performance level. This was done to avoid "overtraining" some animals. A score of 6 indicated that the animal could traverse the beam using the effected hindlimb for greater than 50% of the distance across the beam. A 5 consisted of the animal using the effected hindlimb for less than 50% of the distance. A 4 indicated that the animal could get the effected limb up on the vertical surface of the beam but could not push off the surface without slipping. A 3 described an animal that can pull itself down the beam without getting the effected hindlimb on the vertical surface. A 2 represented an animal that could not traverse the length of the beam, but if placed sideways (with forepaws on the beam) could bring the effected limb up to the vertical surface. A 1 indicated an animal that could not maintain its balance on the beam. The day prior to surgery, all animals were given a single test trial to ensure continued performance at a "7" level.

Surgical Procedure

Following beam training, animals received either a sham (vehicle), unilateral, or bilateral 6-hydroxydopamine (6-OHDA) LC lesion. For surgery, animals were anesthetized with pentobarbital sodium (Nembutal; 21 mg/kg, IP) preceded by ketamine HCl (Ketacet; 60 mg/kg IM) and placed in a small animal stereotaxic apparatus (David Kopf Instruments). Thirty minutes prior to a 6-OHDA or vehicle infusion, animals received 30 mg/kg pargyline, a monoamine oxidase inhibitor. Animals received either a sham infusion (vehicle containing 0.1% ascorbic acid and 0.9% saline) 0.5 mm above the LC or a right unilateral or bilateral 6-OHDA lesion (6 μg/2 μl) of the LC. The coordinates for the LC lesion were −0.8 mm posterior from interaural line, 1.1 mm lateral, and 2.8 mm dorsal to the interaural line. Animals were tested on the beam every other day for 2 weeks. At that time, animals received a right SMCX injury. A craniotomy was performed over the right SMCX, the dura was excised, and the animal received a unilateral suction ablation extending from 2 mm anterior and 4 mm posterior to bregma and 5 mm lateral from the sagittal sinus to a depth of the white matter. A lesion of this magnitude has been found to consistently produce a clear deficit in hindlimb functioning [the area removed is greater than the maximal hindlimb variability exhibited in individual animals; (7,21,23,31)]. The cavity was filled with sterile gelfoam, the wound sutured closed, and the animal returned to the home cage. Animals were tested on the beam every other day for 15 days, beginning at 24 h post-SMCX injury.

Biochemical Analyses

One week following the last testing period, all animals were killed for biochemical assays of NE and histological verification of lesion and infusion placements. The animal was killed by decapitation, and sections of the right and left forebrain cortical tissue were removed, blot dried, weighed, and immediately frozen at −80°C. From decapitation to tissue freezing took approximately 3 min. The forebrain was assayed for NE as a measure of the effectiveness of the 6-OHDA lesion, and the remaining tissue was fixed in formalin, sectioned at 40 μm on a cyrostat, and stained with thionin for verification of 6-OHDA lesion and extent of SMCX ablations.

For the analysis of NE, a glassy carbon electrode set at +0.7 V potential was used to assay levels in forebrain. A citrate-phosphate buffer containing 5% methanol as an organic solvent and 0.008% octyl sulfate sodium (adjusted to pH 3.5) served as the mobile phase. At 1 ml/min, this provided approximately a 4-min elution time for NE on a Beckman column (5 μODS; 25 cm; Beckman Instruments, Fullerton, CA). At the time of decapitation, the forebrain tissue was quickly removed and weighed. The sample was stored at −85°C until biochemical analyses were conducted. The frozen brain sections were homogenized in refrigerator-chilled (4°C) formic acid:acetone (15:85 V/V) and centrifuged for 10 min at 900 × *g* and the liquid decanted into another test tube. The remaining tissue pellet was resuspended in the formic acid: acetone solution, vortexed, recentrifuged, and the solution combined with the previously decanted solution. The combined solution was then washed in heptane:chloroform (8:1 V/V), centrifuged, and the supernatant discarded. The final solution was then frozen in liquid nitrogen and dried down on a refrigerated vacuum centrifuge. Following reconstitution in 0.2 ml of the mobile phase, the samples were analyzed by high-performance liquid chromatography (HPLC) for NE content. HPLC was performed using a BAS chromatograph (Model LC-4B amperometric detector).

Statistical Analyses

Behavioral recovery curves were analyzed using a repeated-measures analysis of variance (ANOVA). Differences in levels of NE between experimental and control groups were reported as a percent drop compared to uninjured controls. Interrater reliability to assess degree of correlation between ratings of observers of the beam walking task was computed using the K statistic. The behavioral data for both bilateral and unilateral sham-lesion groups were not significantly different from each other and both sham groups were combined.

RESULTS

The results for a prior unilateral LC lesion on functional recovery are presented in Fig. 1. The results indicate that in

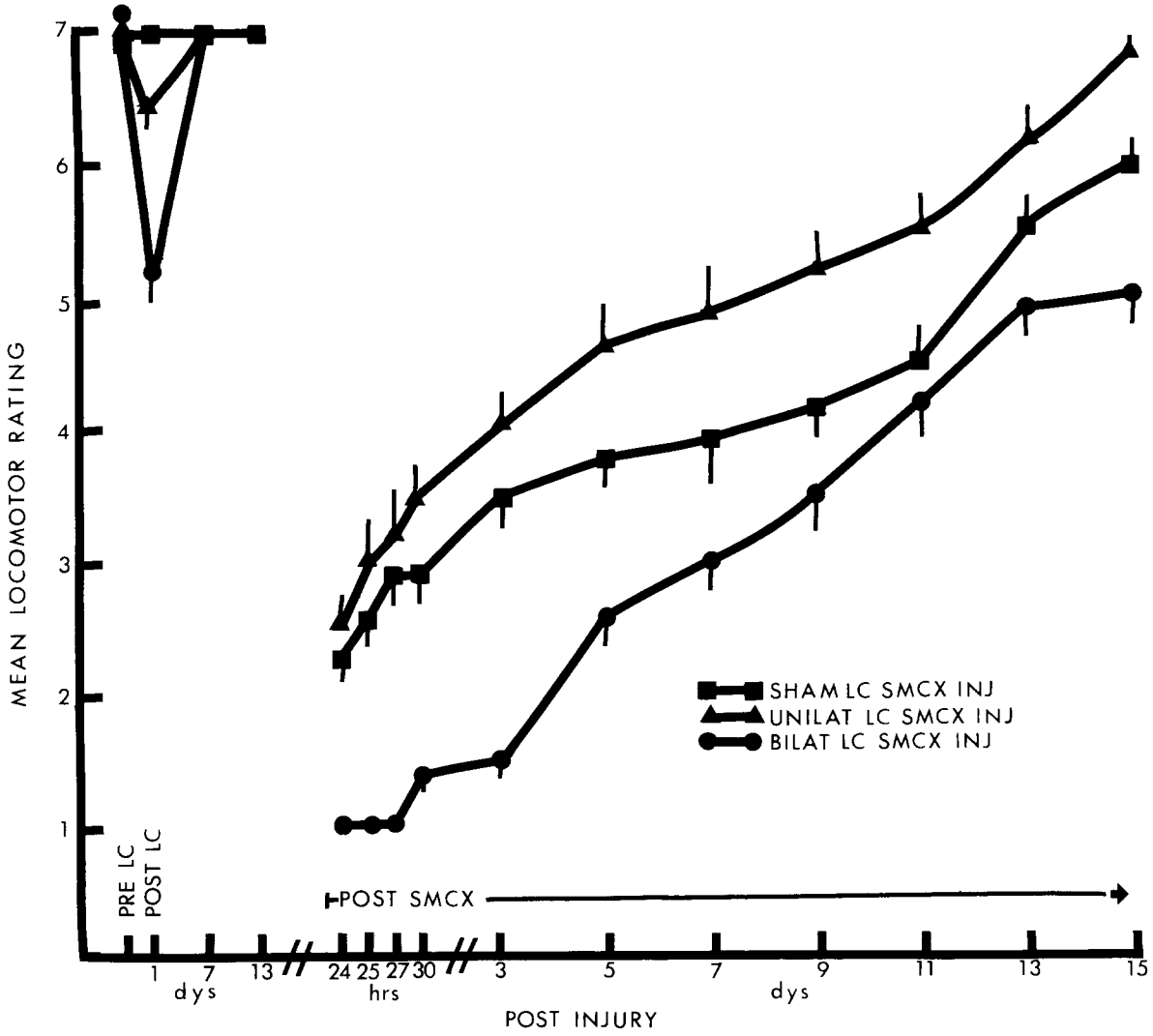

FIG. 1. Effects of a unilateral right or bilateral LC 6-OHDA lesion or sham injury given 2 weeks prior to unilateral right SMCX suction ablation injury on recovery of beam-walking ability. Animals given the unilateral LC lesion demonstrated facilitated recovery compared to animals without LC lesions. Bilateral LC lesions retarded recovery of beam walking compared to the sham LC animals with an SMCX injury. Bars = SEM.

animals with unilateral LC lesions recovery is facilitated compared to sham LC-operated controls, $F(1, 14) = 4.8$, $p < 0.05$. The results for a prior bilateral LC lesion are also presented in Fig. 1. A significant, $F(1, 10) = 16.2$, $p < 0.01$, retardation of recovery occurs compared to sham LC-operated controls. In some animals (either the bilateral or unilateral group), it was clear from histological examination that 6-OHDA was infused into cerebrospinal fluid (CSF) above the LC. Under these conditions, a partial bilateral removal of anterior LC cells occurred (leaving intact the medial to posterior extent of the LC). This procedure resulted in a 20–50% bilateral reduction in forebrain cortical NE levels. Only animals with complete unilateral ($N = 8$) or bilateral ($N = 4$) LC lesions were included in Fig. 1. Completeness of lesion was determined by loss of LC somata with subsequent decline in NE levels in forebrain cortex. Animals with complete lesions of the LC that were used for behavioral analysis had at least 90% reduction in NE levels in forebrain tissue (either unilateral or bilateral).

In Fig. 2, a representative photograph is given showing the extent of the SMCX injury. The photograph also depicts the forebrain tissue removed for biochemical analyses. The lesion volumes for the three groups were estimated from serial sections of the anterior–posterior, medial–lateral, and depth parameters of the ablated tissue. The volumes for the bilateral LC group was 71 mm^3, the unilateral group was 73 mm^3, and the saline group was 69 mm^3. There were no significant differences between groups in terms of the volume of tissue removed.

A representative section of the LC in a vehicle control animal is given in Fig. 3A. Animals with either a unilateral or bilateral 6-OHDA lesion of the LC are depicted in Fig. 3B (bilateral) and 3C (unilateral). In the analysis of the behavioral deficits arising from prior LC lesions presented in Fig. 1, only

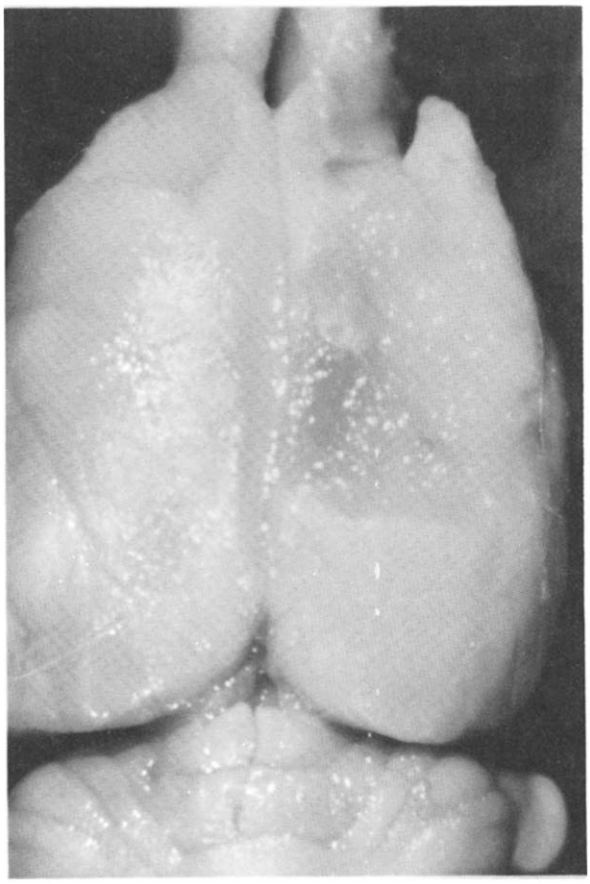

FIG. 2. Brain of an animal with a unilateral SMCX injury. The forebrain tissue of the animal was quickly removed and frozen for biochemical analysis, while the rest of the brain was hardened in formalin.

animals with confirmed loss of LC somata coupled with biochemical verification of drops in NE levels in the terminal axons of the forebrain tissue were used for the study (see below).

Forebrain levels of NE in the right SMCX-injured rats were 287 ± 33 ng/g wet wt in the left frontal cortex and 276 ± 37 ng/g wet wt in the right frontal cortex. (The more posterior SMCX injury had no significant effect on levels of NE in the anterior cortex sampled.) The levels dropped to 25.3 ± 3.6 ng/g wet wt in the right frontal cortex of the right LC unilateral group (left frontal cortex values were 267 ± 28 ng/g). The bilateral LC lesion group dropped to 19.7 ± 2.1 ng/g wet wt averaged for both hemispheres.

DISCUSSION

The results indicated that a prior unilateral lesion of the LC that projects predominantly to the ipsilateral injured SMCX and contralateral cerebellum results in facilitated recovery compared to a procedure that removes all LC input prior to a SMCX injury. One possible explanation for these data is that an upregulation and/or supersensitivity of existing postsynaptic receptor sites had occurred in the interval between LC and SMCX injury (4) to facilitate recovery from the SMCX injury. Given the 2-week time interval between LC lesion and SMCX injury, it cannot be excluded that some compensatory sprouting from the intact LC had developed in areas denervated from the lesioned LC. The most likely area of this overlap would be the cerebellum, where each LC nucleus's projections are strongly bilateral (29,30). A small (approximately 15%) but significant crossover of the ascending cortical projection of both LCs to each hemisphere occurs in rat brain (29,30). After a unilateral cortical injury, it is possible that increases in sprouting from the opposite hemisphere underlie the functional recovery, presumably through modulation of intact tissue adjacent to the injury. However, this is unlikely for several reasons. In an extensive mapping of SMCX at long intervals postinjury, no new responses could be elicited from any adjacent tissue of the entire dorsal surface of the brain (7). Second, large bilateral cortical lesions that remove the terminal LC projection sites to both hemispheres still result in recovery (unpublished observation), and partial bilateral lesions of the anterior LC (which constitute the anterior hemisphere projections) or dorsal bundle lesions result in facilitated recovery (10,35). The anterior soma of the LC predominantly gives rise to the forebrain cortical and hypothalamic projections (29) and, if these projections were important to the recovery process, should result in retardation. The latter procedure does leave the predominantly posterior aspect of the LC intact, and these projections largely constitute the LC input to cerebellum (30). Further evidence implicating the cerebellum in functional recovery arises from several sources. For example, it has been shown that following microinfusions of NE into the ventricle (1,5) or into the contralateral (but not ipsilateral) cerebellum 24 h following a unilateral SMCX injury (8,9) recovery of motor function is greatly accelerated in brain-injured rats.

From the above perspective, it appears that procedures designed to enhance NE functioning in the cerebellum (through sprouting/receptor upregulation, NE infusions, drug manipulations) shortly after injury result in facilitated recovery from the hemiparesis observed after SMCX injury. Recently, we found that α-adrenergic antagonists given peripherally or infused directly into the contralateral cerebellum can reinstate the hemiparesis in animals previously recovered from the SMCX injury (4,10,34), and this drug effect is mimicked by unilateral lesion of the LC that projects to the injured cortex. Furthermore, unilateral lesions of the cerebellum that include the deep cerebellar nuclei result in deficits on the beam walking that animals do not recover from for at least 4 months postinjury (6). Under these latter conditions, both NE agonists and antagonists have no beneficial effects on recovery. Finally, administration of DSP-4, a selective NE neurotoxin, prior to an SMCX injury impairs functional motor recovery (4,19). This neurotoxin initially interferes with all NE systems in the body following an IP injection and then permanently removes the cerebellar and dorsal bundle projections, leaving the ventral bundle intact (17,18,26,27).

A tentative model of the role of the noradrenergic system in recovery of beam walking may now be offered based upon the above evidence. Following a unilateral SMCX injury, cortical tissue as well as fibers from the NE projection are damaged and the animal exhibits a contralateral hemiparesis. The hemiparesis is probably a result of a combination of the loss of descending cortical influences and changes in Purkinje cell output induced by the temporary dysfunction of the NE inhibitory effects on those cells (24). Disrupting one axonal branch (to SMCX) would not be expected to result in the death of the LC soma because bifurcating axonal systems damaged at this distance from the cell body would survive and may even possi-

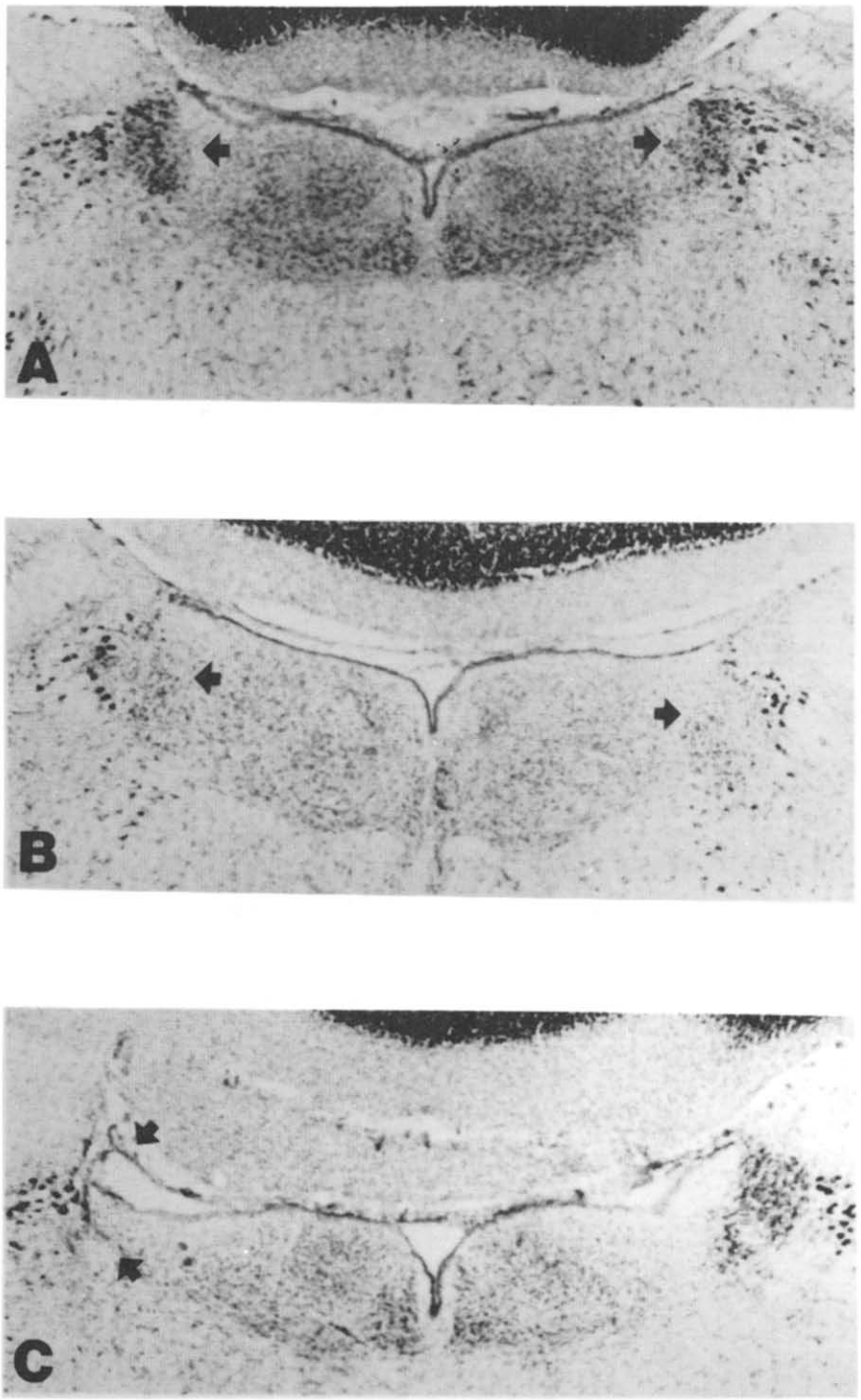

FIG. 3. (A) LC (arrows) of a normal, sham-infused animal. (B) Animal with a bilateral LC lesion (arrows). (C) Animal from the unilateral LC lesion group (arrows).

bly exhibit compensatory arborization of the intact branches [see Schneider in (3,13)]. In the cerebellum, this would preferentially manifest itself as disturbances in synthesis and or turnover but not in levels of NE because compartmentalized stores of NE should remain (17). Over time, the NE system in the cerebellum may be able to compensate for the SMCX branch and provide a sufficient amount of Purkinje cell inhibition to modulate descending motor influences (perhaps through the nucleus ruber) that may help compensate for loss of corticospinal and corticorubral fibers (28). Manipulations of the LC system prior to the SMCX injury shed considerable light on this process. A unilateral LC lesion disrupts both the SMCX

projection and the bilateral LC projection to cerebellum. If this lesion is given 2 weeks prior to the injury, some compensatory sprouting could occur from the intact LC onto vacated Purkinje cell receptor sites to modulate output and functional motor recovery. By varying the interval between LC lesion and SMCX injury, we have been able to establish that supersensitivity to NE infusions occurs in the cerebellum contralateral to the SMCX injury (10). The shorter the duration between LC lesion and SMCX injury, the NE infusions become less effective in facilitating recovery (such infusions, however, still facilitate recovery compared to saline infusions). At 2 weeks' interval, a single infusion of NE into the contralateral cerebellum at 24 h post-SMCX injury results in total recovery on the beam within 1–3 h after the infusion (10).

Taken together, the results suggest that, following a unilateral SMCX injury, a depression in NE functioning occurs in the contralateral cerebellum through simultaneous projections from the same LC cell to both areas (13) that appears to be largely responsible for the hemiparesis, rather than direct SMCX damage. Resolution of the NE depression facilitates recovery of function. These results would also suggest that those tricyclic antidepressants that predominantly act by blocking NE reuptake might provide some therapeutic benefits to brain-injured patients suffering from hemiparesis.

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