Pharmacology Biochemistry and Behavior, Vol. 44, pp. 297-305, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

Unilateral Locus Coeruleus Lesions Facilitate Motor Recovery From Cortical Injury Through Supersensitivity Mechanisms

MICHAEL G. BOYESON,*[1] PAUL J. SCHERER,†
CHARLES M. GRADE‡ AND KURT A. KROBERT§

*Department of Rehabilitation Medicine, University of Wisconsin Medical School, Madison, WI 53706
†Department of Orthopedic Surgery, Mayo Graduate School of Medicine, Rochester, MN 55905
‡Department of Psychiatry, Arizona Health Sciences Center, Tucson, AZ 85724
§Department of Physiology, University of New Mexico, Albuquerque, NM 87131

Received 22 April 1992

BOYESON, M. G., P. J. SCHERER, C. M. GRADE AND K. A. KROBERT. *Unilateral locus coeruleus lesions facilitate motor recovery from cortical injury through supersensitivity mechanisms.* PHARMACOL BIOCHEM BEHAV **44**(2) 297-305, 1993. – Previous research has indicated that noradrenergic infusions into the cerebellum contralateral to a sensorimotor cortex injury facilitate recovery of motor function. In the present study, the locus coeruleus was lesioned at 2 weeks prior to, 1 week prior to, or simultaneous with a right sensorimotor cortex injury, and functional recovery in response to noradrenergic cerebellar infusions was measured using the beam-walk task. When the locus coeruleus lesion was separated from the sensorimotor cortex lesion by 1 week or more, noradrenergic-induced facilitation of functional recovery occurred with the greater effects observed at the 2-week interval. Simultaneous locus coeruleus and sensorimotor cortex injury with cerebellar noradrenergic infusions revealed no difference in functional recovery. The results suggest that denervation supersensitivity and/or sprouting developed in the cerebellum following the locus coeruleus lesions if a sufficient amount of time elapsed before the sensorimotor cortex injury. The heightened sensitivity to noradrenergic infusions in the contralateral cerebellum suggests that noradrenergic changes in this structure underlie the acceleration of functional recovery from the cortical injury.

Sensorimotor cortex Brain injury Norepinephrine Locus coeruleus Cerebellum

RECENTLY, it has been hypothesized that the locus coeruleus (LC) system plays an important role in the rate at which recovery of function occurs after a brain injury. For example, drugs that stimulate the output of LC neurons (directly or indirectly) facilitate recovery from a host of behaviors, whereas drugs that interfere with the output of LC transmission slow recovery (1,14-16,34). In addition, drugs that inhibit LC output reinstate deficits in animals long since recovered from cortical injuries (3,19,20,26,36). With respect to motor recovery, norepinephrine (NE) given intraventricularly, or into the cerebellum contralateral to a unilateral sensorimotor cortex (SMCX) injury, enhances the rate at which the motor recovery occurs in animals (4,8,10). If drugs that block NE alpha$_1$-receptors are infused into the contralateral (but not ipsilateral) cerebellum in animals that have recovered from unilateral SMCX injuries, the deficit is unilaterally reinstated (30).

The above evidence suggests that the mechanism through which the acceleration of recovery of beam-walking ability occurs is thought to be due to changes in NE functioning in the cerebellum that have been disrupted by the SMCX injury (9). The pathway associated with the mechanism is the simultaneous axonal bifurcation of a single LC neuron to both the ipsilateral SMCX and contralateral cerebellum (12,31,32). Damage to one terminal arborization in the SMCX (along with the direct damage to the cortical tissue) transiently affects the functioning capacity of the intact arborization to the contralateral cerebellum (35). Removing one axonal branch at such a long distance from the LC soma would not be expected to result in the death of the LC neuron, and the intact arborization may even exhibit compensatory arborization in the intact branches [see Schneider in (2); (9,38)]. Removing all branches of the LC does not allow for compensatory NE axonal branching (although some postsynaptic receptor sensitivity

[1] Requests for reprints should be addressed to Michael G. Boyeson, Ph.D., Department of Rehabilitation Medicine, University of Wisconsin Medical School, Room 3490, Medical Science Center, 1300 University Avenue, Madison, WI 53706.

may occur) and deleterious effects should be observed on behavioral recovery in animals. Indeed, prior bilateral LC lesions or DSP-4 neurotoxic lesions (3,9,19) retard functional recovery after a subsequent SMCX injury.

One explanation of the opposed behavioral actions of unilateral and bilateral LC lesions prior to an SMCX injury is that, following unilateral LC lesions, the intact LC sprouts to vacant receptor sites and/or receptor supersensitivity occurs in cerebellar tissue. To address this possibility from a functional recovery standpoint, animals received unilateral LC lesions, simultaneous with, 1 week prior to, or 2 weeks prior to a unilateral SMCX injury. At 24 h post-SMCX injury, NE was infused into the cerebellum. It was expected that the closer the LC lesion occurred to the time of the SMCX injury the less effect NE would have on recovery of function because sprouting/receptor changes take some time to develop.

METHOD

Subjects

Sixty-three Sprague-Dawley rats weighing 300–325 g were used as subjects. All animals were individually housed and handled on a daily basis (for approximately 30 s) for 1 week prior to any experimentation. Animals were fed and watered ad lib and kept on a 12 L : 12 D cycle (lights on 0600 h). Behavioral testing took place between 1000 and 1400 h.

Apparatus

The apparatus used to assess beam-walking ability was a long (22 cm), narrow (2.5 cm), elevated (36 cm) beam with a dark goal box (24.8 × 20.3 × 17.8 cm) at the end.

Behavioral Testing

Animals were initially trained to walk the beam as follows. 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. 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 foot-slips on two successive trials (usually within five trials), it was rated the maximum score of 7; 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. The day prior to surgery, all animals were given a single test trial to ensure continued performance at a 7 level. Motivation for the animal to move consisted of a tail tap combined with a hiss. Escape from this stimulation into a darkened box at the end of the beam was easily learned by animals within two to four trials.

Those 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 this procedure tended to eliminate motivational differences between groups (unresponsive animals were motivated more by the experimenter than responsive animals), and treatment/drug effects were less variable with respect to motivational differences in animals and less ambiguous to interpret. Others have reported success with different motivational constraints using the beam-walking task, indicating the robust nature of the task under different conditions [see (21)].

Following the highest score of 7 on the beam, 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 indicated an animal that could use the effected hindlimb for less than 50% of the distance. A 4 indicated that the animal could get the effected limb up on the horizontal 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 horizontal surface. A 2 represented an animal that could not traverse the length of the beam but if placed sideways (with forepaws on the beam while clinging) could bring the effected limb up to the surface. A 1 indicated an animal that could not maintain its balance on the beam unassisted.

Surgical Procedure

Following training, all animals received either a right unilateral 6-hydroxydopamine (6-OHDA) (8 μg/2 μl in 0.1% ascorbic acid and 0.9% saline solution) lesion of the LC, the coordinates for the LC lesion being −0.8 mm posterior from interaural line, 1.1 mm lateral, and 2.8 mm dorsal to the interaural line, or a sham infusion of the vehicle at a point 0.5 mm above the injection coordinates. One group of animals received a simultaneous right SMCX injury by suction ablation of the cortex (2 mm anterior to bregma, 4 mm posterior to bregma, and 5 mm laterally from midline to a depth of white matter). A lesion of this magnitude has been found to produce a consistent deficit in hindlimb functioning [the area removed is greater than the maximal hindlimb variability exhibited in individual animals; (6,23,33)]. The cavity was filled with sterile gelfoam and the animal sutured and returned to its home cage. The control animals (sham LC) also received the SMCX injury. Another group received a right SMCX injury at 1 week post-LC/sham LC injury, and the third group received a right SMCX injury at 2 weeks post-LC/sham LC injury. For all animals at time of SMCX injury, a cannula was inserted into the cerebellum contralateral to the SMCX injury, sealed with dental acrylic, and capped. The lengths of all cannulae inserted into all animals were the same, with the length of the inserting syringe measured to project to 0.1 mm below the tip of the cannula.

At 24 h post-SMCX injury, animals received 150 μg/5 μl l-NE in 0.1% ascorbic acid 0.9% saline solution through the cerebellar cannula. The solution was slowly infused (2 min) into the awake animal following a pretest on the beam. At approximately 30 s postinfusion, animals were tested on the beam and at intervals of 1, 3, 6, and 24 h and every other day for 15 days.

Biochemical Analysis

One week following the last test period, all animals were sacrificed for biochemical assays of NE and histological verification of lesion and infusion placements. The animal was sacrificed by decapitation, and sections of the right and left forebrain cortical tissue were removed, blot dried, weighed, and immediately frozen at −85°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 cryostat, and stained with thionin for verification of 6-OHDA lesion and extent of SMCX ablations.

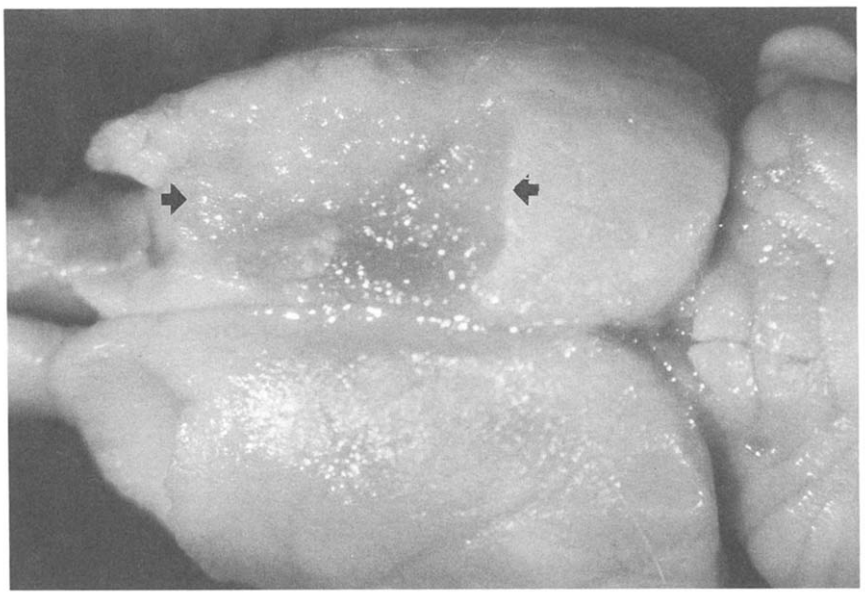

FIG. 1. Typical right sensorimotor cortex ablation (arrows). Note that a missing sample is depicted of each forebrain hemisphere. These samples were utilized for biochemical analyses (see the text).

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 rest of the brain was stored in a formalin-sucrose solution for 2 weeks then histologically cryocut at 40 μm through the SMCX injury and LC area. The quickly removed frozen forebrain samples were homogenized in refrigerator-chilled (4°C) formic acid:acetone (15 : 85 V/V), 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 κ-statistic.

RESULTS

In Fig. 1, a representative SMCX lesion is given. Note that the SMCX lesion borders on the midline superior sagittal sinus. A portion of each forebrain hemisphere is missing because these were rapidly removed and frozen for HPLC analyses while the rest of the brain was fixed in a formalin-sucrose solution. The volume of tissue removed did not differ significantly among the groups of animals when estimated from serial sections. The range of volume extended from the high of 74.1 ± 3.8 mm^3 to a low of 69.8 ± 2.7 mm^3.

In Fig. 2, a representative unilateral LC lesion is depicted from serial sections of the remaining brain. On occasion, it was noted that the infusion itself caused some residual tissue damage. However, an examination of behavioral scores of animals with damage to the LC compared to animals with apparent loss of only LC somata did not reveal any significant behavioral differences on the beam-walking task. In Fig. 3, the cannula infusion point in the cerebellum contralateral to the SMCX injury is shown.

At approximately 4 weeks post-SMCX injury, all animals were sacrificed for analyses of forebrain NE levels. The concentration of NE in each hemisphere of control animals was not significantly different from one another (right forebrain = 291 ± 29 ng/g wet wt.; left forebrain = 283 ± 32 ng/g wet wt.). Following a unilateral LC lesion, the values for the right forebrain tissue dropped to 30 ± .8 ng/g wet wt. compared to 279 ± 9 ng/g wet wt. for the intact hemisphere. These latter values were averaged across all right unilateral LC lesion groups.

The results for the infusion of NE in animals receiving sham LC (SMCX NE) vs. LC lesion (LC SMCX NE) at 2

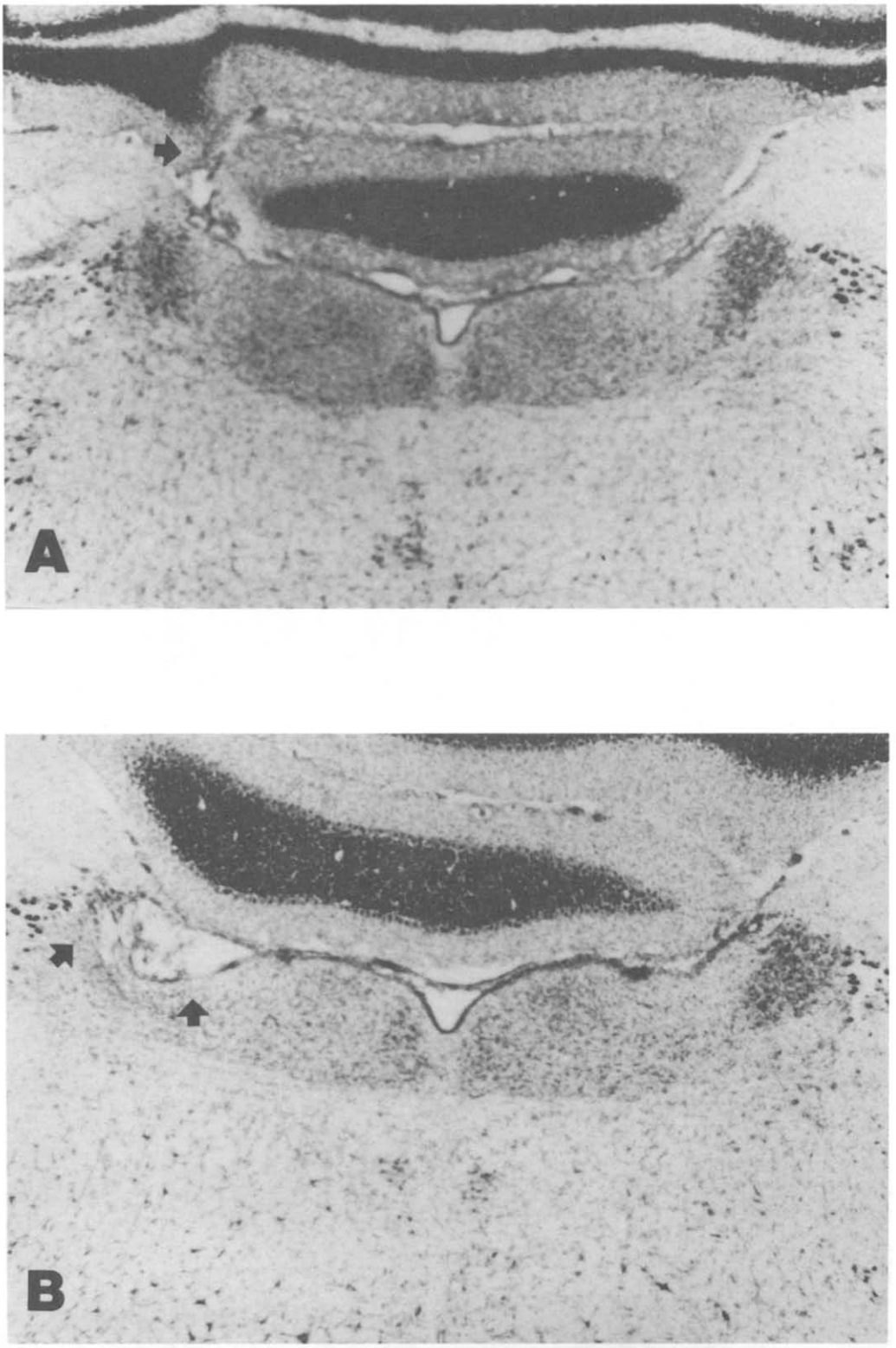

FIG. 2. (A) Effect of an infusion of the vehicle above the locus coeruleus (LC) (arrow). (B). Representative unilateral LC lesion (arrows) induced by an infusion of 6-hydroxydropamine (6-OHDA).

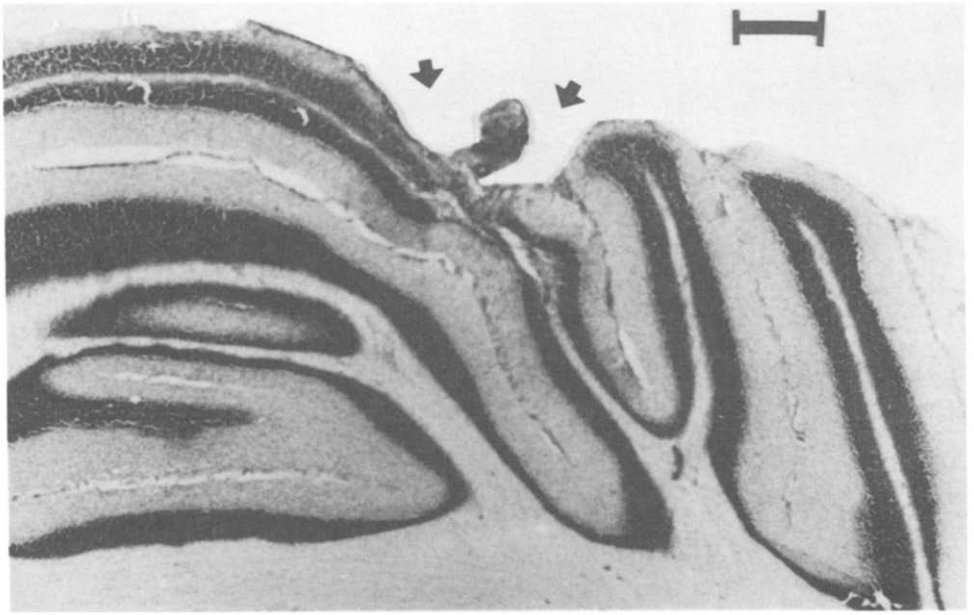

FIG. 3. Infusion point (arrows) of norepinephrine (NE) or vehicle in the cerebellum contralateral to the sensorimotor cortex (SMCX) injury. A similar effect was obtained with the ipsilateral infusion into the cerebellum (not shown). Bar = 0.5 mm.

weeks prior to an SMCX injury are depicted in Fig. 4. Those animals that had received a unilateral right LC lesion 2 weeks prior to a right SMCX injury and were given NE recovered significantly faster than animals with a sham LC and given NE after the SMCX injury. The effects of the NE infusion are seen immediately after the infusion (some animals were observed to be totally recovered as early as the 1-h postinfusion measurement), then drop off by the day 1 postinfusion period. Nevertheless, the recovery of motor ability remains accelerated, $F(1, 12) = 4.9, p < 0.05$, compared to the sham LC group. Those animals receiving vehicle infusions with or without an LC lesion are also depicted in Fig. 4. The NE infusion groups were both significantly accelerated in recovery compared to their vehicle group counterparts [LC SMCX NE vs. LC SMCX VEH, $F(1, 12) = 5.8, p < 0.04$; SMCX NE vs. SMCX VEH, $F(1, 13) = 6.8, p < 0.03$].

The results for infusion of NE into animals receiving the LC lesion or sham 1 week prior to the SMCX injury are presented in Fig. 5. A similar acceleration of recovery is seen in this group after the single infusion of NE with one clear exception: The initial dramatic increase in functional recovery is abbreviated (peaking at 3 h compared to 6 h). Nevertheless, the acceleration of recovery, $F(1, 12) = 5.8, p < 0.04$, is maintained compared to the sham LC group. In addition, an infusion of NE was given to the ipsilateral cerebellum (right) to control for dispersion of NE. This latter procedure did not significantly facilitate recovery of beam-walking ability compared to infusions of NE into the contralateral cerebellum, even though the contralateral cerebellum was made supersensitive through a right LC lesion.

The results for the infusion of NE into animals receiving a simultaneous LC lesion and SMCX injury are presented in Fig. 6. The major difference in recovery of function in these animals is the absence of initial dramatic increase in recovery following NE infusion. Although not significant, these LC animals exhibited some degree of acceleration compared to sham LC animals.

DISCUSSION

The current results are supportive of previous findings indicating the importance of the NE system in recovery of function from an SMCX injury (1,14–16,22) and are also supportive of the involvement of the contralateral cerebellum in the subsequent recovery (4,8,9). By changing the temporal interval between lesions, a classic pattern of denervation supersensitivity (measured by the differential behavioral response to the same concentration of drug) occurred when NE was infused into the contralateral cerebellum. In this respect, less behavioral supersensitivity to the NE infusion would be expected to develop with the simultaneous LC/SMCX injury, and our results confirm this in terms of the NE infusion effects on acceleration of behavioral recovery. The duration of the supersensitive response to beam-walking recovery noted for the 2-week lesion interval, where considerably less dropoff occurred, may be due to the arrival of collateral sprouts from the intact LC (both LCs bilaterally project to cerebellum). If this were the case, then longer time intervals between lesions might reveal no dropoff in recovery in response to NE infusions. In addition, infusions of NE into the cerebellum ipsilateral to the right SMCX injury and right LC lesion failed to accelerate recovery of function (see Fig. 2). This result suggests that excess diffusion of NE is not occurring to the extent that functional recovery is affected and strongly indicates that the functional recovery induced by NE infusion is localized to the contralateral cerebellum. Because the contralateral cere-

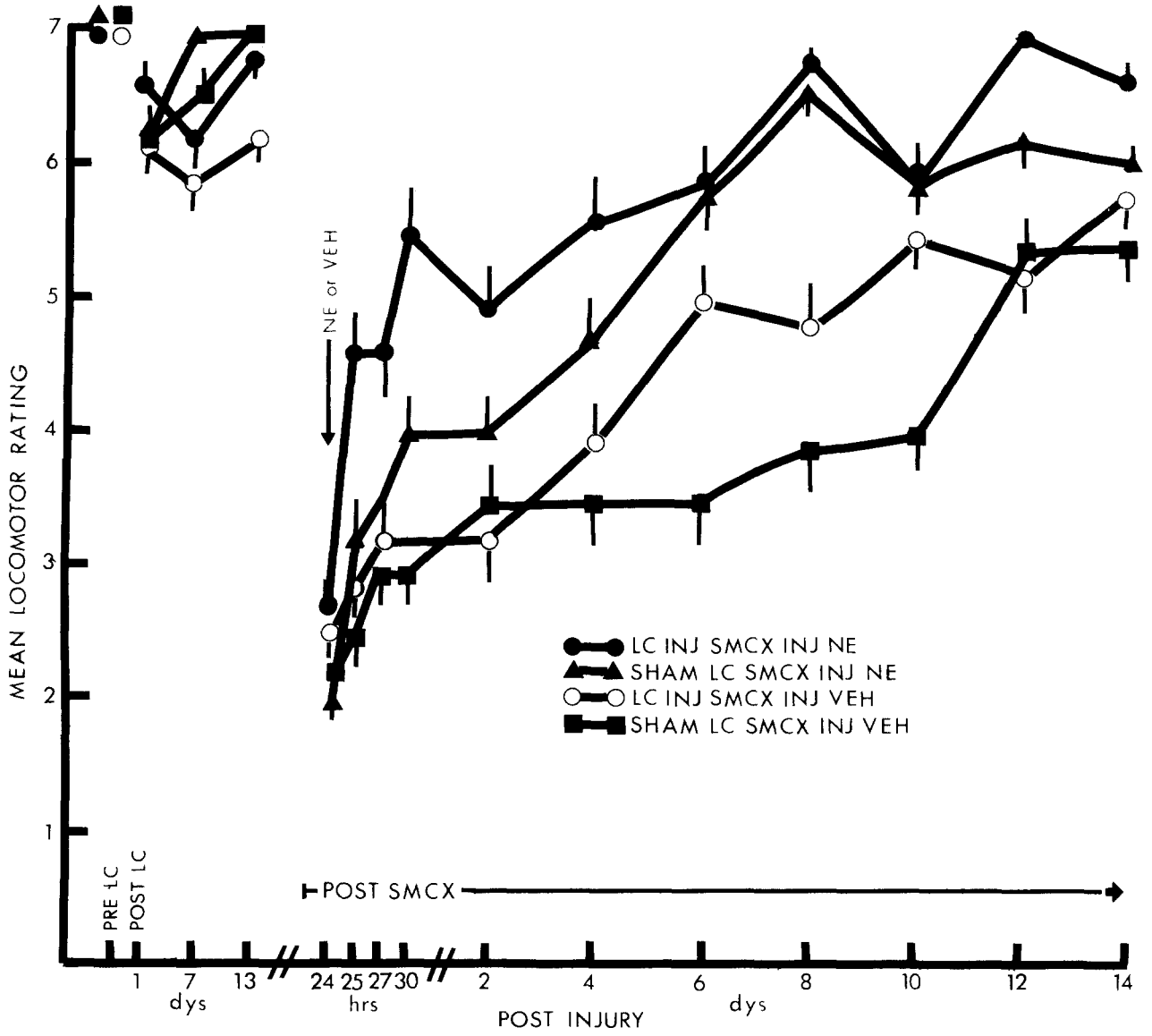

FIG. 4. Effects of a 150-μg infusion of norepinephrine (NE) into the contralateral cerebellum 24 h after a right sensorimotor cortex (SMCX) injury. Animals received either a sham or locus coeruleus (LC) lesion 2 weeks prior to the SMCX injury with an NE or vehicle infusion. Animals' recovery on the beam-walking task was unaffected by the LC lesion in the 2-week interval before the SMCX injury. Following the SMCX injury and subsequent NE infusion, animals with a prior LC lesion exhibited enhanced recovery of function. Both NE infusion groups were significantly improved compared to their vehicle counterparts. Bars = SEM.

bellum affects movement on the same side of the body as the unilateral SMCX injury, this finding is not entirely unexpected.

The LC appears to play a modulatory role in the recovery process after SMCX injury, and from this perspective stimulating the LC system output is a sufficient but not necessary condition for recovery to occur in animals. Recovery of beam-walking ability occurs in animals with bilateral, total LC lesions (9), as well as in animals with peripherally administered DSP-4 (3,21). In the latter case, the two bifurcating NE axonal systems in the brain that appear permanently affected by DSP-4 administration are the projections to the cerebellum and the dorsal (but not ventral) bundle of the LC (17, 18,27,28). The temporal recovery pattern appears to be approximately the same for both lesion and DSP-4 administration [see (3,9)]. In both cases, then, recovery occurs in the absence of the critical LC system, suggesting that the recovery is postsynaptic to the LC system. The recovery does not appear to be mediated by the Purkinje cells of the cerebellum alone because removal of only those cells still results in recovery on the beam (5). However, removal of both Purkinje cells and deep cerebellar nuclei results in a permanent deficit on

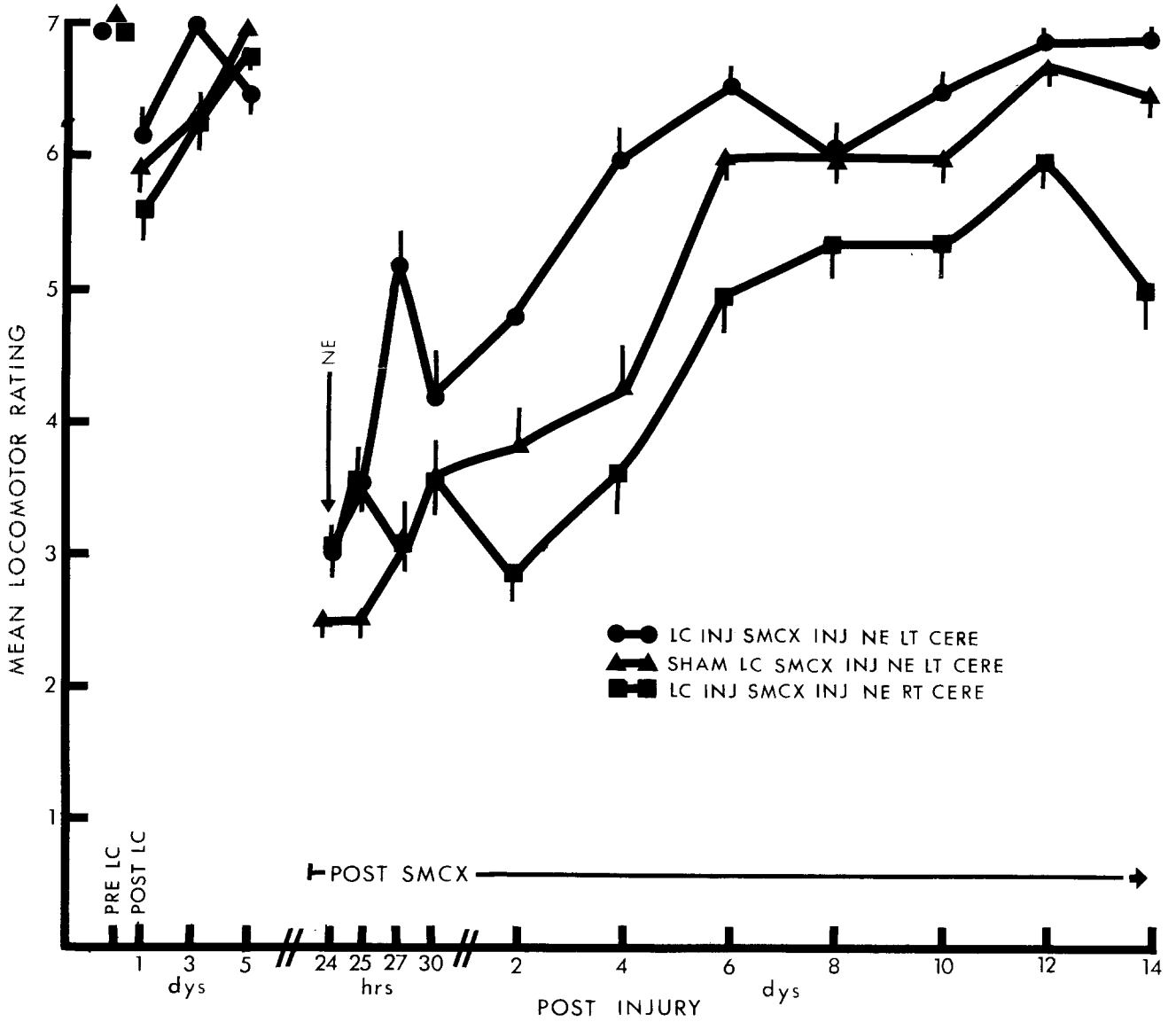

FIG. 5. Effects of only a 150-μg infusion of norepinephrine (NE) (no vehicle) into the cerebellum contralateral *or* ipsilateral to a sensorimotor cortex (SMCX) injury at 24 h after the SMCX injury. Animals received either a sham or locus coeruleus (LC) lesion 1 week prior to the SMCX injury and NE infusion. Animals' recovery on the beam-walking task was unaffected by the LC lesion alone. Following SMCX injury and subsequent NE infusion, animals with a prior LC lesion exhibited enhanced recovery of function only if NE was infused into the contralateral cerebellum. Bars = SEM.

the beam (5). This latter observation would suggest that the areas involved would be connections between the deep cerebellar nuclei and perhaps the nucleus ruber and/or the vestibular nuclei. Before his untimely death, Tsukahara (37) elegantly demonstrated that considerable synaptic remodeling occurs in the nucleus ruber following a cortical injury and subsequent loss of corticorubral influences. Such remodeling may occur not only as a response to loss of corticorubral input but also to influences from the cerebellum because a considerable amount of Purkinje cell output is convergent on the nucleus ruber to affect descending motor influences to muscle (29). Disinhibition of Purkinje cell output through changes in the NE system (25) would in turn have impact on the recovery process following cortical injury [see (3,19,20)]. Whether or not all of the above anatomic connections are causally involved in the recovery from hemiparesis, the role of the corticospinal pathway appears less critical to the recovery process because animals recover on the beam-walking task after bilateral SMCX lesions (24).

Further, these results suggest that the hemiparesis produced by SMCX injury can be compensated for by changes in cerebellar activity. From a clinical viewpoint, these findings also suggest that noradrenergic-acting drugs may be beneficial to human brain injury cases where hemiparesis is present. We

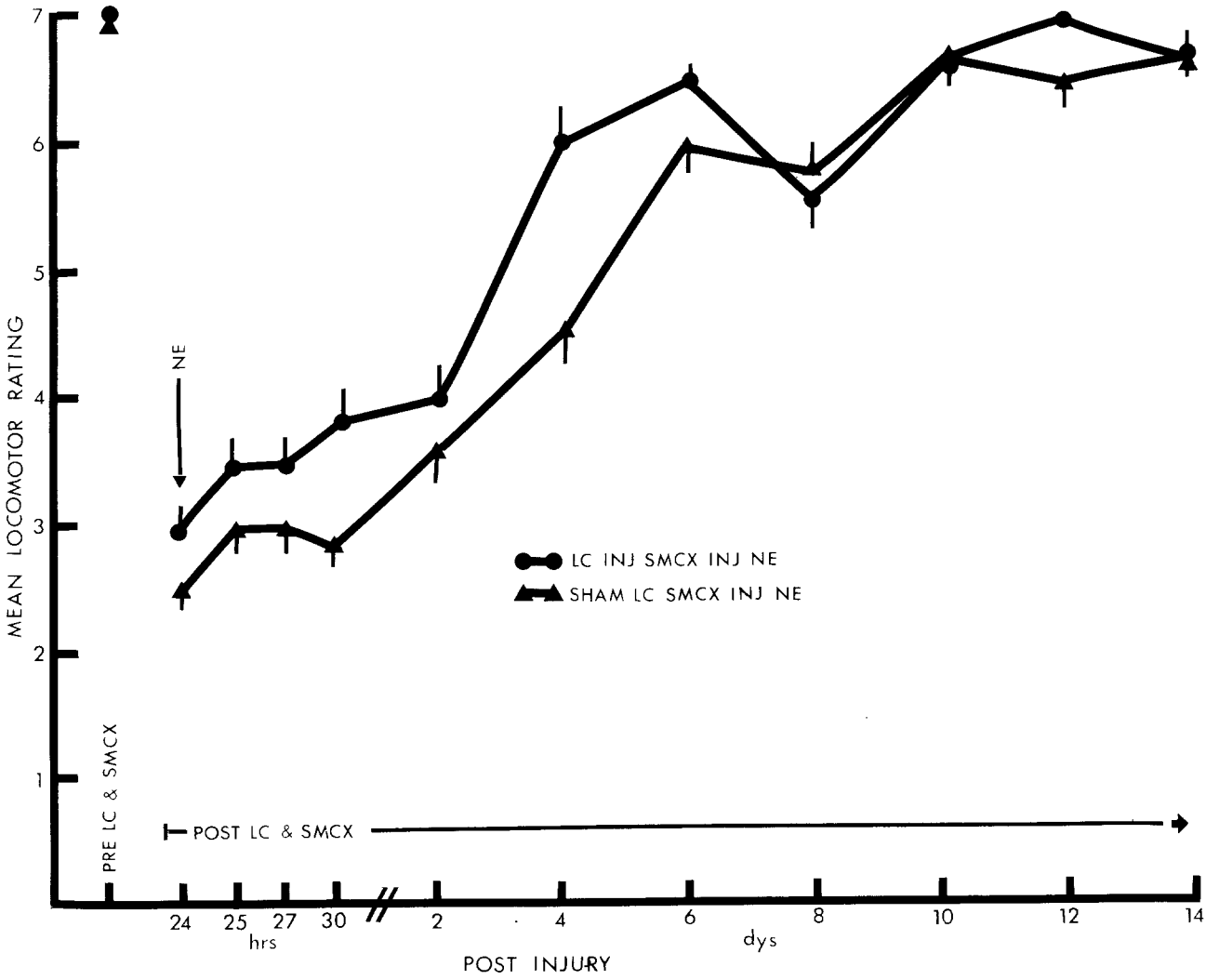

FIG. 6. Effects of a 150-μg infusion of norepinephrine (NE) into the contralateral cerebellum 24 h after a right sensorimotor cortex (SMCX) injury and simultaneous sham or locus coeruleus (LC) lesion. Animals with the simultaneous LC lesion and SMCX injury and NE infusion did not demonstrate facilitated recovery of function on the beam-walking task compared to simultaneous sham LC and right SMCX injury with a NE infusion. Bars = SEM.

recently demonstrated that some typical tricylic antidepressants (those with predominately NE reuptake blocking capacity) have a marked effect on facilitation of motor recovery (7). Atypical antidepressants that predominately act by blocking serotonergic reuptake were found to interfere with functional motor recovery (7). Like the findings of others (11,13), it is necessary for the animal to experience the functional deficit while under the influence of the NE drug. Translated to a clinical perspective, intense motor rehabilitation while under the influence of the NE-acting drug would be necessary to facilitate motor recovery from a cortical injury.

ACKNOWLEDGEMENT

This work was supported by the NIH grant NS23003 to MGB.

REFERENCES

1. Boyeson, M. G. Neurochemical alterations after brain injury: Clinical implications for pharmacologic rehabilitation. Neurorehabilitation 1:33-43; 1991.
2. Boyeson, M. G.; Bach-y-Rita, P. Determinants of brain plasticity. J. Neurol. Rehab. 3:35-57; 1989.
3. Boyeson, M. G.; Callister, T. R.; Cavazos, J. E. Biochemical and behavioral effects of a sensorimotor cortex injury in rats pretreated with the noradrenergic neurotoxin DSP-4. Behav. Neurosci. 106:964-973; 1992.
4. Boyeson, M. G.; Feeney, D. M. Intraventricular norepinephrine

facilitates motor recovery following sensorimotor cortex injury. Pharmacol. Biochem. Behav. 35:497–501; 1990.
5. Boyeson, M. G.; Feeney, D. M. Adverse effects of catecholaminergic drugs following unilateral cerebellar ablations. Restor. Neurol. Neurosci. 3:227–233; 1991.
6. Boyeson, M. G.; Feeney, D. M.; Dail, W. G. Cortical microstimulation thresholds adjacent to a sensorimotor cortex injury. J. Neurotrauma 8:205–217; 1991.
7. Boyeson, M. G.; Harmon, R. Effects of trazadone and desipramine on motor recovery in brain-injured rats. Am. Assoc. Phys. Med. Rehab. (in press).
8. Boyeson, M. G.; Krobert, K. A. Cerebellar norepinephrine infusions facilitate recovery from sensorimotor cortex injury. Brain Res. Bull. 29:435–439; 1992.
9. Boyeson, M. G.; Krobert, K. A.; Grade, C. M.; Scherer, P. J. Unilateral, but not bilateral, locus coeruleus lesions facilitate recovery from sensorimotor cortex injury. Pharmacol. Biochem. Behav. 43:771–777; 1992.
10. Boyeson, M. G.; Krobert, K. A.; Hughes, J. M. Norepinephrine infusions into cerebellum facilitate recovery from sensorimotor cortex injury in the rat. Soc. Neurosci. Abstr. 12:1120; 1986.
11. Crisostomo, E. A.; Duncan, P. W.; Propst, M.; Dawson, D. V.; Davis, J. N. Evidence that amphetamine with physical therapy promotes recovery of motor function in stroke patients. Ann. Neurol. 23:94–97; 1988.
12. Crowley, J. N.; Maas, J. W.; Roth, R. H. Biochemical evidence for simultaneous activation of multiple locus coeruleus efferents. Life Sci. 26:1373–1378; 1980.
13. Feeney, D. M.; Gonzalez, A.; Law, W. A. Amphetamine, haloperidol and experience interact to affect rate of recovery after motor cortex injury. Science 217:855; 1982.
14. Feeney, D. M.; Sutton, R. L. Pharmacotherapy for recovery of function after brain injury. CRC Crit. Rev. Neurobiol. 13:135–197; 1987.
15. Feeney, D. M.; Sutton, R. L.; Boyeson, M. G.; Hovda, D. A.; Dail, W. G. The locus coeruleus and cerebral metabolism: Recovery of function after cortical injury. Physiol. Psychol. 13:197–203; 1985.
16. Feeney, D. M.; Westerberg, V. S. Norepinephrine and brain damage: Alpha noradrenergic pharmacology alters functional recovery after cortical trauma. Can. J. Psychol. 44:233–252; 1990.
17. Fritschy, J. M.; Geffard, M.; Grzanna, R. The response of noradrenergic axons to systemically administered DSP-4 in the rat: An immunohistochemical study using antibodies to noradrenaline and dopa-beta-hydroxylase. J. Chem. Neuroanat. 3:309–321; 1990.
18. Fritschy, J. M.; Grzanna, R. Immunohistochemical analysis of the neurotoxic effects of DSP-4 identifies two populations of noradrenergic axon terminals. Neuroscience 30:181–197; 1989.
19. Goldstein, L. B.; Coviello, A.; Miller, G. D.; Davis, J. N. Norepinephrine depletion impairs motor recovery following sensorimotor cortex injury in the rat. Restor. Neurol. Neurosci. 3:41–47, 1991.
20. Goldstein, L. B.; Davis, J. N. Clonidine impairs recovery of beam walking after a sensorimotor cortex lesion in the rat. Brain Res. 508:305–309; 1990.
21. Goldstein, L. B.; Davis, J. N. Beam walking in rats: Studies towards developing an animal model of functional recovery after brain injury. J. Neurosci. Meth. 31:101–107; 1990.
22. Goldstein, L. B.; Davis, J. N. Influence of lesion size and location on amphetamine-facilitated recovery of beam walking in rats. Behav. Neurosci. 104:320–327; 1990.
23. Hall, R. D.; Lindholm, E. P. Organization of motor and somatosensory neocortex in the albino rat. Brain Res. 66:23–28; 1974.
24. Held, J. M.; Gordon, J.; Gentile, A. M. Environmental influences on locomotor recovery following cortical lesions in rats. Behav. Neurosci. 99:678–690; 1985.
25. Hoffer, B. J.; Siggins, G. R.; Oliver, A. P.; Bloom, F. E. Activation of the pathway from locus coeruleus to rat Purkinje neurons: Pharmacological evidence of noradrenergic central inhibition. J. Pharmacol. Exp. Ther. 184:553–569; 1973.
26. Hovda, D. A.; Feeney, D. M.; Salo, A. A.; Boyeson, M. G. Phenoxybenzamine but not haloperidol reinstates all motor and sensory deficits in cats fully recovered from sensorimotor cortex ablations. Soc. Neurosci. Abstr. 9:1001; 1983.
27. Jonsson, G.; Hallman, H.; Ponzio, F.; Ross, S. DSP-4, a useful denervation tool for central and peripheral noradrenaline neurons. Eur. J. Pharmacol. 72:173–188; 1981.
28. Jonsson, G.; Hallman, H.; Sundstrom, S. Effects of the noradrenaline neurotoxin DSP-4 on the postnatal development of central noradreniline neurons in the rat. Neuroscience 11:2895–2907; 1982.
29. Kennedy, P. R. Corticospinal, rubrospinal, and rubro-olivary projections: A unifying hypothesis. Trends Neurosci. 13:475–479; 1990.
30. Krobert, K. A.; Boyeson, M. G.; Scherer, P. J. The role of the locus ceruleus in recovery of function from sensorimotor cortex injury. Soc. Neurosci. Abstr. 13:1664; 1987.
31. Loughlin, S. E.; Foote, S. L.; Fallon, J. H. Locus coeruleus projections to cortex: Topography, morphology and collateralization. Brain Res. Bull. 9:287–294; 1982.
32. Loughlin, S. E.; Foote, S. L.; Grzanna, R. Efferent projections of nucleus locus coeruleus: Morphologic subpopulations have different efferent targets. Neuroscience 18:307–319; 1986.
33. Neafsey, E. J.; Bold, E. L.; Haas, G., et al. The organization of rat motor cortex: A microstimulation mapping study. Brain Res. Rev. 11:77–96; 1986.
34. Porch, B. E.; Feeney, D. M. Effects of antihypertensive drugs on recovery from aphasia. In: Brookshire, R. H., ed. Clinical aphasiology. Minneapolis, MN: BRK Publishers; 1986:309–314.
35. Ross, R. A.; Joh, T. H.; Reis, D. J. Reversible changes in the accumulation and activities of tyrosine hydroxylase and dopamine-beta-hydroxylase in neurons of nucleus locus coeruleus during the retrograde reaction. Brain Res. 92:57–72; 1975.
36. Stephens, J.; Goldberg, G.; Demopoulos, J. T. Clonidine reinstates deficits following recovery from sensorimotor cortex lesion in rats. Arch. Phys. Med. Rehab. 67:666–667; 1986.
37. Tsukahara, N. Synaptic plasticity in the red nucleus. In: Cotman, C., ed. Neuronal plasticity. New York: Raven Press; 1978:113–130.
38. Weaver, M. S.; Chen, M. J.; Westerberg, V. S.; Feeney, D. M. Locus coeruleus lesions facilitate recovery of locomotor function after sensorimotor cortex contusion in the rat. Soc. Neurosci. Abstr. 14:405; 1988.