Neurotransmitters and Motor Activity: Effects on Functional Recovery after Brain Injury

Larry B. Goldstein

Department of Medicine (Neurology), Duke Center for Cerebrovascular Disease, Duke University, Durham, North Carolina; and Durham Department of Veterans Affairs Medical Center, Durham, North Carolina

Summary: There are complex relationships among behavioral experience, brain morphology, and functional recovery of an animal before and after brain injury. A large series of experimental studies have shown that exogenous manipulation of central neurotransmitter levels can directly affect plastic changes in the brain and can modulate the effects of experience and training. These complex relationships provide a formidable challenge for studies aimed at understanding neurotransmitter effects on the recovery process. Experiments delineating norepinephrine-modulated locomotor recovery after injury to the cerebral cortex illustrate the close relationships among neurotransmitter levels, brain plasticity, and behavioral recovery. Understanding the neurobiological processes underlying recovery, and how they might be manipulated, may lead to novel strategies for improving recovery from stroke-related gait impairment in humans. **Key Words:** Stroke, motor function, brain injury, norepinephrine, recovery.

INTRODUCTION

Impaired walking after stroke is associated both with higher levels of disability and with compromised levels of social functioning. Depending on the level of assistance required, this particular deficit can lead to great increases in caregiver burden and so may necessitate the patient's residence in a formal assisted-living environment. Effective strategies aimed at improving poststroke gait impairments would help mitigate its functional and societal consequences.

Much has been learned about the immediate response of the brain to stroke-related injury, as well as its potential for plasticity during the recovery period. Understanding the roles of specific neurotransmitters as modulators of the recovery process could lead to effective poststroke restorative pharmacotherapy.

EFFECT OF EXPERIENCE AND TRAINING ON FUNCTIONAL LOCOMOTOR RECOVERY IN ANIMAL MODELS

Numerous studies in laboratory animals show that environmental complexity can have a direct impact on anatomical brain plasticity.[1] Housing in complex environments is associated with overall and regionally specific increases in brain weight, cortical depth, hippocampal thickness, callosal size, and cortical glial density[1] and has effects on both neuronal morphology[1,2] and connectivity.[3] It has also long been recognized that housing animals in complex environments (as opposed to a standard cage), either before or after brain injury, can lead to less severe neurological deficits and more favorable outcomes,[4–6] although some debate remains as to whether this represents true recovery or enhancement of compensatory behavioral strategies.[1]

In addition to general environmental factors, a large number of laboratory studies also show the importance of training after brain injury for functional motor recovery.[2,7,8] As summarized in these detailed reviews, exercise can increase levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), enhance neurogenesis, and improve learning. Rehabilitative training is associated with specific improvements in motor function after cortex injury in several behavioral paradigms,[9–14] particularly when this training is coupled with housing in complex environments.[12,13]

Experimental studies in squirrel monkeys suggest that repetitive use of the impaired hand is required for maintenance of the spared portion of the hand representation after motor cortex infarction.[15] Overuse of the affected limb during vulnerable periods after experimental brain

Address correspondence and reprint requests to: Larry B. Goldstein, M.D., Director, Duke Center for Cerebrovascular Disease, Box 3651, Duke University Medical Center, Durham, NC 27710. E-mail: golds004@mc.duke.edu.

injury is, however, associated with both exacerbation of the underlying brain damage, and in some cases, poorer sensorimotor performance.[16–22] In ischemia models, functional outcome is improved despite exacerbation of injury with exercise begun immediately after the injury.[20] Delaying training for longer periods can diminish this effect.[13] Intensive training after the first 3 to 5 days after focal brain injury does not exacerbate lesion size or negatively affect outcome.[11,14]

Based on this extensive literature, it is clear that there are complex relationships among the behavioral experience, brain morphology, and functional recovery of an animal before and after brain injury. These various processes may affect specific neurotransmitter levels, which may in turn affect brain plasticity. Exogenous manipulation of central neurotransmitter levels, however, can directly affect plastic changes in the brain that could modulate the effects of experience and training. These complex interrelationships provide a formidable challenge for studies aimed at understanding neurotransmitter effects on locomotor recovery.

EFFECT OF NOREPINEPHRINE ON NEURAL PLASTICITY

A large body of work has focused on norepinephrine-modulated locomotor recovery after brain injury, illustrating the close relationships among neurotransmitter levels, brain plasticity, and behavior, For example, norepinephrine has been implicated in trophic changes in the central nervous system.[23] Local infusion of 6-hydroxydopamine, which depletes central norepinephrine, blocks the effects of monocular light deprivation in kittens. Local infusion of norepinephrine reinstates plasticity in animals that are no longer sensitive to this insult. Increases in both growth-associated protein 43 and synaptophysin immunostaining in the ipsilateral and contralateral cerebral hemispheres, as well as other brain areas, have been associated with amphetamine given after unilateral sensorimotor cortex injury in rats.[24]

Norepinephrine and behavioral recovery

Pharmacological studies. Numerous experimental studies provide evidence supporting the role of norepinephrine as a modulator of behavioral motor recovery after injury to the motor cortex. Feeney and coworkers[25] first reported that the administration of a single dose of d-amphetamine the day after a unilateral sensorimotor cortex injury in the rat results in an enduring enhancement of motor recovery. This group later extended the observation to other species and other behavioral deficits. For example, postlesion treatment with amphetamine also enhances motor recovery in cats with unilateral or bilateral frontal cortex ablations[26,27] and reinstates stereoscopic vision in cats with bilateral visual cortex lesions.[28,29]

Although amphetamine may influence the release of a variety of neurotransmitters, several lines of evidence suggest that its effect on recovery is related to enhanced release of central norepinephrine. First, direct intraventricular infusion of norepinephrine (but not dopamine) mimics the effect of amphetamine.[30] In addition, pharmacological studies show that the impact on recovery of other adrenergic agonists and antagonists can be predicted based on their effects on the release of norepinephrine from noradrenergic terminals. Both yohimbine and idazoxan (centrally acting α_2-adrenergic receptor antagonists) increase norepinephrine release and enhance motor recovery when administered to rats as a single dose after unilateral sensorimotor cortex injury.[31,32] Clonidine, a centrally acting α_2-adrenergic receptor agonist that decreases norepinephrine release, has a prolonged detrimental effect on motor recovery in rats and reinstates motor deficits when given to animals that had recovered motor function.[33,34] Prazosin and phenoxybenzamine, centrally acting α_1-adrenergic receptor antagonists, are also harmful.[34–36] Coadministration of the butyrophenone haloperidol blocks amphetamine-promoted motor recovery in rats and impairs motor recovery when given alone.[25] Haloperidol also blocks amphetamine-facilitated visual recovery in visually decorticated cats.[29,37] Haloperidol, fluanisone, and droperidol each transiently reinstate motor deficits in recovered rats.[38]

Because haloperidol is a dopamine receptor antagonist, these later experiments might be considered as providing evidence for a dopaminergic effect on motor recovery after brain injury; however, haloperidol is also a noradrenergic receptor antagonist. Radioligand binding studies show that haloperidol is a marginally more potent α_1-adrenergic receptor antagonist than clozapine (K_d 6.1 *versus* 9 nM, respectively), but clozapine is a significantly more potent α_2-adrenergic receptor antagonist than haloperidol (K_d 160 *versus* 3800 nM, respectively). As expected, dose–effect experiments found that haloperidol had increasingly detrimental effects on post–brain injury motor recovery with increasing dose.[39] In contrast, clozapine facilitated recovery at low dose (an α_2-adrenergic receptor antagonist effect) but impaired recovery at higher doses (an α_1-adrenergic receptor antagonist effect; FIG. 1). Thus, the dose-related effect of clozapine on recovery (facilitory at low doses and detrimental at higher doses) and the harmful effects of haloperidol are entirely predictable based on a noradrenergically mediated mechanism.

Lesioning studies. Consistent with the pharmacological data, several additional lines of evidence suggest the

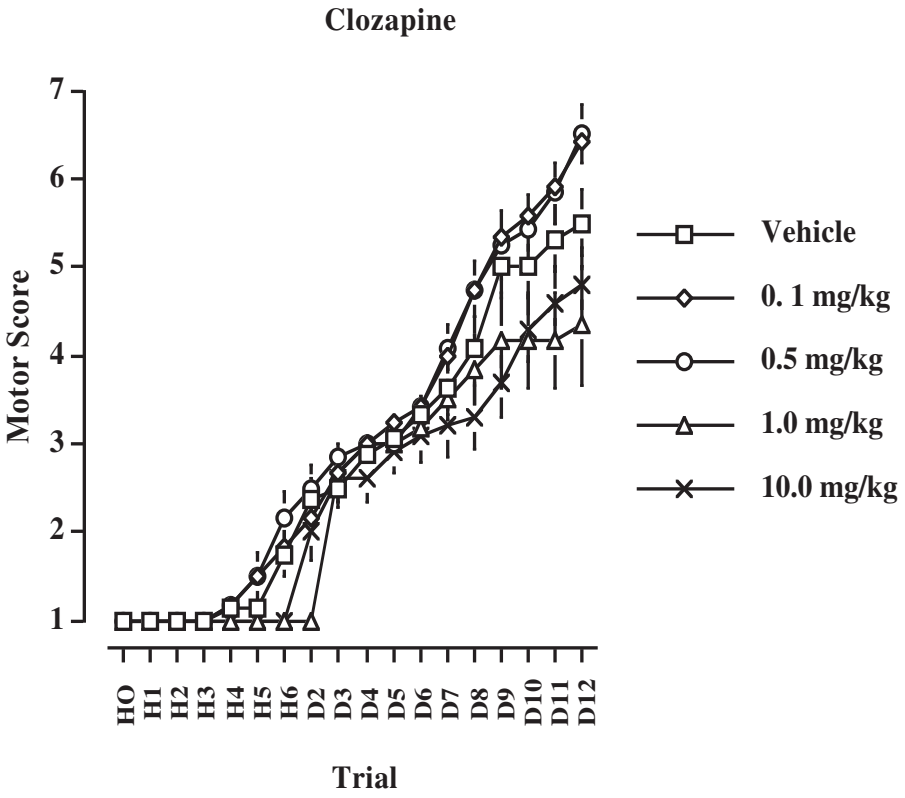

FIG. 1. Effect of clozapine at different doses on locomotor recovery after unilateral sensorimotor cortex injury. Trials are identified in hours (H) or days (D) after the first postoperative behavioral testing trial (zero hours, H0) in which the rat is required to traverse a narrow horizontal beam. The baseline first trial, H0, was given 24 hours after cortex lesion surgery. A single dose of vehicle or drug was given immediately after the baseline trial. Symbols represent locomotor scores for each trial (mean ± SEM). Motor performance was rated on a seven-point scale by an observer blind to the study hypothesis: 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 seconds; 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. Rats given 1.0 or 10.0 mg/kg of clozapine of had poorer overall recoveries than those given 0.1 or 0.5 mg/kg (ANOVA $F_{4,51}$; $p = 0.014$, Fisher's LSD $p < 0.02$, respectively). Clozapine had no effect on beam-walking scores in sham cortex-lesioned rats at any dose (data not shown). Reproduced from Goldstein and Bullman, 2002.[39]

importance of norepinephrine as a modulator of motor recovery after brain injury. The neurotoxin DSP-4 [*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine selectively destroys central noradrenergic neurons. Pretreatment with DSP-4 impaired motor recovery in rats after a subsequent injury to the cerebral cortex, but the norepinephrine depletion had no effect on locomotor activity in rats without a cortical lesion.[40,41] The pontine nucleus locus ceruleus is the major source of noradrenergic projection fibers to the cerebral cortex.[42–44] Cortical damage elicits changes in the norepinephrine content of the locus ceruleus.[45] As expected based on the DSP-4 experiments, bilateral locus ceruleus lesions prior to a unilateral sensorimotor cortex lesion results in poorer behavioral recoveries as compared to controls that had sham locus ceruleus lesions.[46] Again, the locus ceruleus lesions had no effect on locomotion in rats that later had sham cortex lesions.

Although predominately ipsilateral, each locus ceruleus projects to both cerebral hemispheres,[47,48] and unilateral left or right locus ceruleus lesions similarly impair recovery after a subsequent right cortex lesion.[46] Locus ceruleus neurons project to the cerebral cortex and subcortical structures via the dorsal noradrenergic bundle (DNB), which can also be lesioned permitting selective noradrenergic depletion of each hemisphere.[49] 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 (FIG. 2).[50] Moreover, the norepinephrine content in the contralateral but not ipsilateral cerebral cortex in rats with contralateral DNB–sham DNB lesions correlates with the rate of motor recovery.[50] These results are not only consistent with the role of norepinephrine as a modulator of post–brain injury recovery, but suggest that the effect is mediated in the cerebral hemisphere contralateral to the site of cortical injury.

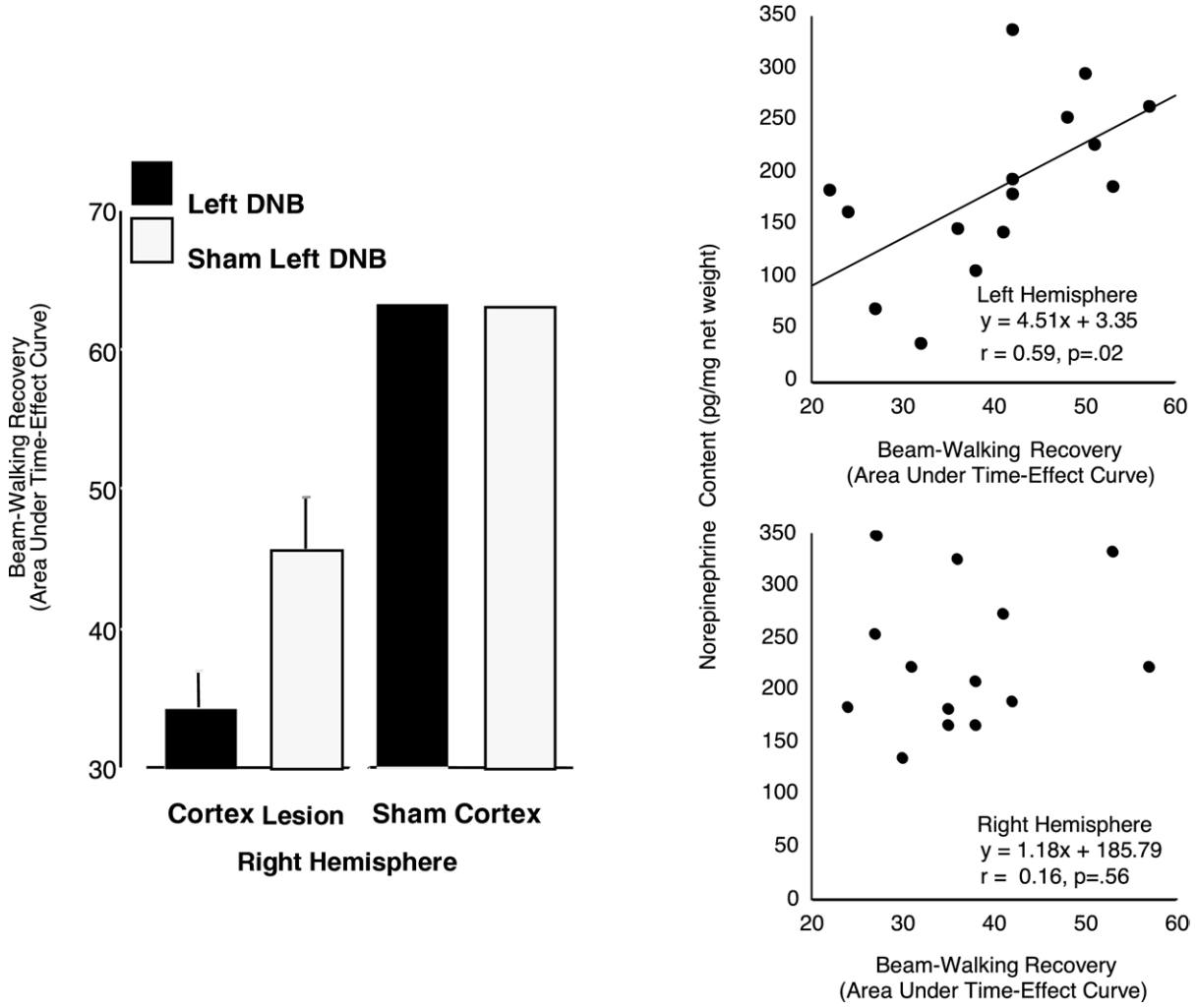

FIG. 2. Effects of prior left dorsal noradrenergic bundle (DNB) lesions on locomotor recovery after a subsequent right sensorimotor cortex lesion. Behavioral testing was performed with the same paradigm as described for FIG. 1. Each animal's recovery was calculated from the area under the curve formed by graphing score against time. The left panel shows recovery for animals with either a left DNB lesion (noradrenergically denervating the left cerebral hemisphere) or sham left DNB lesion prior to a right sensorimotor cortex lesion or sham right sensorimotor cortex lesion (Error bars are +/− SEM). Left DNB lesions had no effect on motor performance in rats with a subsequent sham sensorimotor cortex lesion. Cortex-lesioned rats with prior left DNB lesions had significantly impaired recoveries (areas under the time–effect curves) compared with cortex-lesioned rats with sham DNB lesions (ANOVA $F_{3,16}$, $p < 0.001$; left DNB lesion-cortex lesion *versus* sham DNB lesion-cortex lesion, Fisher's LSD, $p < 0.02$). The right upper panel gives the correlation between recovery and norepinephrine content in the left cerebral hemisphere and the right lower panel shows the lack of correlation between recovery and norepinephrine content in the right cerebral hemisphere in these same animals. There was no effect of a right (ipsilateral) DNB lesion on recovery (data not shown). The results suggest that norepinephrine exerts its influence on locomotor recovery, at least in part, in the cerebral hemisphere contralateral to a sensorimotor cortex lesion. Modified from Goldstein and Bullman, 2002.[50]

Norepinephrine, experience, plasticity, and the contralateral homotypic cortex

After several weeks, there is use-dependent increased dendritic arborization in the homotypic cortex contralateral to a lesion of the forelimb sensorimotor cortex, followed by pruning and synaptogenesis,[8,12,14,51–54] with increases in layer V synapse-to-neuron ratios and dendritic arborizations that can be detected after approximately 30 days.[12,14] The enhanced dendritic arborization is use-dependent (i.e., there are complex interrelationships among the effects of a brain lesion, behavioral experience, and neuroanatomical changes).[54,55] Neither a lesion nor asymmetrical limb-use alone accounts for the increases in contralateral layer V pyramidal neuron dendritic arborizations.[55] These data are consistent with a relationship between recovery and norepinephrine content of the contralateral cerebral cortex.

Interaction between pharmacological intervention and experience or training in functional recovery after focal brain injury

As already noted, neurotransmitter-mediated effects on functional recovery after brain injury depend on the ani-

mal's behavior. For example, with both amphetamine and haloperidol effects on motor recovery in rats are blocked if the animals are restrained rather than given motor practice after drug administration.[25] A smaller effect of the drug is found in rats that are allowed to ambulate freely but are not given specific training, and more dramatic improvements of recovery occur if training is used in combination with the drug.[10] The effect of amphetamine on motor recovery in cats with cortical injuries is also dependent on the animal's experience after lesioning.[26] Similarly, amphetamine-facilitated recovery of stereoscopic vision in visually decorticated cats also depends on visual experience after the drug is given.[28]

Effect of norepinephrine on recovery: mechanism

The cellular mechanisms that underlie learning provide a useful paradigm for considering the possible mechanism of norepinephrine-modulated recovery because the effect is experience dependent. Long-term potentiation (LTP) is the best-understood putative cellular mechanism of learning and memory.[56,57] In the hippocampal formation, LTP is induced by a single, transient, high-frequency stimulation of excitatory neural inputs. Neurotransmitters such as catecholamines,[58–61] GABA,[62–64] and acetylcholine[65,66] can affect LTP. Thus, it is possible that norepinephrine could initially affect LTP induction, which in turn could lead to the neuroanatomical changes discussed.

OTHER NEUROTRANSMITTERS AND MOTOR RECOVERY

Acetylcholine would be expected to facilitate the induction of LTP by suppressing voltage-activated potassium conductance.[57] Activation of the muscarinic cholinergic receptor facilitates the induction of LTP in the rat dentate gyrus.[67] Scopolamine, an anticholinergic, interferes with motor recovery after cortex infarction in rats.[68] Giving acetylcholine has the opposite effect, facilitating recovery in animal brain injury models.[69] It is also possible, however, that the putative effects of cholinergic drugs on recovery might be mediated by their indirect actions on noradrenergic neurons.[70,71]

GABA influences LTP and learning and memory. Stimulation of inhibitory GABAergic inputs to the hippocampal formation,[63,72] as well as indirect GABA agonists such as benzodiazepines, suppress the induction of LTP.[73] Intracortical infusion of the inhibitory neurotransmitter increases the hemiparesis produced by a small motor cortex lesion in rats.[74] Diazepam, an indirect GABA agonist, impedes recovery from the sensory asymmetry caused by anterior-medial neocortex damage in the rat.[75] Amphetamine administration influences the activity of GABAergic neurons, leading to lower extracellular GABA concentrations.[76] This would be expected to enhance the induction of LTP.

More limited data are available concerning serotonin. Fluoxetine combined with training did not alter the degree or rate of recovery of function in rat, compared with nontreated animals.[77]

SUMMARY

There are complex interrelationships among the levels of certain central neurotransmitters, brain plasticity, behavioral experience, and recovery after brain injury. For locomotor recovery after injury to the sensorimotor cortex, extensive data indicate an important role for norepinephrine. Understanding the neurobiological processes underlying recovery, and how they might be manipulated, may lead to novel strategies to improve stroke-related gait impairments in humans.

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