Studies in laboratory animals clearly show that the rate and extent of functional recovery after focal brain injury can be modulated by drugs affecting certain neurotransmitters in the central nervous system. Preliminary clinical studies suggest that similar drug effects occur in humans recovering from stroke. Understanding these pharmacological effects is important because several of the classes of drugs that impair recovery in laboratory experiments are used to treat coincident medical problems in patients who have had a stroke.

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Clinicians have long recognized that most stroke survivors recover over time, albeit to varying degrees. Although the initial severity of the patient’s neurologic deficit is the single most powerful predictor of eventual functional status, a variety of other factors can affect the final levels of impairment, disability, and handicap resulting from stroke. Findings from experiments performed in the laboratory seem to indicate that the rate and degree of recovery can be affected by certain neurotransmitters in the central nervous system (CNS). Because many of the drugs used to treat coincident medical problems in patients who have had a stroke affect the CNS, these drugs also may have an unrecognized effect on the recovery process.

Motor function is one of the most important determinants of the level of post-stroke independence in activities of daily living. Several lines of evidence suggest that motor recovery after injury to the cerebral cortex can be modulated through the effects of norepinephrine on the CNS. Detailed reviews have been published.1-3 For example, in rats, central infusion of norepinephrine hastens locomotor recovery after a unilateral sensorimotor cortex lesion. In contrast, the administration of DSP-4 [N-(chloroethyl)-N-ethyl-z-bromobenzylamine], a neurotoxin that leads to the depletion of norepinephrine in the CNS, has the opposite effect and delays the recovery process. In addition, bilateral or unilateral selective lesions of the locus ceruleus, the major source of noradrenergic projection fibers to the cerebral cortex and cerebellum, also impair motor recovery after a subsequent unilateral cortical lesion.

Several areas of the brain may be involved in mediating the effects of norepinephrine. Unilateral injury to the cerebral cortex in rats results in a bilateral reduction of extracellular levels of norepinephrine in the cerebellum, and infusion of norepinephrine into the cerebellar hemisphere contralateral to but not ipsilateral to the side of a cortical lesion enhances motor recovery. In addition, selective creation of a lesion of the contralateral but not ipsilateral dorsal noradrenergic bundle (through which fibers from each locus ceruleus project to the cerebral cortex and subcortical structures) impairs motor recovery after a subsequent cortical lesion.4 Thus, these experiments are consistent not only with the hypothesis that motor recovery after damage to the cerebral cortex is, at least in part, modulated through the effects of norepinephrine on the CNS but also with the hypothesis that the effects of norepinephrine may be mediated in the contralateral cerebral and cerebellar hemispheres.

These studies were designed in conjunction with a complementary series of experiments in which the levels of norepinephrine in the CNS or its effects were manipulated pharmacologically (Table). In a provocative initial experiment, Feeney and Sutton5 found that, when combined with task-relevant experience, a single dose of dextroamphetamine given the day after a unilateral sensorimotor cortex ablation in the rat resulted in an enduring enhancement of motor recovery. The amphetamine effect found by Feeney and Sutton was extended to functional deficits that occur after focal
lesions produced through a variety of mechanisms, to lesions affecting other areas of the cortex, and to other behaviors. Given the hypothesis that the effect of amphetamine on recovery is exerted through its effect on norepinephrine, other drugs that enhance the release of norepinephrine or decrease its metabolism would be expected to be beneficial. In fact, yohimbine and idazoxan (α2-adrenergic receptor antagonists that increase the release of norepinephrine in the CNS) facilitate motor recovery when given as a single dose after unilateral sensorimotor cortex injury. Phentermine, an amphetamine analog with weaker cardiovascular effects, phenylpropanolamine, and methylphenidate hydrochloride also accelerate motor recovery after experimental focal brain injury.

If drugs that enhance norepinephrine release are beneficial, then drugs that decrease norepinephrine release, increase its metabolism, or block its postsynaptic effects would be hypothesized to be harmful. In experiments designed to test this hypothesis, a single dose of the α2-adrenergic receptor agonist clonidine hydrochloride, given the day after cortex injury, was found to have a prolonged detrimental effect on motor recovery in rats and to reinstate the deficit in recovered animals. Prazosin and phenoxybenzamine, α1-adrenergic receptor antagonists that act on the CNS, also interfere with recovery. In contrast, propranolol, a nonselective β-adrenergic receptor antagonist, has no effect.

In addition to the effect of noradrenergic agents on motor recovery, several other classes of drugs that act on the CNS may affect recovery from other types of behavioral deficits (Table). For example, dopaminergic agents may influence recovery from neglect caused by prefrontal cortical injury. Apomorphine, a dopamine agonist, reduces the severity of experimentally induced neglect, and spiroperidol, a dopamine receptor antagonist, reinstates neglect in recovered animals. Concurrent administration of haloperidol also blocks amphetamine-promoted recovery, and haloperidol, as well as other butyrophenones (fluanisone, droperidol), transiently reinstates the deficits in recovered animals.

Depression is common after stroke and often prompts the use of antidepressant medications. The administration of a single dose of trazodone transiently slows motor recovery in rats with sensorimotor cortex injury and reinstates the hemiparesis in recovered animals. A single dose of desipramine facilitates motor recovery. In contrast, fluoxetine and amitriptyline have no demonstrable effect on motor recovery after experimental focal brain injury.

Intracortical infusion of γ-aminobutyric acid (GABA) was found to increase the hemiparesis produced by a small motor cortex lesion in rats. The short-term administration of the benzodiazepine diazepam, an indirect GABA agonist, permanently impedes recovery from the sensory asymmetry caused by damage to the anteromedial neocortex in the rat. Antianxiety agents that do not act through the GABA-benzodiazepine receptor complex, such as gepirone, do not seem to impair recovery in similar animal models. The deleterious effect of GABA on motor recovery after motor cortex injury is increased by the peripheral administration of phentoyin. Phenobarbital also delays behavioral recovery after injury to the cerebral cortex in laboratory studies. In contrast, neither carbamazepine nor vigabatrin has detrimental effects.

Although the cellular mechanisms underlying the effects on recovery of drugs that act on the CNS remain largely speculative, several general principles have emerged from the experimental studies. First, individual drugs can have varying effects based on the dosage. For example, amphetamine has increasing and then decreasing benefit with increasing dosages. Second, the timing of drug administration may be crucial. Some drugs, such as benzodiazepines, that may be neuroprotective when given soon after the stroke are harmful when given later. Amphetamine may no longer be effective after a therapeutic window of opportunity has passed. Last, the effects of many drugs, particularly the effects of noradrenergic agents on motor re-
covery after injury to the cerebral cortex, are highly dependent on the animal's experience (eg, drug administration must be coupled with training).

The first study of the effects of amphetamine on recovery after stroke in humans was carefully designed to simulate the paradigm used in the laboratory. A detailed review of clinical studies has been published. Eight patients with stable motor deficits were randomized to receive a single dose of amphetamine or a placebo within 10 days of ischemic stroke, with drug administration tightly coupled with physical therapy. The following day, the amphetamine-treated group had a significant improvement in motor performance (P < .05, Wilcoxon rank-sum test), whereas there was little change in the placebo-treated group. A second double-blind, placebo-controlled trial involving 12 patients found no treatment effect, but it differed in several ways from the previous study. A different dosing regimen was used, interventions began more than 1 month after the stroke, and the administration of the drug or placebo was not tightly linked with physical therapy. In a third double-blind, placebo-controlled trial, a short course of treatment began between 15 and 30 days after the stroke, with each dose of amphetamine or placebo given in tight conjunction with physical therapy. Patients treated with amphetamine had significantly greater improvements in motor scores compared with placebo-treated patients (P < .05, Mann-Whitney U test), and that benefit persisted for as long as 10 months after the intervention ceased. In combination with the principles learned from the laboratory, these 3 clinical studies suggest that drug dosage, timing, and the tight coupling of drug therapy with physical therapy may be critical determinants of whether the treatment is efficacious.

Limited prospective studies of other drugs that were hoped to enhance poststroke recovery have been conducted recently. One controlled study of the effect of methylphenidate on poststroke neurologic impairments found no effect of the drug on physical performance despite significant effects on cardiovascular function. However, variables shown to be important from laboratory studies and suggested from the results of the aforementioned clinical trials of amphetamine were not considered in the study design. Trazodone, a drug that impairs recovery from hemiplegia in the rat, was found to reduce disability in patients who are depressed after a stroke. Other studies have found a beneficial effect of fluoxetine (P < .05, Mann-Whitney U test) and no significant effect of the norepinephrine reuptake blockers maprotiline and nortriptyline hydrochloride. Therefore, unlike amphetamine, the effects of antidepressants on functional recovery in humans seem to be different from the effects predicted based on the results of the laboratory studies (Table). These disparate results may have occurred because the drugs were only given in a single dose in the laboratory studies and were given soon after the injury. Again, dosing and timing may be important variables. Preliminary uncontrolled studies suggested that the administration of bromocriptine mesylate, a dopamine agonist, improved fluency in certain patients with aphasia. However, 2 small controlled studies found no differences. These disappointing results may have been due to a variety of factors. One study of the effects of amphetamine on recovery from aphasia resulting from stroke has been completed. Although the results seem promising, the study was uncontrolled.

Determining whether the detrimental effects of drugs anticipated from laboratory studies also occur in humans is difficult but important, because many of these medications are commonly given to patients recovering from stroke. In a retrospective cohort study, the level of motor recovery of patients who had a stroke and who received, either alone or in combination, the antihypertensives clonidine or prazosin, dopamine receptor antagonists, benzodiazepines, or phenytoin (drugs that were anticipated to impair recovery based on the results of laboratory studies) was compared with the level of recovery of a similar group of patients who were not given any of these medications. Patients who received the drugs had poorer levels of recovery than did the control patients. Multivariate regression analysis indicated a significant effect (P = .025) of “drug group” even after correcting for the contributions of other variables, including the initial severity of the deficit. A similar effect was found in a separate cohort of patients with anterior circulation ischemic stroke, who were enrolled as control patients in a short-term interventional stroke trial. Almost 40% received 1 or a combination of drugs hypothesized to impair recovery during the first 30 days after stroke. As with the previous study, stepwise multivariate analyses indicated a negative effect on outcome in the drug group, independent of the degree of the initial motor impairment, comorbid conditions, and other patient characteristics. However, because both studies involved retrospective analyses, whether the reason for the administration of a given drug or the drug itself influenced recovery cannot be determined. Furthermore, the effects of specific “detrimental” drugs, dosage, and timing could not be analyzed.

Physicians caring for patients recovering from stroke should become aware of the potential negative effect of drugs commonly prescribed to treat other conditions. Whenever possible, these drugs should be avoided. As the basic neurobiological factors underlying recovery become better understood, drugs targeted at enhancing the recovery process may become part of the standard treatment of patients who have a stroke.

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