Basic and Clinical Studies of Pharmacologic Effects on Recovery from Brain Injury

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ABSTRACT

Investigations in laboratory animals indicate that certain drugs that influence specific neurotransmitters can have profound effects on the recovery process. Even small doses of some drugs given after brain injury facilitate recovery while others are harmful. Preliminary clinical studies suggest that the same drugs that enhance recovery in laboratory animals (e.g., amphetamine) may have similar effects in humans after stroke. In addition, some of the drugs that impair recovery of function after focal brain injury in laboratory animals (e.g., haloperidol, benzodiazepines, clonidine, prazosin, phenytoin) are commonly given to stroke patients for coincident medical problems and may interfere with functional recovery in humans. Until the impact of pharmacologic agents on the recovering brain is better understood, the available data suggest that care should be exercised in the selection of drugs used in the treatment of the recovering stroke patient. Pharmacologic enhancement of recovery after focal brain injury may be possible in humans.

KEY WORDS
head injury, stroke, recovery of function, drugs, motor function, aphasia, humans, rats

INTRODUCTION

Stroke and traumatic brain injury are major causes of neurologic disability. Although many stroke survivors have significant deficits, most recover some degree of function /53/. This recovery can continue over a period of years in certain individuals /6/; however, spontaneous improvement is largely completed by one month after stroke (Fig. 1) /53,114,124,139,188,189/. Traumatic brain injury affects 200-400 persons per 100,000

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population in the United States /70/. Although most of these individuals have only minor injuries and do not come to medical attention /70/, moderate head injury (Glasgow Coma Scale 9-12) affects 60-75,000 cases per year /132/. Of patients with moderate head trauma, two-thirds are moderately to severely disabled 3 months after the injury /155/.

Because of the prevalence of stroke and traumatic brain injury, therapies that improve recovery would have significant medical, social and economic importance. This review discusses recent insights into the functional processes underlying recovery that have led to the preliminary clinical applications of new treatment strategies designed to enhance function after brain injury.

**RECOVERY AFTER FOCAL BRAIN INJURY**

Biologic processes that influence functional recovery after focal brain damage can be empirically divided into two main, but interrelated, groups. These groups of processes entail the resolution of the pathologic sequellae of the injury and the adaptive responses of brain tissue that was not damaged by the primary lesion (Table 1). The adaptive responses can be further divided into rapidly and more slowly developing processes.

### TABLE 1

Biologic processes influencing functional recovery after focal brain damage

| I. Resolution of pathologic sequellae |
|--------------------------------------|
| 1. Cerebral edema                      |
| 2. Diaschisis                          |
| 3. Denervation supersensitivity        |
| 4. Rapid changes in dendritic spines   |

| II. Adaptive responses                 |
|---------------------------------------|
| 1. Rapid adaptive responses           |
|   - Un-masking                        |
|   - Re-learning                       |
| 2. Slow adaptive responses (neuronal rearrangements) |
|   - Regeneration                      |
|   - Pruning                           |
|   - Collateral sprouting              |
|   - Ingrowth                          |

**Pathologic sequellae**

Cerebral edema commonly accompanies brain injury. Its complex pathophysiology has been extensively reviewed (see /112/). Cytotoxic cerebral edema involves the accumulation of intracellular fluid whereas vasogenic edema entails leakage of proteins and fluid from damaged blood vessels (a defect of the blood-brain barrier). Cerebral edema may produce local functional depression in the area immediately surrounding the primary area of injury. Remote functional depression can be caused by compression of distant normal structures. Clinical worsening and spontaneous improvement in patients after acute brain injury may be due, in part, to the development and subsequent resolution of edema.

Diaschisis, a term originated by the German pathologist Von Monakow /187/, refers to sudden functional depression of brain regions distant from the site of primary injury. Diaschisis has been reviewed by Feeney and is discussed elsewhere in this issue /57,58/. Diaschisis has been demonstrated experimentally in a variety of laboratory animal model systems /31,65,109,183/. In humans, reductions of blood flow and metabolism following hemispheric stroke have been demonstrated by positron emission tomography in the non-injured ipsilateral cerebral hemisphere, the contralateral cerebral hemisphere, and the contralateral cerebellum /68,118,133,182/. Crossed cerebellar-cortical diaschisis occurs in patients with unilateral cerebellar infarction /19/. Capsular or thalamic stroke also can have remote effects on metabolism in the cerebral cortex and cerebellum /142/. The pathophysiologic mechanism underlying diaschisis is not understood /31,58/. Depression of metabolic activity in brain regions distant from the primary site of injury might be a reflection of regional changes in cerebral blood flow. Alternatively, decreased regional cerebral blood flow may be a secondary phenomenon reflecting locally depressed cerebral metabolism. These remote areas of depressed cerebral metabolic activity could result from injury to excitatory projections from the injured region. It has also been suggested that diaschisis could be caused by the release of vasoactive or neuroactive substances from the damaged brain /168/.

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As in the peripheral nervous system, lesions in the central nervous system may also result in enhanced responses of targets to neurotransmitters (denervation supersensitivity) /40/. The potential relationship of this phenomenon to behavioral recovery has been extensively reviewed (see /67/). Briefly, partial damage to the dendritic tree results in an acute decrease in the amount of neurotransmitter available at the synapse. An up-regulation of post-synaptic receptors ensues. Subsequent presentation of a smaller amount of neurotransmitter then results in an exaggerated physiologic response that may restore function. A variety of other short-term synaptic changes may occur /199/ and rapid morphological changes in dendritic spines have been observed in different species under a variety of conditions /76,199/.

**Rapid adaptive responses**

Distinct from processes involved in the resolution of the pathologic sequelae of brain injury, adaptive responses refer to the mechanisms by which uninjured brain assumes functions that were previously performed by injured neurons. Several theoretical types of adaptive responses may occur. One hypothesis is that redundant neural networks may perform functions lost due to brain injury. This hypothesis was suggested by Lashley /117/ and Luria /126,127/ and has also been discussed as un-masking /192/. More recent studies with positron emission tomography in human stroke patients demonstrate metabolic changes that are consistent with unmasking. In uninjured humans, motor movement is associated with increases in regional cerebral blood flow (rCBF) in a circumscribed region in the contralateral primary sensorimotor cortex. However, in patients recovered from stroke that had resulted in hemiparesis, movement of the previously affected limb is associated with significant changes in rCBF in widespread areas of the brain including both ipsilateral and contralateral sensorimotor cortex and cerebellar hemispheres /32,196/.

A second general hypothesis is that the cellular mechanisms that may be responsible for normal learning and memory is long-term potentiation (LTP) /14-16/. LTP has been described by Collingridge and Bliss as a "kind of activity-dependent change in synaptic efficacy that is assumed to provide the physiological basis of information storage in the brain" /37/. In the hippocampal formation, LTP is induced by a single, transient, high-frequency stimulation of excitatory neural inputs. This produces an increase in synaptic responses that can last for prolonged periods of time /15,16/. LTP has been best characterized in the hippocampal formation, but has also been demonstrated in several other brain regions including hypothalamus /38/, visual cortex /4,5/ and motor cortex /113/.

**Slow adaptive responses**

A variety of neuronal rearrangements occur after many types of brain injuries /39,46,67,110,125,152, 153/. Some of these rearrangements would be expected to be beneficial while others are potentially maladaptive and could contribute to the ultimate functional deficit. Davis has classified neuronal rearrangements into four major groups /46/. *Regeneration* refers to the regrowth of an injured neuron's axon to innervate the denervated target. Axonal regeneration would be the ideal rearrangement to restore function. Although controversial and difficult to demonstrate, functional regeneration of axons may occur in the central nervous system /12,69/. *Pruning* occurs in highly collateralized neurons (single neurons with many axons). When one axon is injured, collateral branches extend to reinervate the target /166/. Unlike regeneration, pruning has been clearly demonstrated in the adult brain and should be a beneficial adaptive rearrangement /73-75,91,92, 147/. *Collateral sprouting*, the most extensively studied neuronal rearrangement, refers to neurite outgrowth from an uninjured nerve in response to damage to an adjacent fiber. Sprouting has been demonstrated in the central nervous system /39/ and can result in the formation of electrophysiologically functional synapses /176,185/. Collateral sprouting may be maladaptive because it usually results in the hyperinnervation of the target. *Ingrowth* is the response of an uninjured nerve to a remote injury. A foreign neuron grows to innervate a target in
response to the loss of the target's normal innervation. The most extensively studied example of ingrowth is the expansion of sympathetic fibers from surface blood vessels into the brain parenchyma after certain lesions /43/. Sympathetic ingrowth interferes with recovery after various specific experimental lesions in laboratory animals /93,94/.

**DRUGS AND FUNCTIONAL RECOVERY: FUNDAMENTAL STUDIES**

Drugs can influence recovery through a variety of mechanisms affecting the resolution of pathologic sequelae of brain injury as well as both rapid and slow adaptive brain responses. An individual drug could impact on all of these processes. These drug effects may be either beneficial or detrimental (Table 2).

| Transmitter/Drug | Effect on Recovery |
|------------------|--------------------|
| Norepinephrine   | +                  |
| Amphetamine      | +                  |
| Clonidine        | -                  |
| Haloperidol      | -                  |
| Prazosin         | -                  |
| Propranolol      | 0                  |
| GABA             | -                  |
| Diazepam         | -                  |
| Muscimol         | -                  |
| Phenotoin        | -                  |
| Ro 15-1788       | +                  |
| Acetylcholine    | +                  |
| Scopolamine      | -                  |
| Glutamate        |                   |
| MK-801           |                   |

"+" indicates a beneficial effect on recovery, "+" indicates a detrimental effect, and "0" indicates no effect. Revised from Goldstein /80/. See text for references.

**Catecholamines**

Amphetamine is among the most extensively studied drugs with the capacity to facilitate recovery after focal brain injury. It was recognized as early as 1946 that treatment with amphetamine restored righting and other postural activity in low decerebrate cats /130/. Placing responses returned in hemidecorticate and neodecorticate cats following amphetamine administration /61,128,136/. More recently, an enduring recovery of function has been demonstrated in cats that had been subjected to bilateral visual cortex ablations /62,106/. This lesion results in a complete and permanent deficit of stereopsis. Treatment with amphetamine, when combined with visual experience, resulted in recovery of binocular depth perception. Relearning of a visual discrimination task in visually decorticated rats is also facilitated by amphetamine /25/.

Because motor function is a particularly important determinant of physical function and independence in activities of daily living after brain injury in humans /119/, the impact of drugs on motor recovery after focal cortex injury has been the subject of extensive laboratory investigations. A sensorimotor cortex lesion in the rat does not result in a dramatic motor deficit when the animals are observed on a flat field, but becomes obvious when the animals traverse a narrow elevated beam (beam-walking ability) /29,129/. Feeney et al. devised a simple system for grading this motor deficit and found that a single dose of D-amphetamine administered 24 hours following unilateral sensorimotor cortex ablation accelerated the rate of functional recovery /59,60/. Post-lesion treatment with amphetamine also enhanced motor recovery in cats with unilateral or bilateral frontal cortex ablation /104,136,179/.

Understanding the pharmacologic mechanism of amphetamine-facilitated recovery has been hampered because the drug has diverse central and peripheral effects. Systemic administration of amphetamine may produce raised blood pressure with reflex bradycardia, behavioral arousal and hypermotility /197/. Dextroamphetamine also may induce changes in regional cerebral blood flow and metabolism /134,135/. Furthermore, amphetamine's central actions may be mediated through...
noradrenergic, dopaminergic, or serotonergic neurons /72/. The pharmacologic and behavioral effects of amphetamine are also dose dependent. For example, the levels of norepinephrine in rat brain are decreased when amphetamine is administered in a relatively high dose. This effect is most likely caused by depletion of granular amine stores combined with an inhibition of the re-uptake mechanism /72/. However, acute pharmacologic effects of the drug may also be related to the release of extragranular accumulations of catecholamines /72/. In addition, amphetamine may induce a disaggregation of brain polysomes thereby influencing protein synthesis /138/. The dose-effect curve for amphetamine-facilitated motor recovery in rats formed an inverted 'U' with a decline in response at higher doses /80/. This decline is likely due to amphetamine-induced stereotypes.

One strategy that has been employed to study the pharmacologic basis of the amphetamine effect has been to measure the impact of a series of specific agonists and antagonists on functional recovery. Coadministration of haloperidol blocks amphetamine-promoted recovery /60,105/ and haloperidol impairs motor recovery when given alone /60/. Although haloperidol is a butyrophenone, in addition to its action as a dopamine receptor antagonist, it has antagonist effects at noradrenergic receptors /35,47,146/. Other lines of evidence suggest that amphetamine-promoted recovery of function is noradrenergically mediated. Intraventricular /21/ or cerebellar /22/ infusions of norepinephrine facilitate recovery. Intraventricular administration of dopamine in combination with a dopamine-β-hydroxylase inhibitor or dopamine alone had no effect /21/. Treatment with a centrally acting α₁-adrenergic receptor antagonist (i.e., prazosin) interferes with motor recovery /177,195/. Post-lesion systemic administration of an α₂-adrenergic receptor antagonist (i.e., yohimbine, idazoxan) is beneficial /79,89,177,178,195/, whereas the α₂-adrenergic receptor agonist clonidine impairs motor recovery when given soon after brain injury /85/ and reinstates motor deficits in recovered rats /175,177,178,195/. Furthermore, pretreatment with the neurotoxin DSP-4, a drug that selectively depletes central norepinephrine, slows beam-walking recovery /20,83/. Taken together, these data suggest that amphetamine influences recovery through its effects on central norepinephrine. Although this work was largely carried out in rats with aspiration lesions of the cerebral cortex, the effect of noradrenergic agents on recovery is similar in traumatic cerebral contusion and cortex infarction injury models /49,66,107,108/.

GABA

Intracortical infusion of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) increases the hemiparesis produced by a small motor cortex lesion in rats /23/. The deleterious effect of GABA is increased by the systemic administration of phenytoin /24/, which may act through a GABA-mediated mechanism /33/. The short-term administration of diazepam, a benzodiazepine that acts as an indirect GABA agonist, permanently impedes recovery from the sensory asymmetry caused by anteromedial neocortex damage in the rat /163/. This long-term deleterious effect of diazepam is mimicked by short-term infusion of the GABA agonist, muscimol, into the sensorimotor cortex adjacent to the lesion /100/ and is blocked by coadministration of the benzodiazepine antagonist Ro 15-1788 /97/. Ro 15-1788 alone produces a transient facilitation of recovery /165/. Thus, GABA or GABA agonists interfere with the recovery process whereas GABA antagonists may be beneficial.

Acetylcholine

In 1942 Ward and Kennard reported that cholinergic agonists increased the rate of motor recovery after motor cortex lesions in monkeys /193/. The beneficial effects of cholinergic agonists were blocked by administration of phenytoin /194/. Recent data suggest that the anticholinergic drug, scopolamine, interferes with motor recovery following cortex infarction in rats /48/. As reviewed by Feeney and Sutton, acetylcholine administration appears to enhance recovery of function /63/.

N-Methyl-D-aspartate (NMDA)

The availability of drugs which competitively and non-competitively block specific subtypes of the glutamate receptor has led to trials of these agents
in experimental ischemia. The non-competitive NMDA receptor antagonists MK-801 /13,26,115, 141,143,144/, dextromethorphan and dextrorphan /170-172/, and the competitive NMDA receptor antagonists CGS 19755 and CPP /17,27/ reduce brain injury following focal ischemia. In contrast to the potentially beneficial effect of MK-801 on the local damage caused by ischemia, the administration of this NMDA receptor antagonist reinstated sensory deficits in rats that had recovered from anteromedial frontal cortex injury /8/. The drug had a slightly beneficial effect if given soon after the brain injury. MK-801 had no effect on beam-walking recovery in rats regardless of whether it was administered to the animals soon after the injury or after spontaneous recovery was complete /82/.

**Growth factors/transplants**

The use of growth factors to improve functional outcome following brain injury is the topic for a separate review (see /121/). There are a large number of substances that can promote neuronal survival or growth /121/. Treatment with nerve growth factor (NGF), one of the first of these substances identified, improves spatial learning following nucleus basalis magnocellularis lesions in rats /131/ and prevents neuronal death after brain trauma /116/. Although originally considered a neuronotrophic factor, GM1 ganglioside may have several mechanisms of action /30,54/. Laboratory studies suggest that post lesion administration of gangliosides may improve functional outcome /140,158,159/.

An extensive literature is available that provides evidence for successful structural and functional grafts of homotypic fetal brain tissue (see /184/). For example, fetal neurons grafted to the brains of adult rats with ischemic lesions of the hippocampus become structurally incorporated and establish connections with the host brain /184/. Intracerebral chromaffin cell autografts accelerate functional recovery in adult cats with unilateral frontal cortex ablation /180/.

**DRUGS AND FUNCTIONAL RECOVERY: MECHANISMS**

It is logical that slow adaptive responses to injury such as certain neuronal rearrangements could result in a functional reorganization of the brain that leads to behavioral recovery. However, drugs such as amphetamine have acute, but enduring effects on recovery. In the case of motor function after sensorimotor cortex injury, enhanced recovery occurs within one hour of amphetamine administration with the effect persisting long after the drug has been metabolized /60/. Although several general hypotheses have been offered, the cellular mechanisms underlying these relatively rapid drug effects remain largely speculative. Drugs that influence the release or action of central neurotransmitters could have an impact on both the pathologic sequellae and rapid responses to brain injury in a temporal frame consistent with behavioral observations.

**Potential drug effects on pathologic sequellae of brain injury**

It has been proposed that drugs such as amphetamine may accelerate the resolution of diaschisis and thereby facilitate the functional recovery. As discussed by Feeney previously /57,65/ and elsewhere in this issue, there is considerable experimental evidence in support of this general hypothesis. Exogenous manipulation of the relative levels of central neurotransmitters could also influence the behavioral effects of post-synaptic denervation supersensitivity or impact on the resolution of cerebral edema.

**Potential drug effects on rapid adaptive responses to brain injury**

Understanding the mechanisms of drug effects on rapid adaptive responses is complicated because their impacts may vary depending upon the nature and location of the injury, the specific behavior being measured and the timing of drug administration. Amphetamine administration improved motor outcome after focal cortex injury from an aspiration lesion /60,80/, cerebral contusion /64/ and focal infarction /49,107,108,160/, but had no effect on spatial memory impaired after transient
global ischemia /36/. The administration of pentylenetrazol (PTZ) facilitated recovery from the sensory asymmetry which resulted from unilateral sensorimotor cortex injury in the rat /98,99/. However, PTZ had no effect on motor recovery in these same rats. The potential impact of lesion location and pathophysiologic mechanism is exemplified by the effects of the anticholinergic scopolamine. Treatment with scopolamine accelerated recovery of consciousness following closed head injury in rats /95/. In contrast, scopolamine interfered with motor recovery following unilateral infarction of the rat sensorimotor cortex /48/. The timing of drug administration with respect to the injury may also be critical. The detrimental effect of diazepam on recovery from the sensory asymmetry following unilateral anteriomedial cortex damage in the rat decreased as time between the injury and drug administration increased /98/. MK-801 had a slightly beneficial effect on sensory function in rats if given soon after cortex injury, but was detrimental if given to recovered animals /8/. Despite these complexities, several hypotheses have been offered to explain drug effects on recovery based on their impacts on potential rapid adaptive brain responses. One hypothesis is that certain drugs might facilitate the use of alternative neural networks to perform functions lost due to brain injury (un-masking). Treatment with stimulant drugs such as amphetamine may promote the use of alternative pathways by increasing the size of the cortical receptive field responding to specific peripheral stimuli in rats with cortex injury /49/. Depressants (i.e., GABA or GABA agonists) could interfere with this process and would be expected to be detrimental /165/. The expected effects of drugs on the resolution of diascisis /57/ would be similar to their effects on un-masking.

As discussed above, another hypothesis is that the cellular mechanisms that underlie behavioral recovery may also be responsible for normal learning. This re-learning hypothesis is particularly intriguing because both pre- and post-lesion experience can have an important effect on recovery /86,96,173,174/ and because the impact of certain drugs such as amphetamine is dependent on concomitant task-specific experience /60,62,86,87, 96,104,174/. The best understood putative cellular mechanism of learning and memory is long-term potentiation (LTP) /16/. Catecholamines influence the induction of LTP /103/ and have been implicated in learning and memory /56,161,169/. The administration of amphetamine both facilitates the development of LTP in a dose dependent manner /78/ and enhances memory retrieval /2/. The impact of other classes of drugs on recovery may also be predicted based on their effects on the induction of LTP /80/. For example, stimulation of inhibitory GABAergic inputs to the hippocampal formation /50,51/ as well as the administration of indirect GABA agonists (e.g., benzodiazepines) /154,162/ suppress the induction of LTP. The administration of benzodiazepines impairs learning and memory /123,156/ and they are detrimental if given during the recovery period. Acetylcholine would be expected to facilitate the induction of LTP by suppressing voltage-activated potassium conductance /37/. Activation of the muscarinic cholinergic receptor facilitates the induction of LTP in the rat dentate gyrus /28/. Anticholinergics are potent amnestic agents and impair motor recovery after cortex injury.

Despite the attractiveness of the re-learning hypothesis, it is clear that the effects of all drugs on recovery cannot by predicted solely on the basis of their impact on the induction of LTP. For example, β-adrenergic receptor antagonists interfere with LTP induction /44,45/. However, propranolol has no effect on motor recovery after sensorimotor cortex injury /66/. The development of LTP is mediated, at least in part, by the NMDA sub-type of glutamate receptor /37,181,198/. The administration of NMDA receptor antagonists blocks the induction of LTP, disrupts learning and memory /11,90,137/ and therefore would be expected to be particularly harmful during recovery. The administration of the NMDA receptor antagonist MK-801 reinstated sensory deficits in rats that had recovered from anteromedial frontal cortex injury /8/. However, as discussed above, we recently completed a series of experiments in which we were unable to demonstrate any effect of the MK-801 on beam-walking recovery after unilateral sensorimotor cortex suction-ablation lesions in the rat /82/.

In summary, no single hypothesis is consistent with all of the available behavioral data. The effects of drugs on the recovery process are complex and
could have an impact on a variety of pathologic sequellae and rapid adaptive responses.

Potential drug effects on slow adaptive responses to brain injury

Because the acute effects of certain drugs on behavioral recovery are long-lasting, the relatively rapidly developing physiologic effects must result in more permanent changes in neurons and their connections. Tissue injury can lead to activity-dependent, neuropeptide-mediated neuronal plasticity /52/. Neurotransmitters can have dramatic effects on neurite growth cone development and neurite elongation in vitro and on neural development in vivo (see /122/). In this regard, norepinephrine has been implicated in trophic changes in the central nervous system. The importance of norepinephrine in cortical plasticity was demonstrated by Kasamatsu and coworkers in a classic series of experiments /111/. These investigators used changes in visual cortex ocular dominance that followed brief monocular deprivation as an index of cortical plasticity. Local perfusion of 6-hydroxydopamine blocked the effects of monocular light deprivation in kittens. Local infusion of norepinephrine reinstated plasticity in animals that were no longer sensitive to visual deprivation. Norepinephrine released in the cerebral cortex from locus coeruleus projection fibers has been suggested to lead to synaptic plasticity that may encode learning /42/.

In contrast to the effects of norepinephrine, Schallert and coworkers have found that chronic administration of diazepam after anteromedial cortex injury in the rat has significant detrimental effects on subcortical structures receiving projections from the damaged regions /165/. The striatum was smaller and substantia nigra pars reticulata neuronal loss was greater ipsilateral to the cortex lesion in diazepam-treated animals /164,167/. Thus, both norepinephrine and GABA (in addition to a variety of other neurotransmitters /122/) may influence both rapid and longer-term adaptive responses to brain injury.

DRUGS AND FUNCTIONAL RECOVERY: CLINICAL STUDIES

The use of drugs to improve recovery after brain injury in humans had been attempted as early as the 1940s. More recent preliminary clinical studies indicate that many of the same drugs that influence recovery in laboratory animals have similar effects on recovery in humans.

Amphetamine facilitated recovery in humans

Anecdotal reports indicate that treatment with amphetamine improves cognitive function in young adults with post-traumatic organic brain syndrome /55,120/. Motivation in elderly patients refractory to rehabilitation procedures also improves with amphetamine treatment /34/. These effects are likely due to the stimulant effects of the drug. However, several other anecdotal reports and small controlled trials suggest that treatment with amphetamine may enhance functional recovery after focal brain injury under certain conditions.

A small prospective, double-blind study was carried out to determine whether amphetamine-facilitated motor recovery occurs in humans after stroke /41/. The study was carefully designed to simulate the paradigm used in the laboratory experimental studies. A group of eight patients with stable motor deficits within 10 days of ischemic stroke were randomized to receive either a single dose of amphetamine or placebo. Motor function was measured with a reliable and validated scale, the Fugl-Meyer Assessment /71/. Within three hours of drug administration, all of the patients underwent intensive physical therapy (i.e., drug administration was coupled with task-specific experience). The following day, the patients' abilities to use their affected limbs were reassessed. Overall, the amphetamine-treated group had a significant improvement in motor performance while there was little change in the placebo-treated group (Fig. 2). However, because this study involved only a small group of highly selected patients, the results may not be applicable to stroke patients with other types of deficits. Because only short-term motor recovery was measured, the longer-term efficacy of amphetamine treatment is unknown. Until recently, this study provided some of the only controlled data
of a beneficial effect of amphetamine treatment on motor recovery in humans.

Boruc and colleagues presented a preliminary report of a double-blind, placebo-controlled study designed to determine whether treatment with amphetamine would enhance motor recovery in patients undergoing inpatient stroke rehabilitation /18/. Five patients were treated with amphetamine and five received a placebo daily for 17 days with a final assessment one week after the last day of drug administration. The effect on motor performance was measured with the Fugl-Meyer Assessment. Although the final motor score was higher in amphetamine-treated patients (70±16 vs. 37±7), the difference was not statistically significant. In contrast to the prior trial, this study included a more heterogeneous group of stroke patients treated with amphetamine or placebo beginning a longer period of time after stroke. Importantly, it is uncertain whether the patients received physical therapy in conjunction with drug administration.

A second double-blind, placebo-controlled trial of the effects of amphetamine on motor recovery in rehabilitation patients has recently been performed /190/. This study also included five amphetamine-treated and five placebo-treated patients. Drug or placebo was given once every 4 days for 10 sessions beginning 15 to 30 days after stroke. Each dose was given in conjunction with a session of intensive physical therapy. Motor function was again measured with the Fugl-Meyer Assessment with the final evaluation one week after the last dose. Patients treated with amphetamine had significantly greater improvements in motor scores compared to placebo-treated patients (median change in Fugl-Meyer score of 26 vs 13 points, p=0.047). Although preliminary, these results suggest that amphetamine may enhance motor recovery in human stroke patients when drug administration is combined with task-relevant experience.

Speech pathologists have been particularly interested in studying the effects of drugs on language recovery after stroke. Preliminary studies indicate that the administration of bromocriptine improves fluency in certain aphasics /1,7,157/ and that treatment with amphetamine may accelerate recovery from aphasia in stroke patients /102/. A larger feasibility study of the effects of amphetamine on language recovery after stroke was recently carried out (Fig. 3) /191/. Six aphasic patients had language function rated with the Porch Index of Communicative Ability /148/ 10 to 30 days after stroke. Based on this initial evaluation, 6 month language scores were predicted for each patient. All patients were then given 10 mg of D-amphetamine followed by speech therapy every 4th day for 10 sessions. The patients' actual scores after 3 months were then compared with their 6 month predicted scores. Most patients achieved or exceeded their 6 month predicted scores by the time of the 3 month evaluation. A randomized prospective trial is now planned.

![Fig. 2: Amphetamine and motor recovery after stroke. In a double blind trial, eight patients with stable motor deficits were randomized to receive a single dose of 10 mg of D-amphetamine or placebo followed by physical therapy within 10 days of ischemic stroke. The differences in Fugl-Meyer scores between baseline and 24 hours after treatment for the amphetamine-treated stroke patients and controls are shown. See text for details. Modified from Crisostomo et al. /41/](image-url)
Other drugs and recovery in humans

Early reports suggested that cholinergic agents might facilitate recovery following brain injury in humans /145,186/. However, much of the data concerning the impact of cholinergic drugs on recovery of function is old and inadequate by current standards.

GM1-ganglioside has been the subject of clinical trials for the treatment of patients with a variety of neurologic disorders including a recent report of benefit in individuals with spinal cord injury /77/. Small trials in stroke patients suggest that the drug may be of some benefit /3,9,10/. However, the clinical significance of the reported effects in these studies is unclear and one trial failed to demonstrate any impact of the drug on recovery in stroke patients /101/. The preliminary results of a large clinical trial of GM1-ganglioside in the treatment of patients with acute stroke have recently been presented /161/.

"Deleterious" drugs after stroke

Although the previous discussion has focused on the use of drugs to enhance recovery after stroke, it is important to recognize that the laboratory studies suggest that some drugs may be detrimental (Table 2). We carried out a retrospective study of physician prescribing patterns to determine what drugs were used in the treatment of stroke patients /84/. Over 80% of individuals were taking at least one drug at the time of the stroke. Sixty-five percent of patients were receiving multiple drugs. Antihypertensives such as clonidine and prazosin and sedative hypnotics including benzodiazepines were among the most commonly prescribed agents (Fig. 4). Thus, several of the drugs that have deleterious effects on recovery of function in laboratory animals were commonly prescribed for stroke patients for the treatment of coincident medical conditions.

Determining whether the detrimental effects of drugs anticipated from laboratory studies also occur in humans recovering from stroke is difficult. Largely anecdotal reports indicate that treatment with haloperidol /63,149/ and certain antihypertensives /150/ may interfere with language recovery in patients with aphasia following stroke. We performed a retrospective study that tested the hypothesis that drugs that are harmful during recovery in laboratory animals would interfere with motor recovery in human stroke patients /88/. These potentially deleterious drugs included the antihypertensives clonidine and prazosin, neuroleptics, benzodiazepines, and phenytoin. The motor recoveries of stroke patients who received one or a combination of these drugs were compared to the recoveries of a similar group of patients who were not given any of these agents. The two groups
of patients were similar with respect to a variety of characteristics including age, blood pressure, gender, and medical comorbidity. Motor function was measured prospectively with the Fugl-Meyer Assessment by observers who were blind to the study hypothesis. Although the results of this study need to be interpreted with caution, patients who received one or a combination of the hypothesized “detrimental” drugs at the time of stroke or during the subsequent hospitalization had significantly slower motor recoveries than a comparable group of patients who did not receive one of these drugs (Fig. 5). A multivariate analysis indicated a significant effect of “drug group” after correcting for the contributions of other variables including the initial severity of the deficit.

![Graph](image)

**Fig. 4:** Drugs prescribed after stroke. The drugs prescribed for patients admitted to the hospital within 48 hours of a carotid distribution ischemic stroke were recorded /84/. The percentages of patients prescribed the indicated drugs are shown. This study indicates that several of the drugs that have deleterious effects on recovery of function in laboratory animals are commonly prescribed for stroke patients for the treatment of coincident medical conditions. From Goldstein /81/.

**Fig. 5:** “Detrimental” drugs and motor recovery after stroke. Motor function was measured prospectively with the Fugl-Meyer Assessment in a cohort of patients with ischemic stroke /71/. The medications taken by these patients at the time of stroke or during the subsequent hospitalization were determined by review of their medical records. The patients were then divided into two groups. One group (“detrimental” drug group) had received one or a combination of the drugs hypothesized to be harmful based on laboratory animal experiments (see text). The remaining patients, all of whom had received at least one drug, were included in the “neutral” drug group. Patients in the “detrimental” drug group had greater initial deficits and recovered motor function slower than patients in the “neutral” drug group. Reproduced from Goldstein et al. /88/.

**SUMMARY**

The development of an understanding of the basic neurobiology underlying functional recovery after focal brain injury is leading to new strategies for the treatment of patients with stroke and
traumatic brain injury. It is clear that certain drugs influence behavioral recovery in laboratory animals after brain injury. These drug effects can be either beneficial or detrimental. Similar drug effects may occur in humans. It is important to recognize that some of the drugs used to treat coexisting medical conditions may be harmful. Until we better understand the true impact of these potentially detrimental drugs on recovery, care should be exercised in the use of these drugs in the treatment of patients after brain injury. In combination with new treatments designed to limit acute damage and salvage injured neurons, new strategies aimed at facilitating functional recovery offer the hope of improved outcomes for the brain-injured patient.

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