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Amphetamine, Haloperidol, and Experience Interact to Affect Rate of Recovery After Motor Cortex Injury

Abstract. *Rats subjected to unilateral ablation of the motor cortex and placed on a narrow beam displayed transient contralateral paresis. An immediate and enduring acceleration of recovery was produced by a single dose of* d-*amphetamine given 24 hours after injury. This effect was blocked by haloperidol or by restraining the animals for 8 hours beginning immediately after amphetamine administration. A single dose of haloperidol given 24 hours after injury markedly slowed recovery. This effect was also blocked by restraining the animals.*

Despite major advances in the understanding of brain function, no medical treatments have been developed to promote recovery from brain injury; only secondary events, such as bleeding or edema, are treated to prevent further neuronal destruction. However, with time there may be marked spontaneous recovery of function in brain-injured animals. For example, after unilateral damage to the motor cortex there is a contralateral paralysis and loss of locomotor ability which may, depending on the species, be reversed over time. In humans these deficits can persist indefinitely, whereas recovery occurs within months in the cat (*1*) and within 2 weeks in the rat (*2*). The initial loss of function and subsequent recovery may be manifestations of a transient depression of neural functions in intact areas remote from but connected to the area of injury (*3*).

The concentration of catecholamines reportedly is reduced in rat and cat brainstem and in human cerebrospinal fluid following cerebral infarction (*4*). If depression of catecholamine levels contributes to the behavioral syndrome seen after cerebral injury, then it should be possible to reverse some of the deficits by pharmacological manipulation of catecholaminergic systems. The drugs *d*-amphetamine and haloperidol, which have potent opposing actions on catecholamines and neuronal activity (*5*), were used to test this hypothesis.

The subjects were 111 male albino rats (300 to 350 g) trained to run along a narrow beam to escape white noise and bright light (*6*). For surgery each animal was given ketamine hydrochloride (60 mg/kg, intramuscularly) as a preanesthetic; 5 minutes later, the animals were anesthetized with sodium pentobarbital (21 mg/kg, intraperitoneally). A wide craniotomy was performed over one hemisphere and the motor cortex was removed unilaterally by suction (*7*). Twenty-four hours after surgery the ability of each animal to negotiate the beam was evaluated in a single trial. Immediately thereafter the animals were given intraperitoneal injections of saline (N = 16); amphetamine at doses of 0.5 mg/kg (N = 8), 1 mg/kg (N = 10), 2 mg/kg (N = 13), or 4 mg/kg (N = 8); amphetamine (2 mg/kg) followed 2 minutes later by haloperidol (0.4 mg/kg) (N = 6); or haloperidol alone (0.4 mg/kg) (N = 6).

Each animal underwent one trial on the beam every hour for 6 hours after drug administration and at 12 and 24 hours. These trials were continued every other day for at least 15 days or until the animals recovered their agility. Locomotion was evaluated by two observers, one of whom did not know which drug treatment had been given to the animal on the beam (*8*).

To determine whether practice on the beam during amphetamine or haloperidol intoxication facilitated recovery, an additional 44 animals were treated as described above except that for 8 hours beginning immediately after drug administration the animals were confined to cages whose small size (7 by 17 by 15 cm) prevented locomotion. These animals received saline (N = 20), amphetamine (2 mg/kg) (N = 19), or haloperidol (0.4 mg/kg) (N = 5).

The trials held 24 hours after motor cortex ablation but before drug administration demonstrated a complete inability of all the animals to walk or run on the beam. After 1 hour, the rats given amphetamine at 2 or 4 mg/kg and given hourly tests while intoxicated showed significant improvements ($P < .01$) compared to their baseline performance and to the performance of the control group (Fig. 1A) (*9*). A dose of 0.5 mg/kg had no effect, and 1 mg/kg did not significantly improve performance. The performance of subjects given 2 mg/kg continued to improve for 3 to 6 hours ($P < .01$). Animals that had been unable to stand on the beam before drug administration could traverse the beam 6 hours after the 2 or 4 mg/kg dose of amphetamine. The control subjects showed no significant improvement during this period. Movies shown in slow motion indicated that, after 24 hours, the improvement of animals given amphetamine and practice on the beam was similar to that achieved by the control subjects after 1 or 2 weeks. They displayed an increased ability to use the affected limbs and to accurately place them on the horizontal surface of the beam. Improvement was most notable in the hind limb.

The animals given amphetamine and practice maintained their improved motor performance over the weeks of testing. The performance of the group receiving 2 mg/kg was significantly better ($P < .05$) than that of the control group for 5 days. In a similar experiment, Hovda and Feeney (*1*) found that beam-walking ability was restored more rapidly in cats given amphetamine 10 days after unilateral removal of the motor cortex than in control cats.

Confinement to prevent locomotion blocked the facilitation of recovery produced by amphetamine. The rate of recovery in these animals was the same as that in restrained controls (Fig. 1B). Therefore, a dose of amphetamine accelerates recovery of locomotion after motor cortex injury only if the animal is given practice during the period of drug

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action. No significant differences in recovery rate were observed between the restrained group given saline and the group given saline and practice. Hence, practice contributed to improvement only in animals given amphetamine.

Haloperidol (0.4 mg/kg) blocked the facilitation of recovery produced by amphetamine and practice (Fig. 1C), suggesting that the acceleration of recovery by amphetamine is dependent on dopamine. When given alone, a single dose of haloperidol (0.4 mg/kg) administered 24 hours after injury severely retarded recovery of locomotion (Fig. 1C). This effect, like that of amphetamine, was prolonged and could be blocked by restraining the animals for 8 hours after drug treatment (Fig. 1D). The retardation of recovery in animals given haloperidol and allowed to practice is not due to the sedative properties of this drug, since the same dose given to five recovered control animals 45 days after injury had no effect on their agility, as determined hourly for 6 hours after the injection and at 24 hours.

Thus, after cortical ablation, a catecholamine agonist, *d*-amphetamine, accelerates the recovery of walking and running on a narrow beam. This acceleration is blocked by a low dose of the dopamine receptor blocker haloperidol. When given alone, haloperidol retards recovery. These results depend on locomotor experience during the first 8 hours after drug administration, since confinement of the animals during that period blocks the effects of both drugs.

Administration of these drugs after motor cortex injury may alter the activation of circuitry involved in locomotion, circuitry that is depressed by the injury. Since the animals showed a significant improvement in beam-walking on the first trial after receiving amphetamine, the drug may temporarily reverse a functional depression in undamaged areas (*10*). However, since locomotor experience is essential for the maintenance of the improvement, this aspect of the results may be produced by learning during drug intoxication (*11*). A role for catecholamines in other types of neural plasticity has also been proposed (*12*).

Our observations are similar to those of Gage and Olton (*13*) and Marotta *et al.* (*14*), who gave rats single doses of *d*-amphetamine or catecholamine precursors 24 hours after the septal nuclei were lesioned. Recovery from hyperemotionality was accelerated in these animals. That amphetamine facilitates recovery from such dissimilar lesions (septal nucleus and motor cortex) and of such dissimilar behavior (reduction of emotionality and improvement of locomotion) supports the hypothesis that catecholamines play a nonspecific role in recovery from brain injury.

These findings may have important implications for the rehabilitation of patients with brain damage due to stroke or trauma. Stimulation of catecholaminergic systems in conjunction with physical therapy may facilitate the often slow and frustrating recovery from such injury. Several case studies support this hypothesis (*15*). Finally, haloperidol and perhaps other butyrophenone or phenothiazine derivatives, commonly used for

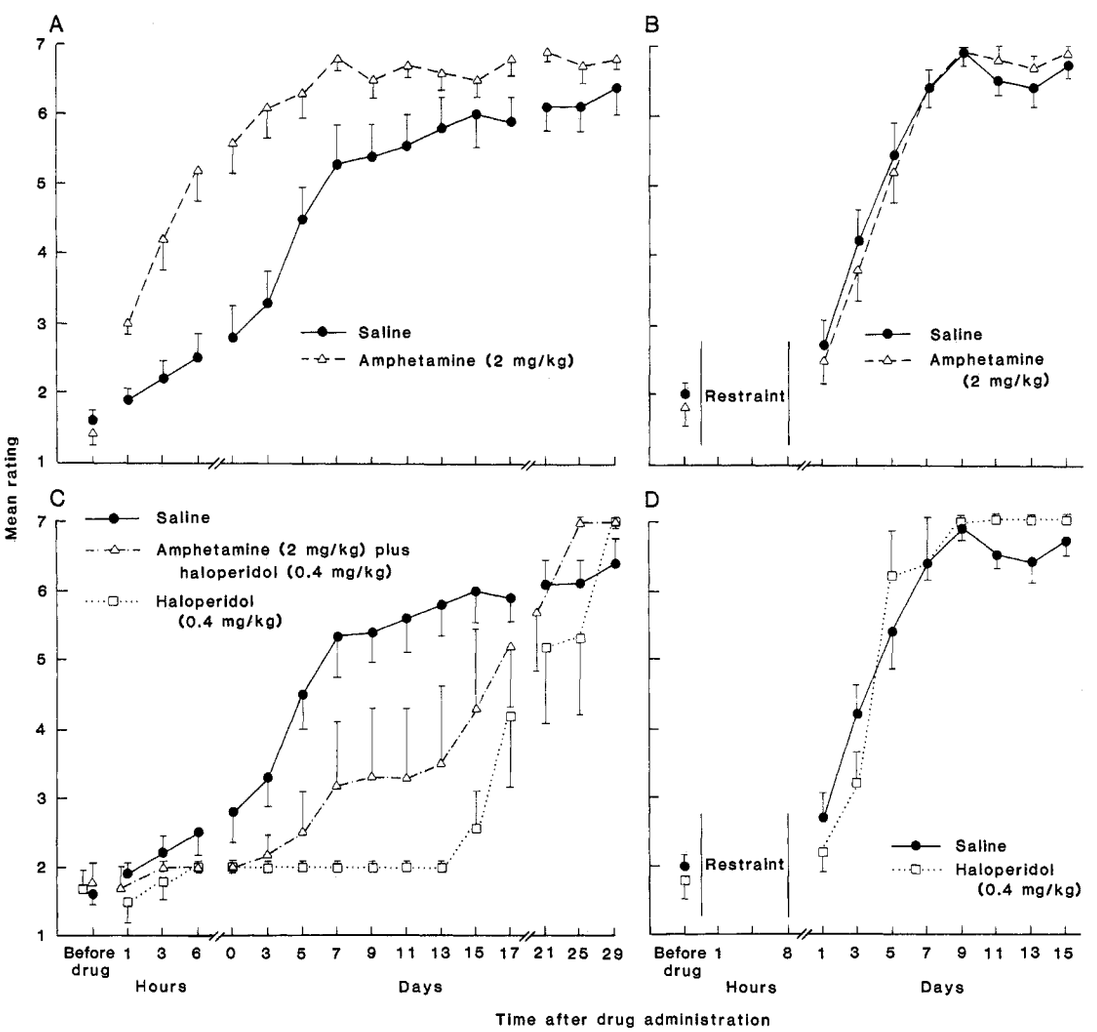

Fig. 1. (A to D) Mean ratings of rat locomotion after unilateral ablation of the motor cortex. Prior to surgery all animals received scores of 7. Note the enduring acceleration of recovery in animals given a single dose of amphetamine 24 hours after surgery (A). This effect was blocked by preventing locomotion during drug intoxication (B) or by administering haloperidol (C). This effect was also blocked by preventing locomotion (D). Vertical bars represent standard errors of the mean.

their antipsychotic effects, may be contraindicated during recovery from brain injury because they block catecholamine receptors (*16*) and may slow the recovery of function.

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6. Beam-walking was studied since rats with motor cortex lesions show little movement dysfunction on a broad, flat surface but display a marked deficit when placed on a narrow beam. In the first days after unilateral ablation of the motor cortex, the contralateral limbs (especially the hind limb) hang off the beam and the animal may fall. In training and testing, the animal was placed on one end of a wooden beam (122 by 2.5 cm), close to the sources of noise and light. The noise was terminated after the animal traversed the beam into a dark goal box (24.5 by 18 by 20 cm). Training consisted of two trials every other day until the animal could run the length of the beam with no more than two foot slips, a criterion reached within 10 days.
7. After the experiments the subjects were anesthetized with pentobarbital and perfused with saline and Formalin. The brains were removed and photographed, and the lesions were verified by studying frozen sections stained with thionine. Occasionally a lesion involved the dorsal striatum and hippocampus. In most cases the entire motor cortex was removed from one hemisphere [R. D. Hall and E. P. Lindholm, *Brain Res.* **66**, 23 (1974)]. There were no systematic differences among the groups in the amount or area of brain removed.
8. The experimenters had extensive practice using the rating scale before the experiments began. There was a 98 percent agreement in ratings between the informed experimenter and the uninformed experimenter, and the few disagreements never involved more than one category. On the rating scale, an animal received a 7 if it traversed the beam normally with no more than two foot slips; a 6 if it traversed the beam and used the affected limbs to aid more than 50 percent of its steps along the beam; a 5 if it used the affected limbs in less than half of its steps along the beam; a 4 if it traversed the beam and at least once placed the affected hind paw on the horizontal surface of the beam; a 3 if it traversed the beam while dragging the affected hind limb; a 2 if it was unable to traverse the beam but placed the affected hind limb on the horizontal surface of the beam and maintained balance; and a 1 if it was unable to traverse the beam and could not place the affected hind limb on the horizontal surface.
9. A repeated measures analysis of variance (ANOVA) was performed to compare the groups. For the animals given practice, amphetamine had a significant effect on recovery [$F(1, 27) = 20.683$, $P < .001$] (Fig. 1A), as did haloperidol [$F(2, 25) = 6.034$, $P < .007$] (Fig. 1C). These drugs did not affect recovery in the restrained animals (Fig. 1, B and D). The same analysis performed on the dose-response data gave $F(4, 45) = 4.16$, $P < .01$. Newman-Keuls tests were conducted to make specific comparisons between groups at different times after drug administration; these probability values are reported in the text.
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Velocity Signals Related to Hand Movements Recorded from Red Nucleus Neurons in Monkeys

Abstract. *Neural activity of the red nucleus was studied in monkeys trained to operate devices requiring shoulder, elbow, wrist, hand, or finger movements. Single cell activity was more closely related to movements of the hand and fingers than to movements of the other joints. Discharge consistently preceded movements by a constant time interval; duration of discharge was highly correlated with the duration of movement; and discharge rate was highly correlated with movement velocity. These data suggest a role for the rubrospinal pathway in the initiation and control of hand movements.*

The magnocellular division of the red nucleus (designated RNm) is the origin of one of several large-fiber tracts that descend from the brainstem to the spinal cord. Signals from the cerebellum and motor cortex converge on RNm neurons to produce motor commands. These commands are then conducted in the rubrospinal tract to propriospinal neurons, segmental interneurons, and, in primates, directly to motor neurons (*1*). The specific nature of the motor commands transmitted by the RNm is poorly understood. We investigated the particular categories of movement controlled by the RNm and also the temporal and parametric features of these nerve signals.

Since lesions of the rubrospinal pathway result in deficits in the control of distal joints of the extremities in both monkeys and cats (*2*), we were interested in knowing how the discharge of RNm neurons varies as the animal performs movements of the hand and fingers. Microelectrode recording has been used in studies in which trained monkeys (*3–5*) and cats (*6*) performed tasks that emphasized motion about more proximal joints, from the wrist to the shoulder, and limited to a single category of movement. We have now examined the relations of the RNm neurons to hand and finger movements using several manipulanda in order to compare relations at different joints (*7*).

A device, which we call the twister (Fig. 1A), operates like a motorcycle throttle. Twister rotation is sensed by a potentiometer circuit that drives a position trace on a visual tracking display. A pair of horizontal traces on the tracking display designate a target zone. A monkey is required to manipulate the position trace between the horizontal traces by rotating the twister, in order to obtain a liquid reward. The monkey's head and body are restrained, and a tungsten microelectrode used for recording (0.2 to 1 megohm impedance) is positioned in the animal's brain with a standard chamber and microdrive (*8*). Operation of the twister requires a coordinated hand movement, mainly involving the action of finger and wrist muscles (confirmed by intramuscular electromyographic recording). Other movements were tested with the same tracking display and different manipulanda. One device required push-pull movements of the whole limb, and other devices were designed to isolate movements of the fingers, thumb, wrist, elbow, or shoulder. During the study of each neuron, we supplemented quantitative observations on one to four devices with a qualitative examination of the neural activity associated with reaching for and manipulating food objects.

Our results are based on 327 single-unit recordings from well-characterized RNm neurons in two male rhesus and one male cynomolgus monkey. During

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