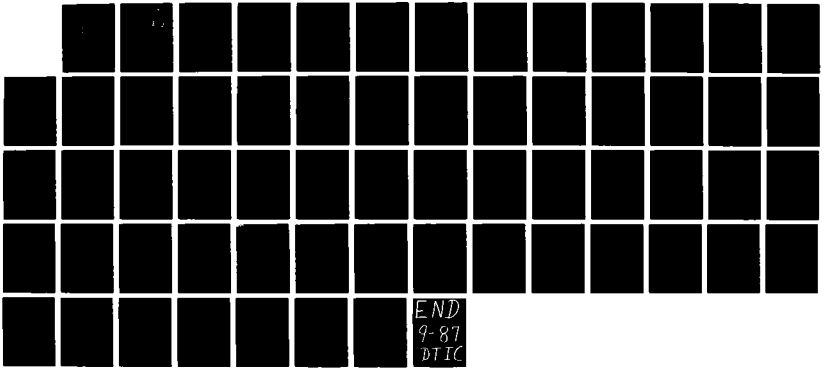
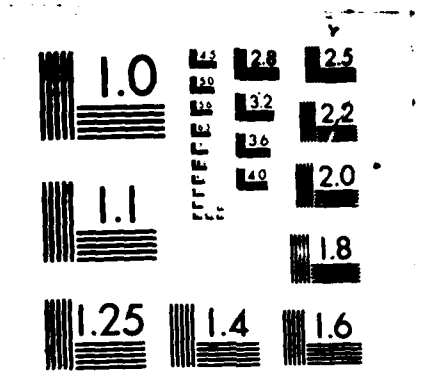
AD-A183 526 FEASIBILITY STUDY OF PHARMACOLOGICAL TREATMENT TO REDUCE MORBIDITY AND MORTALITY AFTER BRAIN INJURY(U) NEW MEXICO UNIV ALBUQUERQUE D M FEENEY 01 MAY 87 1/1

UNCLASSIFIED DAMD17-86-C-6144 F/G 6/15 NL





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FEASIBILITY STUDY OF PHARMACOLOGICAL TREATMENT TO REDUCE MORBIDITY AND MORTALITY AFTER BRAIN INJURY

Annual Report

Dennis M. Feeney

May 1, 1987

Supported by:

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-86-C-6144

The University of New Mexico
Albuquerque, New Mexico 87131

AD-A183526

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No 0704-0188
Exp Date Jun 30 1986

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release: Distribution unlimited
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION The University of New Mexico 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) Albuquerque, New Mexico 87131	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING / SPONSORING ORGANIZATION U.S. Army Medical Research & Development Comm. 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD17-86-C-6144
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick, Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 62772A; PROJECT NO 3S162 772A874; TASK NO AA; WORK UNIT ACCESSION NO 144

11 TITLE (Include Security Classification)
Feasibility Study of Pharmacological Treatment to Reduce Morbidity and Mortality After Brain Injury

12 PERSONAL AUTHOR(S)
Dennis M. Feeney, Ph.D.

13a TYPE OF REPORT	13b TIME COVERED	14 DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Annual Report	FROM 4/14/86 TO 4/13/87	1987 May 1	60

16 SUPPLEMENTARY NOTATION

17 COSATI CODES		
FIELD	GROUP	SUB-GROUP
06	15	
06	05	

18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
Keywords: Cortex, contusion, brain injury, recovery of function

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

A single dose of d-amphetamine (AMP), combined with task relevant experience, produces an enduring acceleration of recovery of locomotor ability after unilateral sensorimotor cortex ablation. Norepinephrine (NE) has been implicated in mediation and maintenance of these effects. This study examined the effect of AMP, specific NE agonists and antagonists and electroconvulsive seizures (ECS) using a model of cortical contusion on recovery of beam-walking ability. Rats were given a single drug or saline injection (i.p.) 24h after a contusion of the right sensorimotor cortex. Beam-walking tests were conducted 1, 3, 6, and 24 hours postinjection continuing every other day for 15 days. For mild contusions, prazosin (4 mg/kg) retarded recovery and a trend toward accelerated recovery was observed for yohimbine (10 mg/kg). Propranolol (10 mg/kg) and methoxamine (1, 4 or 8 mg/kg) showed no effects. These results indicate a role for norepinephrine in recovery after cortical contusion but do not clarify receptor type mediating this effect.

(continued on reverse)

20 DISTRIBUTION / AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	Unclassified

22a NAME OF RESPONSIBLE INDIVIDUAL	22b TELEPHONE (Include Area Code)	22c OFFICE SYMBOL
Judy Pawlus	(301) 663-7325	SGRD-RMI-S

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted
All other editions are obsolete

SECURITY CLASSIFICATION OF THIS PAGE

19. Abstract. Continued

After recovery from cortical injury, continued NE function may be important for maintaining locomotor ability. Therefore, fully recovered sham or contused rats were injected 30d postinjury with either propranolol (10 mg/kg), clonidine (.4 mg/kg), prozosin (4 mg/kg) or phenoxybenzamine (PBZ; 10 mg/kg). It was found that clonidine, prazosin and PBZ, but not propranolol, reinstated locomotor deficits on the beam-walking task.

Seizures frequently occur following brain injury, increase NE turnover and have been hypothesized to enhance recovery of function. To test this proposition, we investigated the effects of electroconvulsive seizures on recovery of motor function after cortical contusion in rat. It was found that animals receiving two seizures showed accelerated recovery on the beam-walking task whereas those receiving seven seizures did not.

FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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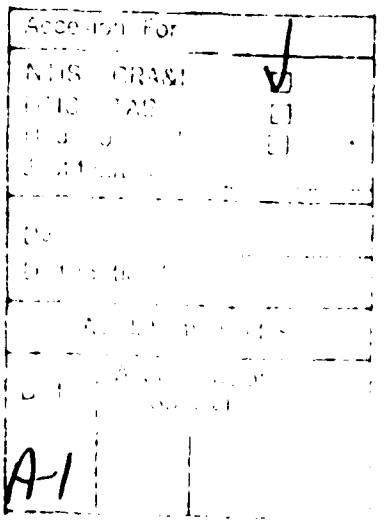

INTRODUCTION

In a recent series of experiments, d-amphetamine (AMP), when combined with relevant experience during the period of drug action, has been shown to promote recovery of locomotor function after unilateral sensorimotor cortex ablation in rat and cat. In these studies, the rates of recovery of motor ability, compared to saline controls, were accelerated within hours after a single injection of AMP and recovery endured beyond the period of drug action. Other pharmacological, biochemical and metabolic experiments (8,9,23,38,63) indicate that the mechanism of this effect involves a modulation by norepinephrine (NE) of depressed cerebellar function (8,9). Additionally, in a rat stroke model, this treatment regimen reduced mortality as well as morbidity (56) and a preliminary study of human stroke patients with hemiparesis showed an acceleration of recovery compared to placebo controls (15).

The most frequent cause of permanent disability is cerebral trauma (61) and a model of cortical contusion producing hemiparesis in rats has been developed (21). The purpose of this series of investigations was to determine if this treatment regimen would also promote recovery of function in this model and to begin to determine the mechanisms of the effect. Because of the greater edema and shock forces acting upon structures remote from the focal impact contused cortex, traumatic injury may respond differently from injury produced by suction ablation or stroke. The AMP acceleration of recovery of locomotor function, measured by beam-walking ability after sensorimotor cortex ablation, has been shown in rat and cat (22,36). However, whether there is a similar beneficial effect on recovery of other motor deficits is unknown. To determine if

such treatment would benefit fine movement, recovery of the grasping ability of the forepaw was also measured subsequent to contusion in the rat. After establishing this treatments' effectiveness, other drugs having more limited actions on NE receptor subtypes were investigated. Additionally, based on results from the ablation model, the maintenance of recovery has been hypothesized to involve the alpha adrenergic system (61). Drugs which block these receptors reinstate locomotor deficits in animals recovered from sensorimotor cortex ablation (61). This was also examined in rats fully recovered from focal contusion in the present experiments. The AMP promotion of recovery of locomotor function after sensorimotor cortex ablation is proposed to involve remote effects of cortical injury upon brainstem noradrenergic neurons (24) and the cerebellum and biochemical measurements of the levels and metabolites of NE support the hypothesis (8). Preliminary catecholamine biochemical measures after AMP treatment using the contusion model was conducted in the present studies. Finally, seizures are a frequent sequalae of contusion of the sensorimotor cortex in man (25,37) and also have very marked effects on catecholamines and increase NE turnover (38,50). The effects of seizures on recovery of function is unknown; therefore, this was also investigated.

METHODS AND MATERIALS

Subjects. Approximately 450 Sprague-Dawley rats weighing 250-350 g purchased from Harlan-Sprague-Dawley, were used in these experiments. Animals were housed individually in standard wire-mesh cages, maintained

on a 12:12 hour light:dark cycle, and unless otherwise specified, given food and water ad libitum.

Apparatus. To test locomotor ability, a beam identical to that previously described in Feeney et al. (1982) was used. This apparatus consisted of a long (122 cm), narrow (2.5 cm) elevated (36 cm) wooden beam with a large, dark goal box similar in appearance to the animals home cage attached to the end of the beam. A bright (60 watt) light source was positioned above the starting point and a speaker placed at the start position broadcast a loud (approximately 62 dB) tape recorded white noise. This noise was terminated when the animals entered the large (24.8 x 20.3 x 17.8 cm) goal box.

To train and test forepaw dexterity, a chamber measuring 24.5 x 19 x 19 cm was used. The lid, back wall and two side walls were made of wood, the front wall of clear plexiglas, and the floor was wire mesh. A square aperature measuring 1.7 x 1.7 cm, located 2 cm from the floor, was centered in the front plexiglas wall to accommodate a 4" tube for delivering rat food pellets.

Drugs. The drugs employed were: d-amphetamine sulphate (AMP; 2 mg/kg); the alpha 1 receptor antagonists prazosin HCl (4 mg/kg) and phenoxybenzamine HCl (PBZ; 10 mg/kg); the alpha 1 agonist methoximine HCl (1, 4, or 8 mg/kg); the alpha 2 receptor antagonist yohimbine HCl (10 mg/kg); the alpha 2 receptor agonist clonidine HCl (0.4 mg/kg); and the beta adrenergic antagonist propranolol HCl (10 mg/kg). These drugs and their particular doses were selected based on previous studies using the ablation model. All were administered by i.p. injection.

Procedures.

Surgery: All rats received either a contusion injury or served as sham operate controls. The procedure for producing the contusion injury is described in detail elsewhere (Feeney et al. 1981). The apparatus consists of a stainless steel guide tube through which a weight was dropped to produce impact forces of 200, 400, 600, 800 or 1000 g/cm. The device was mounted on a stereotaxic carrier and the base of the device consisted of a stainless steel circular footplate which the falling weight struck.

For surgery, all animals were given ketamine HCl (60 mg/kg, i.m.) as a preanesthetic, followed 10 min later by pentobarbital (21 mg/kg, i.p.) and then placed in the stereotaxic apparatus. The scalp was cleansed with Ioprep and asceptic techniques used throughout surgery. The scalp was opened and a craniotomy performed over the right hemisphere. The center of the footplate was positioned 1.5 mm posterior and 2.5 mm lateral to bregma. This represents the overlapping sensorimotor cortex, is relatively flat and accessible and when contused produces an observable deficit in beam-walking and forepaw grasping ability. The footplate was positioned so that it rested upon the surface of the dura, which was left intact. To prevent contused cortex from herniating into the opening, craniotomies were only slightly larger than the diameter of the footplate and after impact, the boneflap was replaced and the scalp sutured closed. Sham-operates were treated identically except that no weight was dropped.

Beam-walk: Within one week after receipt of the animals they were trained to traverse the beam. The first training day consisted of giving animals

three non-rated trials using a successive approximation procedure. On trial one the rat was placed on the beam just outside the goal box; on trial two at the midway point on the beam; and on trial three at the start position. On the next day, and every other day thereafter, each rat received a single, rated trial on the beam from the start point. Locomotor performance and ability in traversing the beam was rated by two observers, one blind to all treatment conditions, using the 7-point rating scale described in Table 1. Criterion for the successful completion of beam-walk training was defined as achieving a presurgery score of "7" on three successive trials.

Upon reaching criterion, rats received a 200, 400, 600, 800 or 1000 g/cm contusion or craniotomy to the right sensorimotor cortex. At 24 +/- 1 hour postsurgery the animals were given a single trial on the beam. Within five minutes following this test the animals received a single i.p. injection of drug (i.e. AMP, prazosin, propranolol, yohimbine or methoxamine) or saline and were returned to their home cage. Postdrug tests on the beam-walking task were given at 1, 2, 3, 6 and 24 hours and then every other day for 15 days unless otherwise specified. Beam-walking sessions within any one experiment were conducted at the same time every day except on the day of drug administration and the 24 hour post-drug test.

See Table 1

Paw Reach: Five days prior to training, rats were placed on a 22:2 hour food deprivation schedule. All animals were maintained on this regimen

during the initial presurgical training and during the postsurgical testing out to day 29. After day 29, forepaw testing sessions were conducted only once a week. Therefore, at this point, food was accessible to all animals in their home cages on all days except for the three preceding the weekly test session. On these three days, the 22:2 hr food deprivation schedule was reinstated.

Presurgical forepaw training consisted of conditioning rats to use their left forepaw to obtain a food pellet. During each session, the experimenter placed a food pellet in the end of the plastic tube and positioned it in the front wall aperature. If the rat attempted to retrieve the pellet with the right forepaw, the tube was retracted. If the rat attempted to retrieve the pellet with the left forepaw, the tube remained in place until the animal successfully grasped and consumed the pellet.

On a few trials, the rat successfully retrieved the pellet with its right paw before the tube was removed. Although counted and recorded as trials, only those trials on which the animal used its left forepaw were counted and scored according to the following 5 point rating scale: 1) no attempt to use left forelimb, 2) reached, but could not grasp, 3) reached, grasped, but dropped, 4) reached, grasped, but could not release pellet, and 5) reached, grasped and released into mouth. This procedure was continued during each session until the rat had successfully used or attempted to use its left forepaw on a total of 10 trials. Training sessions were conducted every day prior to surgery until the animal reached a criteria of 8 out of 10 successes on 3 successive days.

Once criterion was reached on this task and the beam-walking task, rats received a 400, 600 or 800 g/cm contusion injury to the right

sensorimotor cortex. Postsurgical forelimb ability was tested at 3, 6 and 24 hours post-injection of AMP or saline and continued every other day for 29 days and then once a week for 5 days. Postsurgical test procedures were conducted in the same manner as presurgical training and at the same time of day except on the day of drug administration and the 24 hour post-drug test.

Inducing Seizures: Contused (600 g/cm only) rats were randomly assigned to a control group or one of two experimental groups. The control group received only the contusion injury. The first experimental group was administered two electroconvulsive seizures (ECSs), one at 6 hr and a second at 24 hr after contusion. The second experimental group received seven ECSs, beginning at 6 hr following the contusion and then every hour for 5 hr; a final ECS was given 24 hr after the injury just before the beam-walking test. To control for any possible effect of time between the last ECS and behavioral testing the final ECS in both experimental groups was administered just prior to the first postcontusion behavioral test.

Electroconvulsive seizures were administered through miniature alligator clips on the ears using a Lafayette ECS generator (model A615B). A current of 50 mA for a duration of .5 s provoked seizures in all animals.

Reinstatment of Deficit: Thirty days after contusion (400 g/cm only) all animals recovered beam-walking ability and were used to determine if maintainance of recovery could be pharmacologically reinstated. Recovered-injured animals were compared to sham operates controlling for any simple sedating effects of the drugs. The animals were given

a single injection of either propranolol (10 mg/kg); clonidine (0.4 mg/kg); prazosin (4 mg/kg) or PBZ (10 mg/kg). They were then given single beam-walking tests at 1, 3, 6, 24 and 48 hours postdrug and rated by the experimenters as has been previously described.

Histology: After completion of the behavioral pharmacology studies, the animals were sacrificed by barbiturate overdose and perfused with 50-100 ml 0.9% saline followed by 250-500 mL 10% buffered formalin. The brains were removed, fixed in 10% formalin for one week and then allowed to sink in a 30% sucrose-formalin solution. Frozen section, 40 μm thick, were cut on a cryostat, stained with thionin, dehydrated in a graded series of alcohols, coverslipped and examined by light microscopy. For the animals receiving amphetamine or ECs, the extent of the area of necrosis was estimated by projecting every fifth section onto a calibrated grid and compared to the saline controls.

Biochemical measures of catecholamines and their metabolites: Using high performance liquid chromatography (HPLC) with electrochemical detection, the levels of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), norepinephrine (NE), and 3-methoxy-4-hydroxyphenylglycol (MHPG) were determined bilaterally in several brain regions at 2, 6 and 16 days postinjury. Animals receiving 400, 600 or 800 g/cm injuries and amphetamine or saline were compared. Behavioral testing was conducted on these animals until the day of sacrifice to ensure that they receive experience and to determine if measures of behavioral recovery correlated with levels of neurotransmitter and metabolite.

For HPLC analysis, rats (n = 2 per group) were decapitated using a Harvard small animal decapitator. All instruments used were kept on ice. The scalp was removed with a sharp, blunt scissors. Curved Miltex Rongeurs (6 in) were used to remove the skull to expose the brain for extraction. The dura was removed and a spatula (Fisher 21-401-10) was used to separate the brain from the floor of the cranial vault and to cut the optic nerves. The interval between decapitation and the brain being put on an iced watch glass was less than 2 minutes. The dissection of the brain was implemented using forceps, a safety razor, brass punch (1.0. 3.5 mm) and a small drill bit to remove samples from the punch. For areas not done with the punch, a safety razor and forceps were used to obtain a core section of approximately the same size. Nine samples were taken from both the left and right sides of the brain for a total of 18 samples: caudate putamen (punch), hypothalamus, thalamus (punch), hippocampus, cortex lateral to the injury (temporal lobe), substantia nigra (ventral tegmentum) locus coeruleus (medulla), cerebellar cortex, cerebellar nuclei. Each tissue sample was individually wrapped in aluminum foil with a label which indentified the animal tissue section and date. The total time from decapitation to freezing (-70 C) was also recorded. HPLC was employed to determine the relative amounts of NE, MHPG, DA, and DOPAC in 18 the brain regions. The homogenization buffer consisted of 0.1 M NaH_2PO_4 adjusted to pH 4.0, 1 mM octane sulphonic acid, and 30 % of this final volume of acetonitrile. The mobile phase consisted of 0.1 M Na_2HPO_4, 0.1 M citric acid adjusted to pH 4.3, and octane sulphonic acid which was subsequently added such that its final concentration was 1 mM. Finally, one-tenth of the final volume of mobile phase of acetonitrile was added. Mobile phase was pumped through the column (Bioanalytical Systems,

ultrasphere XL-ODS, 3 um particle size) on which the sample was fractionated. Isoproterenol served as the internal standard. The sample was then detected on a Bioanalytical Systems LC-4B/17A amperometric detector with a glassy carbon electrode. The potential had to be maintained at 1.3 V for optimal sensitivity for detection of MHPG. An Ag/AgCl electrode served as the reference. The concentrations of the neurotransmitters, metabolites and standard in the samples were determined using an integrator (Hewlett-Packard-3390A) which derived the areas under the peaks.

Brain tissue was homogenized in 0.2 mL homogenization buffer on ice (4 C) for 6 sec in a dismembrator. The homogenate was then centrifuged at 12,000 g in a Savant high speed centrifuge for 20 min. The pellet was saved for protein determinations as described by Lowry et al. (1951). The supernatent was then resuspended in homogenization buffer and recentrifuged for an additional 20 min, and a 5 uL aliquot sample was injected through the column which was run at a flow rate of 0.8 mL/min. The retention times for NE, MHPG, DOPAC, and DA were 1.3, 1.52, 2.04, and 2.3 min, respectively. The area computed by the integrator was used to calculate their amounts.

RESULTS

Behavioral Pharmacology.

Effects of AMP on Beam-walking Recovery after Contusion Injury. A series of pilot studies were conducted to evaluate the effects of various contusion impact forces (200, 400, 600, 800 and 1000 g/cm) in relation to differential doses of AMP (1.0, 1.5, 2, 2.5 and 3 mg/kg) and their combined effects on beam-walking performance. The data revealed that the 200 g/cm contusion force produced minimal disability on the beam with

scores ranging from "4" to "6" on the 24 hr postinjury test trial. Given that animals receiving this contusion injury spontaneously recovered locomotor ability (i.e., attained a score of "7") too rapidly for any therapeutic effects of drug intervention to be evaluated, the 200 g/cm force was not utilized in any further investigations. Even though, all other contusion forces produced significant deficits in locomotor ability with 24 hr postinjury test trial scores ranging from "2" to "3", complete spontaneous recovery was severely retarded after the 1000 g/cm contusion injury; 23 days as compared to 15 days for all other impact forces. Interestingly, complete recovery continued to be severely retarded after the 1000 g/cm contusion force even when the dosage of AMP was increased to 3 mg/kg. Given the severity of the disability caused by this injury, the 1000 g/cm impact force was also dropped from further investigations.

To assess the effects of AMP on recovery of locomotor ability after these various contusion impacts, animals were given a single injection (i.p.) of AMP (2 mg/kg) or saline immediately after the 24 hr postinjury test trial and were further tested at 1, 3, 6 and 24 hours postinjection. Behavioral testing was subsequently conducted every other day for 29 days.

The effects of AMP (2 mg/kg) on recovery of locomotor ability after either a 400 or 800 g/cm contusion injury are presented in Figure 1.

See Figure 1

As can be seen in this figure, a single dose of AMP given 24 hours after a 400 g/cm contusion injury was effective in accelerating recovery of beam-walking ability compared to the spontaneous recovery rates for saline

controls with the same type of injury ($F_{1,15} = 13.58$, $p < .01$). However, AMP was not effective in accelerating recovery after a contusion injury of 800 g/cm, even when a second injection was administered to rats on day 3 postinjury ($p > .10$). Although not depicted in this figure, animals receiving a 600 g/cm contusion injury displayed behavior in between those receiving a 400 g/cm and an 800 g/cm injury. However, as with the 800 g/cm impact animals, AMP was ineffective in accelerating recovery of beam-walking ability in relation to the saline controls receiving the same 600 g/cm injury ($p > .10$).

Effects of AMP on Forepaw Dexterity after Contusion. Figure 2 depicts the effects of AMP on recovery of forepaw dexterity after either 400 or

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See Figure 2

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800 g/cm contusion forces. A single dose of AMP given to animals with a 400 g/cm contusion 24 hours post-injury did not significantly alter recovery of forepaw dexterity as compared to saline controls ($p > .10$). As well, no beneficial effects of AMP (2 mg/kg) on performance of this task were observed in rats with an 800 g/cm contusion injury even though AMP was administered at both 24 and 72 hours after surgery ($p > .10$). Although not shown, rats receiving a 600 g/cm contusion injury and given a single dose of AMP 24 hours post-injury, displayed performance very similar to those animals receiving a 400 g/cm contusion injury. As with the 400 g/cm impact, AMP did not significantly alter recovery of forepaw ability ($p > .10$). In all groups, no additional improvement in animals' ability to reach, grasp and retrieve food pellets was seen beyond the

period illustrated in Figure 2, although testing was continued through day 85 post-injury.

A trauma dose-response effect on deficits was readily evident in both the forepaw dexterity and the beam-walking tasks. Although more pronounced in the forepaw task, Figures 1 and 2 indicate that more severe deficits and slower spontaneous recovery were present after an 800 g/cm as compared to a 400 g/cm contusion impact. All in all, the 400g/cm impact contusion was found to produce the most consistent behavioral deficit with injury primarily limited to the sensorimotor cortex. Because of this and the fact that this impact was receptive to AMP treatment using the beam-walk task, it was the most extensively investigated in further studies employing drugs with more specific actions. However, due to the lack of any effects of AMP on recovery of forepaw grasping ability this behavioral measure was not used in other drug studies.

AMP and Volume of Cavitation. The average volume of cavitation observed in these studies for the 400, 600 and 800 g/cm impact is presented in Table 2. Regardless of the severity of contusion, the average volume of

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See Table 2

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cavitation observed for animals receiving AMP was not significantly different from saline controls (all p's $< .05$). There was however, an effect of contusion force. That is, the average volume of cavitation in animals receiving the 800 g/cm impact was significantly larger than in those receiving the 400 g/cm impact ($F_{1,36} = 5.49$; $p < .05$). Animals receiving the 600 g/cm impact also showed greater cavitation than those

receiving the 400 g/cm force (F 1, 34 = 6.44; $p < .05$). There was no difference in the size of cavitation between the 600 and 800 g/cm forces ($p > .01$).

Effects of Seizures on Beam-walking Recovery. A 600 g/cm contusion force was used in these studies because it produced a large area of necrosis and moderate behavioral deficits on the beam. The beam-walking results for the 2 ECS, 7 ECS and Control groups are illustrated in Figure 3.

See Figure 3

Statistical analysis indicated that the animals receiving a 600 g/cm contusion followed by 2 ECSs performed significantly better on the beam-walking task than the animals receiving only a contusion ($p < .05$). Animals receiving 7 ECSs after contusion were not significantly different from the contusion alone control group on this task ($p > .10$). These volumes were calculated from animals sacrificed on day 16.

ECS and Volume of Cavitation. The average volume of cavitation observed ECS for the animals receiving only contusion was not significantly different ($p > .10$) from that reported in our previous study for the 600 g/cm impact (see Table 2). However, multiple ECSs after the contusion markedly reduced the volume of the injury. The animals receiving seven seizures had significantly ($p < .001$) smaller areas of necrosis than animals receiving contusion alone while the reduction in area of necrosis was not significant for the 2 seizure group. The average volume of necrotic cavitation was reduced 17.2% in the 2 ECS group and 66% in the

7 ECS group as compared to control animals.

Effects of Drugs with Specific Actions on Beam-walking Recovery. The effects of propranolol (10 mg/kg), prazosin (4 mg/kg), yohimbine 10 mg/kg) and methoxamine (1, 4 & 8 mg/kg) are illustrated in Figures 4-9. The drug effects were compared to sham controls for sedation effects as well as saline controls.

Consistent with the notion that the facilitory effects of AMP may be mediated by the alpha adrenergic receptor system, the beta adrenergic receptor antagonist propranolol showed no effects. As can be seen in Figure 4, animals given propranolol displayed no facilatory effects on beam-walking ability as compared to saline controls ($p > .10$). Two

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See Figure 4

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further findings were also consistent with this notion. First, the alpha 1 antagonist prazosin significantly retarded recovery. Figure 5 shows that recovery of beam-walking ability for animals given this drug was much slower compared to the spontaneous recovery rates for saline controls ($F\ 1,23 = 6.80$; $p < .05$). Further, this effect was not due to any sedative

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See Figure 5

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action produced by the drug since the drug injected sham animals displayed no disability on the beam as compared to saline injected sham animals ($p > .10$). Second, the alpha 2 antagonist yohimbine appeared to

accelerate recovery. The data depicted in Figure 6 indicates a trend for yohimbine to promote recovery, however, the effect was not statistically significant ($p = .13$). Somewhat less consistent with the above results was the data

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See Figure 6

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from animals receiving the alpha 1 agonist methoxamine. Regardless of the dosage, 1, 4 or 8 mg/kg, methoxamine was ineffective in accelerating recovery of beam-walking ability. As suggested by Figures 7-9, there was no difference between any of these groups and the saline controls (all p's $> .10$).

See Figures 7, 8 and 9

Effects of Drugs with Specific Actions on Reinstatement of Deficits. Beam-walking ability for fully recovered sham or contused rats after the 30 day post-injury injection of either propranolol (10 mg/kg), clonidine (.4 mg/kg), prazosin (4 mg/kg) or PBZ (10 mg/kg) are illustrated in Figures 10-13. Again for statistical analysis, the drug effects in contused animals were compared to sham controls for sedation effects as well as to saline controls.

As can be seen in Figure 10, propranolol, the beta adrenergic receptor antagonist, did not reinstate locomotor deficits ($p < .05$).

See Figure 10

Likewise, as seen in Fig 11, neither did the alpha 2 agonist clonidine

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See Figure 11

($p < .05$). On the other hand, both of the alpha 1 antagonists, prazosin and PBZ significantly reinstated deficits. As suggested by Figures 12 and 13, there were significant differences in locomotor ability between sham operates and injured animals receiving prazosin ($F\ 1,27 = 7.57$; $p < .05$) or PBZ ($F\ 1, 43 = 6.66$; $p < .05$) .

See Figures 12 and 13

HPLC

Biochemical data are from the first completed analysis of all brain regions sampled for single animals in each group for each contusion force, time point, and drug treatment. Comparisons of just a few selected regions is consistent with the hypothesized effect of AMP treatment of NE turnover 16 days after injury in the cerebellum. In the right cerebellar cortex, HPLC analysis revealed MHPG/NE ratios of 14.2/83.6 and 10.1/68.7 for AMP and saline treatment, respectively, following 400 g/cm impact at 2 days postinjury; in the left cerebellar cortex, MHPG/NE ratios were 0/45.6 and 0/173.2 for AMP and saline treatment, respectively. Note, however, (See Appendix) that the left cerebellar cortex in these animals shows higher NE turnover at 16 days due to AMP treatment compared to the right cerebellar cortex and compared to the saline-treated animals as previously predicted (8).

In the right cortex lateral to the injury, following 400 g/cm impact at 2 days post-injury, DOPAC/DA ratios were 11.1/11.1 and 12.8/4.7 for AMP and saline treatment, respectively; in the left cortex, the DOPAC/DA ratios were 63.0/65.8 and 10.2/114.0 for AMP and saline treatment, respectively.

In the right caudate-putamen, DOPAC/DA ratios were 135.1/1071.6 and 115.9/879.0 for AMP and saline treatment, respectively; and in the left caudate-putamen, the ratios were 103.9/1058.8 and 163.7/999.9, due to AMP and saline treatment, respectively, following 400 g/cm impact at 2 days.

At 16 days, following 400 g/cm impact, DOPAC/DA ratios in the right cortex were 40.0/454.0 and 39.7/519.4 for AMP and saline treatment, respectively; in the left cortex, the ratios were 21.0/202.4 and 44.0/539.1 for AMP and saline treatment, respectively. In the right caudate-putamen, the ratio of DOPAC/DA was 261.0/1404.0 and 172.0/1443.2 for AMP and saline treatment, respectively; and in the left caudate-putamen, the same ratio was 6.8/44.0 and 146.0/1281.6 for AMP and saline treatment, respectively. See Appendix for HPLC data for all brain regions examined at 2 and at 16 days post injury for these animals and for others at 600 and 800 g/cm injuries (16 days).

DISCUSSION

The data from these experiments on cortical contusion suggest that drug which stimulate NE receptors or cause NE release can promote recovery of some motor functions after cortical contusion. Additionally, the maintainance of that recovery is dependent upon continued alpha-adrenergic function. However, beneficial effects are apparently limited

by the severity of the contusion. A single dose of AMP promoted recovery of beam-walking ability after unilateral sensorimotor cortex contusion after 400 g/cm impact injuries but not after 600 or 800 g/cm injuries. There are two reasonable explanations for the lack of any beneficial effect of AMP administration after 800 g/cm contusions; insufficient drug treatment or the more extensive injuries possibly including subcortical structures which mediate some of the effects of AMP. While two administrations of AMP were also ineffective for severe contusions, other studies of extensive cortical and subcortical injuries in a model of stroke in rat have shown beneficial effects of prolonged AMP (1 mg/kg/day for 7 days) administration (56). This remains to be studied after severe contusion.

It is apparent from this data that recovery of all sensorimotor deficits after cortical contusion are not equally benefited by AMP. Even for the 400 g/cm injuries, which showed a significant acceleration of recovery of beam-walking, no beneficial effect was seen on recovery of forepaw grasping ability. This lack of effect on deficits of fine movement of the digits after cortical contusion is probably not due to this ability being a strict cortically bound function, as substantial spontaneous recovery was observed even after 800 g/cm contusions. Again, whether forepaw grasping, or locomotion (after severe contusions) would benefit from more prolonged drug administration after contusion is unknown. These behavioral data on the effects of AMP after cortical contusion do indicate that AMP treatment of some deficits after cortical contusion are amenable to pharmacotherapy. However, further work is necessary to determine if severe contusions and fine motor deficits are treatable by pharmacotherapy.

The possible neurochemical mechanism(s) of the AMP effect in promoting recovery of function are diverse since AMP directly influences many neurotransmitters including acetylcholine, gamma-aminobutyric acid (13), and serotonin (4,28,52,58). However, the AMP acceleration of recovery of locomotor function is blocked by the catecholamine antagonist, haloperidol, indicating a catecholamine role in this effect (22). Additionally, intraventricular NE, but not DA, accelerates recovery of function (8). The NE released after AMP administration stimulates both alpha-1 and alpha-2 receptors (39,49) and this would preclude clarification of the NE receptor subtype in this effect. The locus coeruleus (LC) is the major source of cerebral NE (3,27,51) and AMP decreases firing of these neurons, probably by acting on their alpha-2 receptors which have a negative feedback onto LC cells (32). However, many of the noradrenergic effects of AMP are attributed to its catecholamine release from presynaptic terminals and blocking reuptake (4,13,16,30,55), as well as inhibiting monoamine oxidase and slowing breakdown of released catecholamines (35).

Because of these diverse effects of AMP, the data from the present study using drugs with more limited action on NE receptors help clarify the mechanism of the AMP effect on recovery of function. Like previous work using the ablation model, the neuropharmacological data from these contusion studies using drugs with more specific actions than AMP, suggest a role for NE in mediating beneficial effects on recovery. Prazosin exhibits relative specificity and/or acts preferentially as a post-synaptic alpha-1 receptor antagonist (5,11). Yohimbine preferentially blocks alpha-2 receptors (31) and increases the firing of LC neurons through actions on post-synaptic autoreceptors (33). Clonidine

is the prototypical alpha-2 agonist, stimulating both pre- and post-synaptic alpha-2 receptors and should reduce NE release from LC neurons (46,62). However, the dose used in this study may activate both alpha-1 and alpha-2 adrenoceptors (1). The alpha adrenergic receptor antagonist, PBZ, binds irreversibly to these receptors in the CNS (48) and inhibits reuptake (10,14). However, PBZ also affects DA (41), GABA (6), and opiate receptors (54). The beta-1 and beta-2 receptor antagonist propranolol may also block serotonin receptors (65). Methoxamine is a selective alpha-1 agonist. Because of the multiple effects of most drugs, clarification of NE involvement in promoting and maintaining recovery of function can best be achieved by observing complementary effects of purported agonists and antagonists. Additional information can be obtained by observing similar patterns on recovery by several drugs with several compounds having demonstrated similar actions on receptor subtypes and lack of effects of stimulation of other subtypes. The drug doses used in the present study were selected from dose-response studies previously conducted using the ablation model (61), except for methoxamine which had not been previously studied in recovery of function. The alpha-1 adrenergic antagonist, prazosin, markedly slowed recovery of beam-walking after contusion. The alpha-2 antagonist yohimbine should increase NE release by blocking inhibition of LC neurons, produced a trend toward accelerating locomotor recovery. The dose of yohimbine used in this study significantly accelerated recovery of beam-walking ability in the ablation model (61) but only approached significance in this study. The alpha-1 agonist, methoxamine, was ineffective, however, which may be due to its very short half-life. The beta-1 adrenergic antagonist, propranolol, also had no effect suggesting that the noradrenergic basis of the AMP effect

may be specific to the alpha receptor subtype. If NE activation (or NE release) of alpha-1 NE receptors by AMP is the basis of AMP's effect on recovery of locomotion, then alpha-1 agonists should be effective in promoting recovery. Experiments giving either multiple doses or continuous infusion of methoxamine should be conducted as this hypothesis predicts beneficial effects on recovery. However, this model may represent only a complex series of events in the pharmacological manipulation of the rate of recovery of function after cortical injury. Experiments examining the effects of intraventricular NE and DA infusion and LC or substantia nigra lesions on recovery after contusion are in progress to further test this hypothesis.

Based on observations of a dramatic reinstatement of symptoms in recovered animals by drugs blocking alpha adrenergic receptors, it has been proposed that continued activity in this system is necessary for maintaining recovery of function (23,57). The data from the present study of contusion confirm the previous observations in the ablation model. The alpha-adrenergic antagonists, prazosin and phenoxybenzamine, reinstated deficits as did the alpha-2 agonist, clonidine. This effect is not simply due to sedation, since beam-walking deficits are reinstated only in the affected limbs and the deficits due to sedation seen in sham operated animals is significantly less than in contused animals. Moreover, a similar sedation effect is seen in sham control animals after administration of the beta antagonist, propranolol, but the contused animals are not more severely affected than the control rats. This further suggests that the maintenance of recovery is mediated by alpha-adrenergic receptor activity.

A similar "vulnerability" of the injured brain to drug manipulation has

been demonstrated in other models. Marshall (45) reported that administration of the catecholamine synthesis inhibitor, alpha-methyl-para-tyrosine, or the DA receptor blocker, spiroperidol, to rats months after unilateral lesions producing sensory neglect dramatically reinstated symptoms.

There are several theories and proposed mechanisms for recovery of function (26), but since the drug effects observed in these studies appear within an hour, mechanisms which require time, such as sprouting or denervation supersensitivity, are inadequate explanations for these results. Two possible mechanisms, not requiring time (sparing and diaschisis), that could account for the AMP effect on recovery of function were examined in this series of investigations. First, there is some evidence indicating that in a rodent stroke model, AMP reduces the extent of necrosis and this sparing of cortical tissue could promote recovery (56). However, no effect of AMP treatment on the volume of necrosis produced by the impact injury was found in this study. However, seven ECSs reduced the volume of necrosis without affecting beam-walking recovery and two ECSs accelerated recovery without reducing the extent of injury. The different AMP effect on extent of necrosis between the experiments could be due to a variety of factors such as the prolonged drug administration in the stroke model and only a single dose in this study. Importantly, however, this reduction of the volume of necrosis cannot be the primary mechanism of the AMP effect on behavioral recovery since after 400 g/cm contusions, two ECSs accelerated locomotor recovery without effect upon the extent of injury. A second mechanism proposed to account for the drug acceleration of recovery is that AMP treatment acts upon remote intact structures, depressed by the injury, and relieves a

diaschisis (20). The evidence for the second hypothesis is based upon the observation that AMP produces an enduring alleviation of depressed 2-deoxyglucose (2-DG) utilization in areas remote from the ablation (19,24). Further support for the proposed attenuation of a diaschisis comes from biochemical data indicating depressed levels of NE and MHPG in the LC and cerebellum contralateral to the sensorimotor cortex ablation. In this model of hemiplegia, AMP produces an enduring increase in NE turnover in these structures after ablation (8). The HPLC data from this investigation, while too limited for any conclusion, is consistent with the proposition that AMP produces an increased NE turnover in the cerebellar cortex contralateral to a sensorimotor cortex contusion. As in the previous work, this effect apparently persists long after drug administration. The methodology for developed in this work for rapidly measuring levels of NE, MHPG, DA and DOPAC allows sampling of a wide variety of areas. Previous work had been limited to measuring levels of NE and MHPG in cerebellum and the region of the locus coeruleus. However, preliminary data from this study observed increased NE turnover in AMP treated animals compared to saline controls in many regions after contusion. The HPLC data from this investigation, while too limited for any conclusion, is consistent with the proposition that AMP produces an increased NE turnover which persists long after drug administration. The methodology developed in this work for rapidly measuring levels of NE, MHPG, DA and DOPAC allows sampling of a wide variety of brain areas. Previous work on recovery and AMP administration had been limited to measuring levels of NE and MHPG in the cerebellar cortex and in the region of the LC. However, preliminary data from this study observed increased NE turnover in AMP-treated animals compared to saline controls in many

regions after contusion (See Appendix). At 2 days, DOPAC/DA ratios were virtually identical in the right cortex, but displayed a dramatic drop in turnover rate in the left cortex (contralateral to injury) as a result of saline treatment compared to that of AMP. In the right caudate-putamen, the rate of DA turnover decreased slightly due to saline treatment while in the left caudate-putamen, the AMP-treated group displayed slightly lower turnover ratios.

At 16 days, the effect in the cortex ipsilateral to injury was unchanged but in the left cortex, the rates of DA turnover reversed; that is, although both DOPAC and DA were 2-fold higher, the level of DOPAC was still 10% higher than that of DA. Finally, in the right caudate-putamen, the DOPAC/DA ratio increased from 0.12 to 0.18 at 16 days, suggesting that time is necessary for DA to increase its rate of turnover as a result of AMP treatment; the saline-treated rats in this structure displayed a lower rate of DA turnover. It seems, therefore, that with time, the contralateral homologue (in this case, the caudate-putamen, which receives most of its afferent projections from the DA-rich cell bodies of the substantia nigra) will increase its metabolism, implicating a delayed response to the metabolic changes occurring in the opposite (ipsilateral) hemisphere. The left caudate-putamen showed a similar trend to that of the right. Due to the extremely small sample sizes, statistical analyses could not be conducted and will have to await further experiments to increase said sample sizes. Nevertheless, this new and efficient HPLC technique will allow an extensive investigation of the effects of this treatment regimen on catecholamines and their metabolites after brain injury. Regarding AMP alleviation of metabolic depression after contusion, studies have just begun using 2-DG autoradiography to

quantitatively investigate this question. Dopamine and DOPAC were also depressed after injury, but no differences were observed between AMP treatment and controls. This new and efficient HPLC technique will allow an extensive investigation of the effects of this treatment regimen on catecholamines and their metabolites after brain injury. Regarding AMP alleviation of metabolic depression after contusion, studies have just begun using 2-DG autoradiography to quantitatively investigate the question.

Seizures are a frequent sequalae early after brain injury, especially in the first weeks after sensorimotor cortex damage in man (25). Seizures evoke a sustained increase of NE turnover and previous work also reported a similar effect after AMP treatment in sensorimotor cortex ablated animals (8). This effect of seizures could enhance recovery of locomotor function after contusion. Schallert (57), discussing the retardation of recovery of sensory neglect by anticonvulsant drugs after cortical ablation, predicted that seizures would have a beneficial effect on recovery if they were not too frequent. In the experiments examining the effects of ECS on recovery of beam-walking after sensorimotor cortex contusion, an acceleration of recovery was observed following 2, but not 7, ECSs. Using a different model of recovery of function and focal seizures rather than ECS, he confirmed our observations that seizures can accelerate the remission of symptoms of cortical injury (personal communication). The only reports of beneficial effects of seizures on motor deficits in humans has been in Parkinson's Disease patients given ECS for depression (1,40,42). It has been hypothesized (19) that seizures occurring early after injury may have evolved as a repair process for

brain injury and that early post-traumatic seizures may be a beneficial response to cerebral damage gone awry, similar to malignancies or autoimmune disease. Whatever the basis of the effects of seizures on recovery of function and given the retardation of recovery by some anticonvulsant drugs (57), the very early prophylactic administration of such drugs to brain-injured patients may be contraindicated. Determining the scientific basis for drug therapy and drug contraindications in cases of brain injury continues to be a promising line of research. The current studies have provided some hope for a treatment for some cortical contusions and advanced our understanding of the mechanisms of drug effects on recovery of function after brain injury. Recent case reports (18) and preliminary studies (15) suggest that observations of the beneficial effects of AMP and harmful effects of catecholamine antagonists can be extended to cases of human brain injury. Ongoing work will further elucidate the mechanism(s) involved in this potential medical therapy for a previously untreatable condition.

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APPENDIX

Concentrations (pg/0.05 mg protein) of NE, MHPG, DOPAC, and DA in all examined brain regions following a single injection of either AMP or saline in rats with a right unilateral contusion in the sensorimotor cortex. Said rats were sacrified at 2 or at 16 days (last column) postinjury for HPLC analysis. Abbreviations: Sampl, sample; contus, contusion force of impact of 0 (sham craniotomies), 400, 600, and 800 g/cm; Drug T, drug treatment with either a=(AMP) or s=(saline); Hemis, hemisphere of either r=(right) or l=(left); structur, structure of cp=caudate-putamen, h=hypothalamus, t=thalamus, hp=hippocampus, cx=cerebral cortex, cbn=cerebellar nuclei, vt=substantia nigra (ventral tegmentum), ml=locus coeruleus (medulla), cb=cerebellar cortex.

APPENDIX

File: Metabolism Data
Report: metabolism2

Sampl	Contus	Drug	T	Hemis	Structur	NE	MHPG	DOPAC	5A
1	4	a	r	cp		15.1	6.0	135.1	1071
2	4	a	r	h		160.1	0	4.0	18.
3	4	a	r	t		83.8	12.1	7.6	28.
4	4	a	r	hp		105.8	4.9	0	0
5	4	a	r	cx		50.4	27.9	11.1	11.
6	4	a	r	cbn		158.6	14.1	0	0.
7	4	a	r	vt		92.1	0	10.1	64.
8	4	a	r	ml		261.9	17.5	5.8	14.
9	4	a	r	cb		83.6	14.2	0	0
10	4	a	r	cp		0	6.9	115.9	879.
11	4	a	r	h		335.8	7.2	3.0	27.
12	4	a	r	t		278.4	10.0	10.6	43.
13	4	a	r	hp		122.7	17.5	133.6	922.
14	4	a	r	cx		118.3	16.9	12.8	8.
15	4	a	r	cbn		314.3	29.6	0	1.
16	4	a	r	vt		85.8	5.6	9.6	63.
17	4	a	r	ml		290.4	9.7	5.6	22.
18	4	a	r	cb		68.7	10.1	0	4.
19	0	a	r	cp		16.2	0	105.0	948.
20	0	a	r	h		207.7	0	5.0	20.
21	0	a	r	t		143.4	7.4	30.3	279.
22	0	a	r	hp		155.2	10.0	6.52	84.
23	0	a	r	cx		230	14.0	22.2	183.
24	0	a	r	cbn		119.6	17.3	0	4.
25	0	a	r	vt		125.7	0	14.0	71.
26	0	a	r	ml		243.5	13.8	5.4	3.
27	0	a	r	cb		69.5	13.6	0	0
28	8	a	r	cp		23.1	0	98.6	1032.
29	8	a	r	h		434.1	17.3	0	43.
30	8	a	r	t		266	6.6	13.6	99.
31	8	a	r	hp		205	8.8	0	20.
32	8	a	r	cx		143.6	16.5	63	762.
33	8	a	r	cbn		91.4	14.4	0	3.
34	8	a	r	vt		117.2	5.5	12.2	85.
35	8	a	r	ml		319.3	17.4	5.2	9.
36	8	a	r	cb		58.6	5.2	0	0
37	0	a	r	cp		7.8	5.6	90.5	1235.
38	0	a	r	h		254.4	3.8	3.9	27.
39	0	a	r	t		164.3	6.5	2.8	13.
40	0	a	r	hp		150.5	14.2	0	21.
41	0	a	r	cx		159.5	11.1	5.8	51.
42	0	a	r	cbn		98.2	15.8	0	0
43	0	a	r	vt		120.2	0	11.3	66.
44	0	a	r	ml		206.2	10.9	3.2	7.
45	0	a	r	cb		81.4	15.8	0	0
46	4	a	r	cp		25.5	0	155.3	1282.
47	4	a	r	h		399.2	14.9	4.8	144.
48	4	a	r	t		247.7	8.6	16.6	82.
49	4	a	r	hp		170.0	19.5	35.4	448.
50	4	a	r	cx		114.3	2.0	39.7	513.

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Sampl	Contus	Drug	T	Hemis	Structur	NE	MHPG	DOPAC	DA	
51	4	s	r		cbn	84.0		6.7	[illegible]	
52	4	s	r		vt	120.0	0	20.3	[illegible]	
53	4	s	r		ml	255.9	12.6	6.9	[illegible]	
54	4	s	r		cb	81.8	7.8	0	0	
55	6	a	r		cp	18.4	0	92.0	[illegible]	
56	6	a	r		h	275.9	10.5	5.8	22.5	
57	6	a	r		t	225.9	7.5	9.0	50.5	
58	6	a	r		hp	140.4	9.8	5.9	4.7	
59	6	a	r		cx	167.2	11.7	28.2	361.5	
60	6	a	r		cbn	68.0	8.3	0	0	
61	6	a	r		vt	116.0	0	13.7	75.4	
62	6	a	r		ml	238.3	8.3	3.7	[illegible]	
63	6	a	r		cb	45.1	5.1	0	0	
64	6	s	r		cp	58.1	7.7	122.5	[illegible]	
65	6	s	r		h	294.6	5.4	[illegible]	[illegible]	
66	6	s	r		t	87.2	0	6.1	[illegible]	
67	6	s	r		hp	231.1	12.9	10.4	[illegible]	
68	6	s	r		cx	189.5	12.3	11.9	[illegible]	
69	6	s	r		cbn	123.9	13.6	0	[illegible]	
70	6	s	r		vt	118.7	0	13.1	[illegible]	
71	6	s	r		ml	333.9	14.8	5.3	[illegible]	
72	6	s	r		cb	167.9	15.7	0	0	
73	8	a	r		cp	8.7	11.0	163.2	[illegible]	
74	8	a	r		h	378.7	16.7	8.3	63.9	
75	8	a	r		t	240.1	13.3	3.1	25.1	
76	8	a	r		hp	178	17.1	7.4	1.8	
77	8	a	r		cx	229.5	24.1	42.1	[illegible]	
78	8	a	r		cbn	162.8	22.3	0	3.3	
79	8	a	r		vt	196.9	9.1	14.4	[illegible]	
80	8	a	r		ml	227.5	20.9	7.8	7.3	
81	8	a	r		cb	65.1		4.1	[illegible]	
82	4	a	l		cp	2.2	4.8	103.9	[illegible]	
83	4	a	l		h	522.6	40.2	4.1	43.7	
84	4	a	l		t	193.1	8.7	0	10.4	
85	4	a	l		hp	43.9	6.4	12.6	[illegible]	
86	4	a	l		cx	71.3	0	6.3	[illegible]	
87	4	a	l		cbn	70.6	19.3	0	[illegible]	
88	4	a	l		vt	88.9	4.6	9.2	[illegible]	
89	4	a	l		ml					
90	4	a	l		cb	45.6	0	0	0	
91	4	s	l		cp	0	9.6	163.7	[illegible]	
92	4	s	l		h	491.5	18.3	7.7	[illegible]	
93	4	s	l		t	170.0	8.7	8.5	[illegible]	
94	4	s	l		hp	166.0	11.5	41.9	[illegible]	
95	4	s	l		cx	286.935	11.8	10.2	[illegible]	
96	4	s	l		cbn	125.9	21.4	0	[illegible]	
97	4	s	l		vt	145.0	6.6	16.1	[illegible]	
98	4	s	l		ml	347.5	7.8	4.4	[illegible]	
99	4	s	l		cb	173.2	0	0	[illegible]	
100	0	a	l		cp	17.7	5.6	132.2	[illegible]	

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Sampl	Contus	Drug	T	Hemis	Structur	NE	MHPG	DOPAC	DA	
101	0	a	1		h	292.9	12.3	3.1	44.5	
102	0	a	1		t	263	10.9	7.6	30	
103	0	a	1		hp	84.5	13.4	28.8	31.3	
104	0	a	1		cx	245.6	18.0	270.2	243.2	
105	0	a	1		cbn	116.7	21.4	0	0	
106	0	a	1		vt	138.7	5.1	14.2	72.6	
107	0	a	1		ml	304.5	12.7	6.3	13.1	
108	0	a	1		cb	33.2	15.1	0	0	
109	8	a	1		cp	2929	7.7	137	1200.2	
110	8	a	1		h	424.3	8.7	0	24.6	
111	8	a	1		t	229.2	9.6	12.5	78	
112	8	a	1		hp	169.7	17.2	17.2	230.5	
113	8	a	1		cx	121.3	5.5	0	5.3	
114	8	a	1		cbn	144.2	17.5	0	5.3	
115	8	a	1		vt	78.5	0	10.4	65.3	
116	8	a	1		ml	242.3	18.5	2.7	6.9	
117	8	a	1		cb	75.1	19.9	0	0	
118	0	a	1		cp	16.9	9.7	134.4	1380.0	
119	0	a	1		h	188.6	0	0	21.5	
120	0	a	1		t		7.0			
121	0	a	1		hp	188.4	14.6	0	2.2	
122	0	a	1		cx	135.5	12.7	9.9	104.7	
123	0	a	1		cbn	105.2	19.1	0	0	
124	0	a	1		vt	111.9	0	7.7	32	
125	0	a	1		ml	247	11.5	55.5	9.6	
126	0	a	1		cb	64	21.4	0	0	
127	4	a	1		cp	11.6	0	146	1281.6	
128	4	a	1		h	392.8	7.7	3	35.6	
129	4	a	1		t	201	8.0	3.3	12.9	
130	4	a	1		hp	178	17.8	0	16	
131	4	a	1		cx	210	19.6	44	539.1	
132	4	a	1		cbn	172	15.9	0	4.3	
133	4	a	1		vt	123.8	5.5	19	97	
134	4	a	1		ml	240	0	3.47	8.2	
135	4	a	1		cb	73.9	14.9	0	0	
136	6	a	1		cp	18.4	6.7	92.1	1318.9	
137	6	a	1		h	285	6.5	4.6	22.5	
138	6	a	1		t	273	5.0	11	52.6	
139	6	a	1		hp	183	14.2	0	11.2	
140	6	a	1		cx	225	13.6	0	4.8	
141	6	a	1		cbn	100.4	13.6	0	0	
142	6	a	1		vt	115.7	0	0	7.2	
143	6	a	1		ml	245	10.0	5.9	9.4	
144	6	a	1		cb	55	16.2	0	0	
145	6	a	1		cp	14.5	7.9	149	1281.3	
146	6	a	1		h	318	5.8	4.7	44	
147	6	a	1		t	199	8.0	4.4	18.2	
148	6	a	1		hp	147.2	11.6	10.7	64.3	
149	6	a	1		cx	145	10.6	15.5	186	
150	6	a	1		cbn	116.0	14.7	0	2.6	

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Sampl	Contus	Drug	T	Hemis	Structur	NE	MHPG	DOPAC	DA	
151	6	a	1	vt		118.0	0	12.6	68.3	16
152	6	a	1	ml		282	14.5	5.7	12	16
153	6	a	1	cb		95	17.3	0	0	16
154	8	a	1	cp		33	12.7	359.6	1314	16
155	8	a	1	h		420.0	18.9	4.2	2.6	16
156	8	a	1	t		162.6	13.6	20.8	99.2	16
157	8	a	1	hp		152	7.5	0	0	16
158	8	a	1	cx		225	21.0	28	357.5	16
159	8	a	1	cbn		115	15.5	0	0	16
160	8	a	1	vt		240	17.2	0	14	16
161	8	a	1	ml		358	26.1	6.2	11.4	16
162	8	a	1	cb		57	11.1	0	2.2	16
163	0	a	r	cp		47	9.2	135	1186.6	16
164	0	a	r	h		549	13.3	0	30.8	16
165	0	a	r	t		484	14.4	12.5	77.8	16
166	0	a	r	hp		241	10.2	3.7	21.6	16
167	0	a	r	cx		283	15.8	7.9	52.9	16
168	0	a	r	cbn		111	20.0	0	5.8	16
169	0	a	r	vt		100	0	12.1	71.8	16
170	0	a	r	ml		294	16.0	3.56	8.6	16
171	0	a	r	cb		75	19.9	0	5.7	16
172	6	a	r	cp		23	6.4	127.4	1119.8	16
173	6	a	r	h		449	14.7	.3	35.7	16
174	6	a	r	t		461.4	22.6	8.2	54.3	16
175	6	a	r	hp		178	8.0	0	6.2	16
176	6	a	r	cx		189	27.3	47	502.1	16
177	6	a	r	cbn		117	24.7	0	8.55	16
178	6	a	r	vt		106	0	11.8	63.0	16
179	6	a	r	ml		353	29.3	5.1	15.3	16
180	6	a	r	cb		67.8	24.7	0	0	16
181	0	a	r	cp		15.7	0	81	925.5	16
182	0	a	r	h		379	9.9	3.8	35.8	16
183	0	a	r	t		177	0	3.4	14	16
184	0	a	r	hp		136	10.0	0	3.4	16
185	0	a	r	cx		122	11.2	19.5	272	16
186	0	a	r	cbn		83	13.4	0	5.0	16
187	0	a	r	vt		130	0	17.5	93.4	16
188	0	a	r	ml		322.5	32.3	4.54	7.4	16
189	0	a	r	cb		66	18.4			16
190	6	a	r	cp		43	21.7	196.2	1272.4	16
191	6	a	r	h		538	20.5	5.5	60	16
192	6	a	r	t		569.856.8	30.2	17	96	16
193	6	a	r	hp		108	6.8	0	21	
194	6	a	r	cx		112	28.9	26.8	361.77	16
195	6	a	r	cbn		87	43.5	0	6.1	16
196	6	a	r	vt		65	0	16	79.4	16
197	6	a	r	ml		183.5	20.9	4.9	7.6	16
198	6	a	r	cb		57.9	45.1	0	0	16
199	4	a	r	cp		57.6	23.6	172	1443.2	16
200	4	a	r	h		539.2	22.6	6.5	60.6	16

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Sampl	Contus	Drug	T	Hemis	Structur	NE	MHPG	DOPAC	DA	
201	4	s	r	t	383	24.4	6.7	12.4	16	
202	4	s	r	hp	148	12.2	0	12	16	
203	4	s	r	cx	257	16.2	17.7	186	16	
204	4	s	r	cbn	141	21.2	0	2.3	16	
205	4	s	r	vt	77	0	9.3	58	16	
206	4	s	r	ml	242	16.4	4.2	9.4	16	
207	4	s	r	cb	35.8	21.1	0	0	16	
208	0	a	r	cp	9.6	7.7	117	1042	16	
209	0	a	r	h	408	9.4	4.1	35	16	
210	0	a	r	t	231	11.3	9.3	29	16	
211	0	a	r	hp	150	13.1	0	4	16	
212	0	a	r	cx						
213	0	a	r	cbn	92	16.4	0	2	16	
214	0	a	r	vt	72	0	5.7	48	16	
215	0	a	r	ml	250.6	16.7	3.8	13	16	
216	0	a	r	cb	58	13.0	0	13.4	16	
217	4	a	r	cp	101	23.6	261	1404	16	
218	4	a	r	h	546	16.5	4.2	52	16	
219	4	a	r	t	253	10.0	7.02	23.96	16	
220	4	a	r	hp		17.7				
221	4	a	r	cx	259	46.9	40	454	16	
222	4	a	r	cbn	112	39.4	18.	87.2	16	
223	4	a	r	vt	111	0	19.7	94	16	
224	4	a	r	ml	447	27.1	6.9	15.1	16	
225	4	a	r	cb	89	37.3	0	6.4	16	
226	4	s	r	cp	88	41.9	304	1778	16	
227	4	s	r	h	807	32.0	6.4	68	16	
228	4	s	r	t	389	34.1	12.3	50	16	
229	4	s	r	hp	124	8.0	6.4	6.6	16	
230	4	s	r	cx	223	20.3	26.2	26.3	16	
231	4	s	r	cbn						
232	4	s	r	vt	180		14	84	16	
233	4	s	r	ml						
234	4	s	r	cb						
235	0	s	r	cp	37	23.8	223	1430	16	
236	0	s	r	h	710	23.5	5.2	62	16	
237	0	s	r	t	388	27.9	15	64	16	
238	0	s	r	hp	267	31.6	0	8.2	16	
239	0	s	r	cx	235	31.8	11.1	122	16	
240	0	s	r	cbn	206	51.9	4	5.4	16	
241	0	s	r	vt	89	0	14.1	66	16	
242	0	s	r	ml	372	42.0	7.02	16.2	16	
243	0	s	r	cb	63	47.6	0	6	16	
244	0	s	l	cp	162	9.6	144	1091	16	
245	0	s	l	h	463	11.5	2.2	36	16	
246	0	s	l	t	345	11.0	21.4	173	16	
247	0	s	l	hp	149	14.1	80	743	16	
248	0	s	l	cx	383	15.3	16.5	138.9	16	
249	0	s	l	cbn	93	18.6	0	0	16	
250	0	s	l	vt	103	0	11.9	67.7	16	

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Sampl	Contus	Drug	T	Hemis	Structur	NE	MHPG	DOPAC	DA	
251	0	s	1	ml		297	17.8	3.9	10	15
252	0	s	1	cb			20.3	0	0	16
253	6	s	1	cp		68.8	6.5	163	1058	16
254	6	s	1	h		153	9.9	0	22.3	16
255	6	s	1	t		282	18.8	4.1	35.9	16
256	6	s	1	hp		172	13.7	0	11.4	16
257	6	s	1	cx		202	22.4	0	10.8	16
258	6	s	1	cbn		88.6	29.9	0	7.06	16
259	6	s	1	vt		142	0	13.1	72.8	16
260	6	s	1	ml		275	22.7	4.32	5.2	16
261	6	s	1	cb		66.3	26.7	0	0	16
262	8	a	1	cp		18.8	0	123	1092	16
263	8	a	1	h		565	10.7	4.8	35	16
264	8	a	1	t		180	0	3.8	18	16
265	8	a	1	hp		103	8.3	0	0	16
266	8	a	1	cx		152.2	8.9	0	20.5	16
267	8	a	1	cbn		115	20.9	0	0	16
268	8	a	1	vt		90	0	10.2	49	16
269	8	a	1	ml		214	11.4	4	5.8	16
270	8	a	1	cb		71	13.4	0	0	16
271	6	a	1	cp		29.2	16.2	165	1193	16
272	6	a	1	h		427	14.3	4.3	24	16
273	6	a	1	t		394	25.0	23.5	130	16
274	6	a	1	hp		121	15.5	0	8.3	16
275	6	a	1	cx		248	26.0	0	8.1	16
276	6	a	1	cbn		65	36.4	0	6	16
277	6	a	1	vt		92.3	0	10.1	50.6	16
278	6	a	1	ml		204	20.1	5.6	9.9	16
279	6	a	1	cb		66	44.4	0	0	16
280	6	s	1	cp		156	17.2	194	1365	16
281	6	s	1	h		352	42.3	2.86	21.4	16
282	6	s	1	t		250	30.4	7.16	24.5	16
283	6	s	1	hp			10.6			
284	6	s	1	cx		152	0	0	20.5	16
285	6	s	1	cbn		122	30.7	0	0	16
286	6	s	1	vt		123	6.7	18.4	99	16
287	6	s	1	ml		182	18.5	0	6.8	16
288	6	s	1	cb		50	20.5	0	5.5	16
289	0	a	1	cp		17.4	8.3	133.7	1175	16
290	0	a	1	h		330	7.6	0.	27	16
291	0	a	1	t		241	6.9	7.5	33	16
292	0	a	1	hp		95	7.3	0	1.2	16
293	0	a	1	cx		190	8.4	12	8	16
294	0	a	1	cbn		87	19.1	0	7.8	16
295	0	a	1	vt		140	7.8	13	73	16
296	0	a	1	ml		191	13.4	2	6	16
297	0	a	1	cb		18	15.6	0	34	16
298	4	a	1	cp		24.8	17.3	214	1332	16
299	4	a	1	h		459	14.6	0	41	16
300	4	a	1	t		400	27.5	6.8	44	16

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Sampl	Contus	Drug	T	Hemis	Structur	NE	MHPG	DOPAC	[illegible]	[illegible]
301	4	a	1	hp	191	18.0	0	[illegible]	[illegible]	[illegible]
302	4	a	1	cx	247	27.6	21	[illegible]	[illegible]	[illegible]
303	4	a	1	cbn	146	38.6	0	[illegible]	[illegible]	[illegible]
304	4	a	1	vt	117		14.4	[illegible]	[illegible]	[illegible]
305	4	a	1	ml	359	28.1	5.4	[illegible]	[illegible]	[illegible]
306	4	a	1	cb	82.8	28.8	0	[illegible]	[illegible]	[illegible]
307	4	a	1	cp	30	10.8	127.6	[illegible]	[illegible]	[illegible]
308	4	a	1	h	302	5.0	5.7	[illegible]	[illegible]	[illegible]
309	4	a	1	t						
310	4	a	1	hp						
311	4	a	1	cx	289	17.1	1.5	[illegible]	[illegible]	[illegible]
312	4	a	1	cbn						
313	4	a	1	vt	87	23.9	8.5	[illegible]	[illegible]	[illegible]
314	4	a	1	ml	24.8	13.2	3.1	[illegible]	[illegible]	[illegible]
315	4	a	1	cb	248	20.3	3.1	[illegible]	[illegible]	[illegible]
316	0	a	1	cp	36	27.2	250	[illegible]	[illegible]	[illegible]
317	0	a	1	h	655	9.6	2	[illegible]	[illegible]	[illegible]
318	0	a	1	t	554	40.4	11.3	[illegible]	[illegible]	[illegible]
319	0	a	1	hp	133	20.3	0	[illegible]	[illegible]	[illegible]
320	0	a	1	cx	292	40.2	4	[illegible]	[illegible]	[illegible]
321	0	a	1	cbn	143	32.4	0	[illegible]	[illegible]	[illegible]
322	0	a	1	vt	155	6.0	22.2	[illegible]	[illegible]	[illegible]
323	0	a	1	ml	319	36.7	5	[illegible]	[illegible]	[illegible]
324	0	a	1	cb	54	33.3	0	[illegible]	[illegible]	[illegible]

Table 1

Rating scale for assessing behavioral impairment on the beam-walking task.

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7. Animal that can traverse the narrow elevated beam normally with no more than 2 footslips of the left hindlimb.
6. Animal that is able to locomote across the beam using the left hindlimb to aid in more that 50% of its steps on the beam.
5. Animal that can traverse the beam while using the left hindlimb to aid less than 50% of its steps on the beam.
4. Animal that can traverse the beam, placing the foot of the left hindlimb on the horizontal surface of the beam without using the limb to aid in forward locomotion.
3. Animal that can traverse the beam while dragging the affected hindlimb or showing treading/stepping motions with the left hindlimb, but is not capable of placing the left hindfoot on the horizontal surface of the beam during the traversal.
2. Animal that is unable to traverse the beam, but is able to place the left hindlimb on the beam.
1. Animal that is unable to traverse the beam or place the left hindlimb on the beam.

Table 2

Contusion Force	Sacrificed	Average Volume	
		AMP (2 mg/kg)	Saline
400 g/cm	Day 60	93.96 ± 20.66 (n=6)	218.89 ± 62.45 (n=7)
400 g/cm	Day 85	134.34 ± 25.18 (n=8)	135.81 ± 21.67 (n=8)
600 g/cm	Day 85	224.62 ± 45.62 (n=10)	200.92 ± 26.69 (n=10)
800 g/cm	Day 85	237.70 ± 47.78 (n=12; 2 inj.)	219.30 ± 51.27 (n=10)

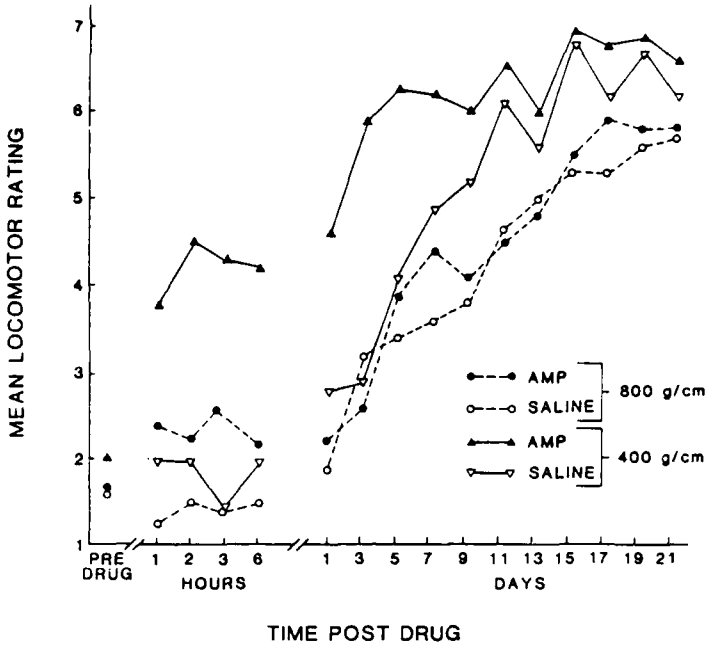

Figure 1. Mean ratings and SEM of beam walk locomotor ability after unilateral contusion injury (400 g/cm and 800 g/cm) to the right sensorimotor cortex of rats. Animals with 400 g/cm injury received a single dose of either d-amphetamine (2 mg/kg) or saline 24 hours after injury. Animals with 800/cm injury received a second injection on day 3 postinjury.

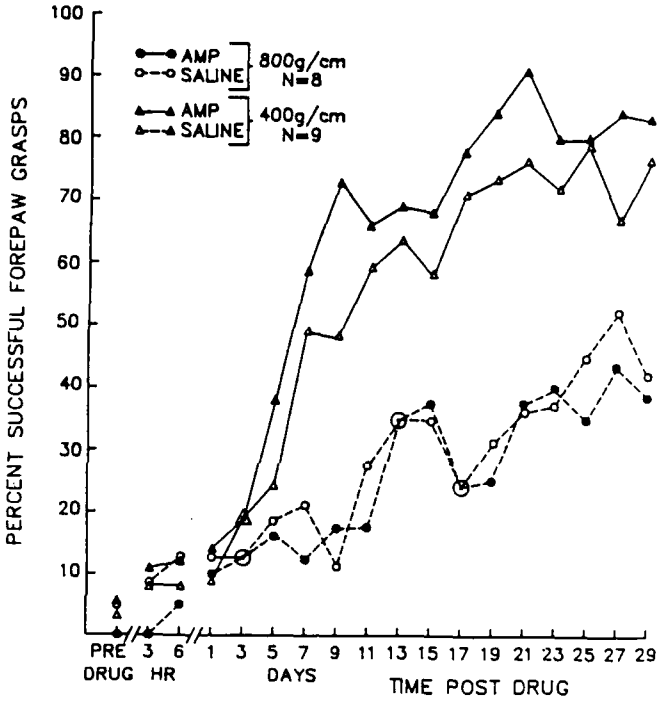

Figure 2. Mean percent successful retrieval of food pellets with the left forepaw by rats with unilateral contusion injury (400 g/cm and 800 g/cm) of the right sensorimotor cortex. Saline or d-amphetamine (2 mg/kg) was administered at 24 hours postinjury for the 400 g/cm impact group, with the 800 g/cm impact group, receiving a second injection on day 3 postinjury.

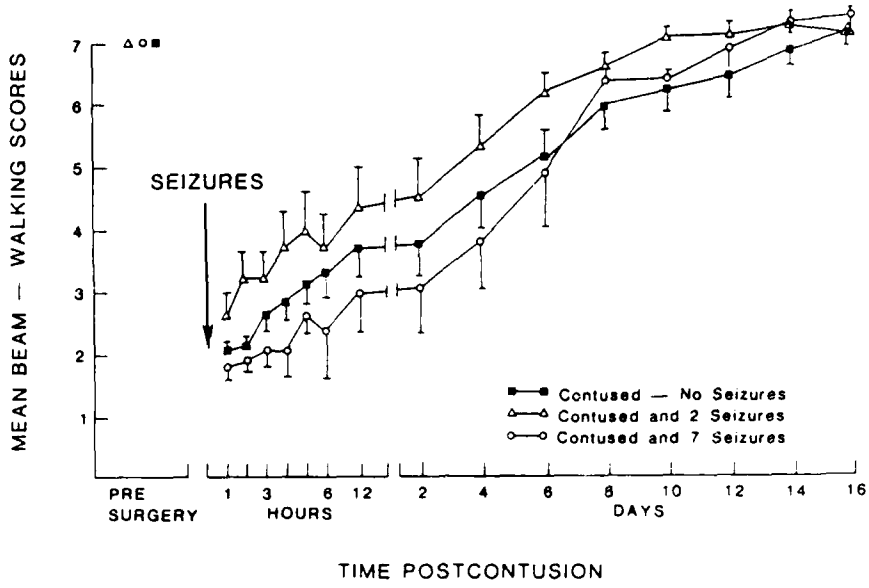

Figure 3. Mean and SEM spontaneous activity scores 3 days prior to and for 15 days after contusion of rats receiving: One ECS at 6h and 24h after surgery; six ECSs beginning at 6h after surgery (spaced at 1h intervals) and 1ECS 22h after surgery; and no ECS group. Activity was significantly depressed for both the ECS groups compared to the no ECS group.

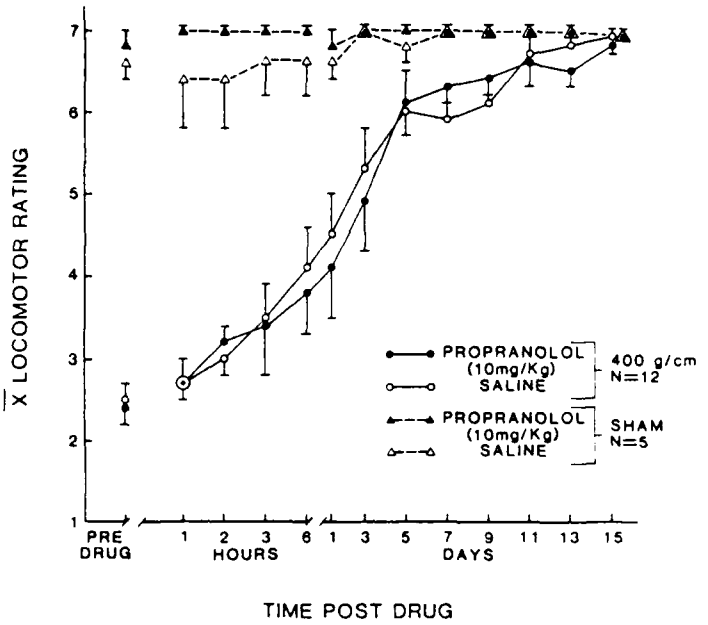

Figure 4. Mean ratings and SEM of beam walk locomotor ability for sham control group and 400 g/cm contusion injury group. Saline (i. p) or propranolol (10 mg/kg; i. p.) was administered to both groups at 24 hours postinjury.

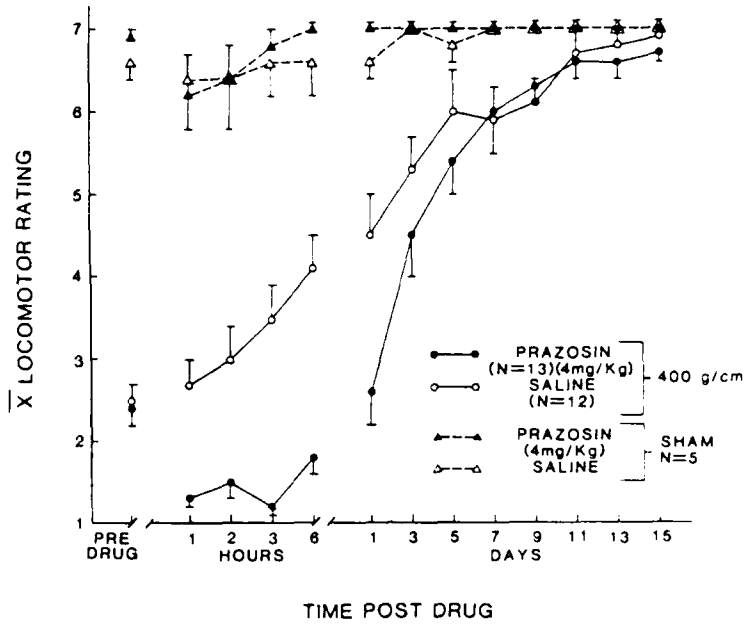

Figure 5. Mean ratings and SEM of beam walk locomotor ability for sham control group and 400 g/cm contusion injury group. Saline (i. p.) or prazosin (4 mg/kg; i. p.) was administered 24 hours postinjury.

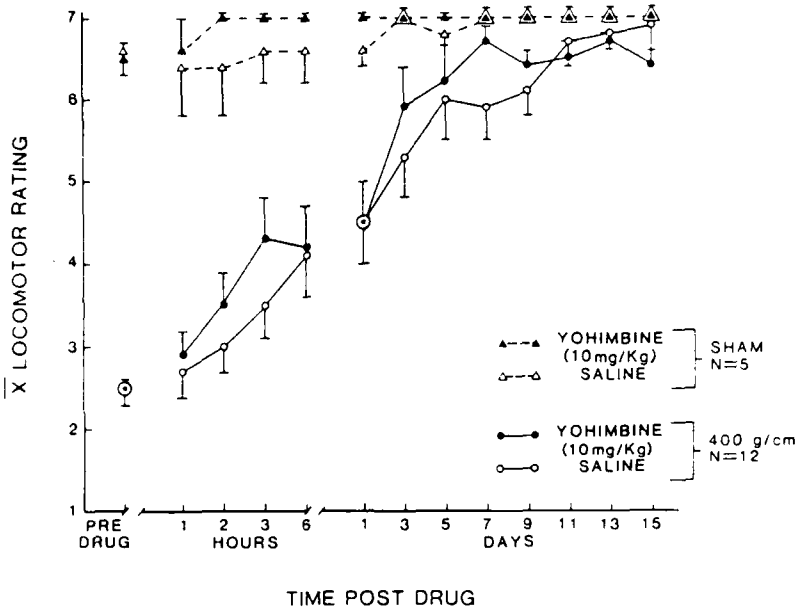

Figure 6. Mean ratings and SEM of beam walk locomotor ability for sham control group and 400 g/cm contusion injury group. Saline (i. p.) or yohimbine (10 mg/kg; i. p.) was administered 24 hours postinjury.

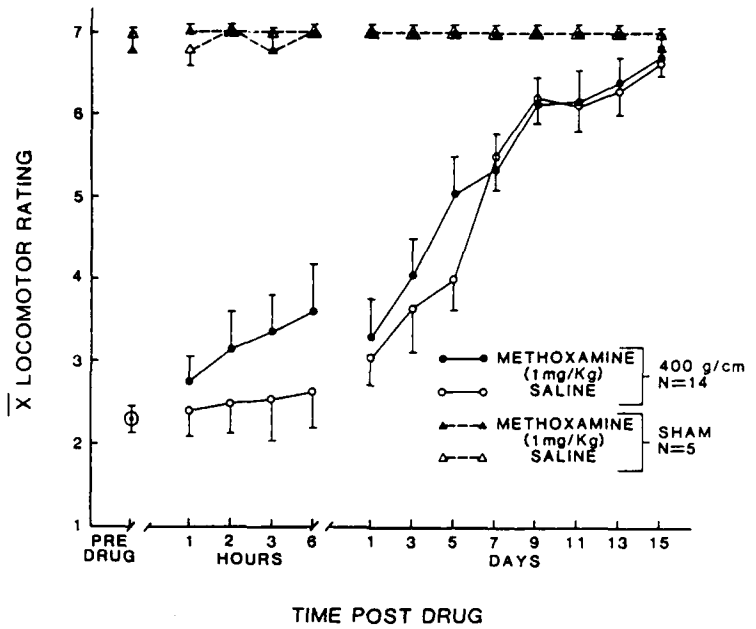

Figure 7. Mean ratings and SEM of beam walk locomotor ability for sham control group and 400 g/cm contusion injury group. Saline (i. p.) or methoxamine (1 mg/kg; i. p.) was administered at 24 hour postinjury.

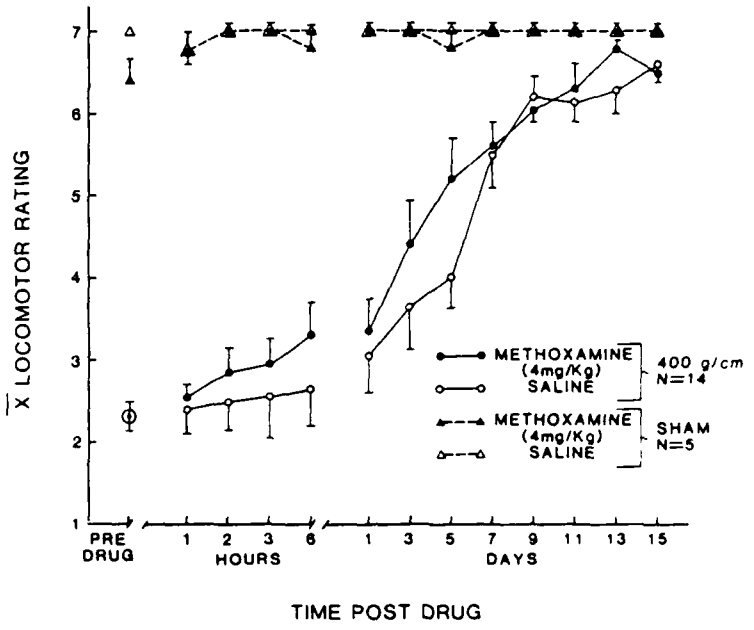

Figure 8. Mean ratings and SEM of beam walk locomotor ability for sham control group and 400 g/cm contusion injury group. Saline (i. p.) or methoxamine (4 mg/kg; i. p.) was administered 24 hours postinjury.

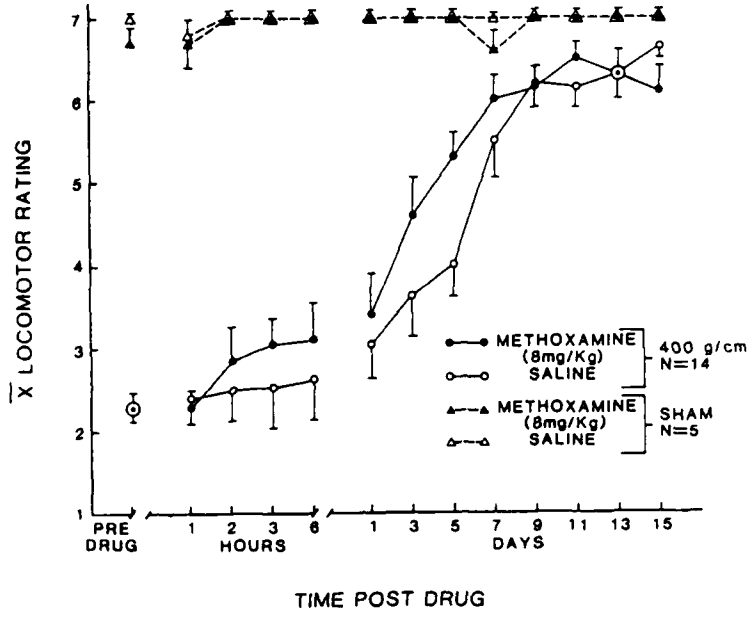

Figure 9. Mean ratings and SEM of beam walk locomotor ability for sham control group and 400 g/cm contusiion injury group. Saline (i. p.) or methoxamine (8 mg/kg; i. p.) was administered 24 hours post injury.

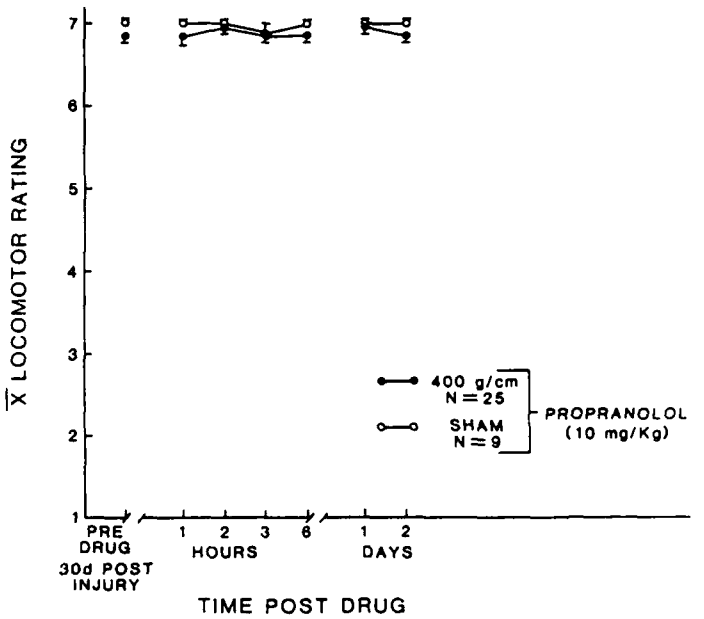

Figure 10. Mean ratings and SEM of beam walk locomotor ability 30 days post injury, for sham control and 400 g/cm contusiion groups. Both groups received a single injection of propranolol (10 mg/kg: i. p.).

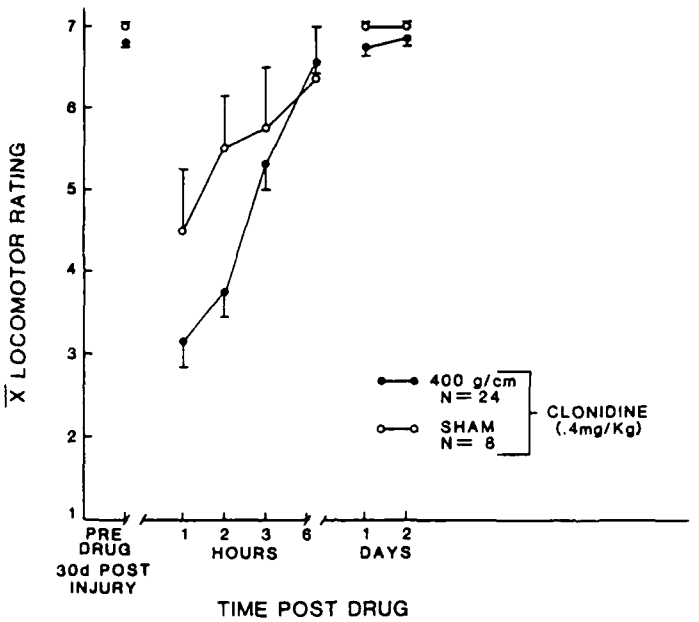

Figure 11. Mean ratings and SEM of beam walk locomotor ability 30 days postinjury, for sham control and 400 g/cm contusion groups. Both groups received a single injection of clonidine (4 mg/kg; i. p.).

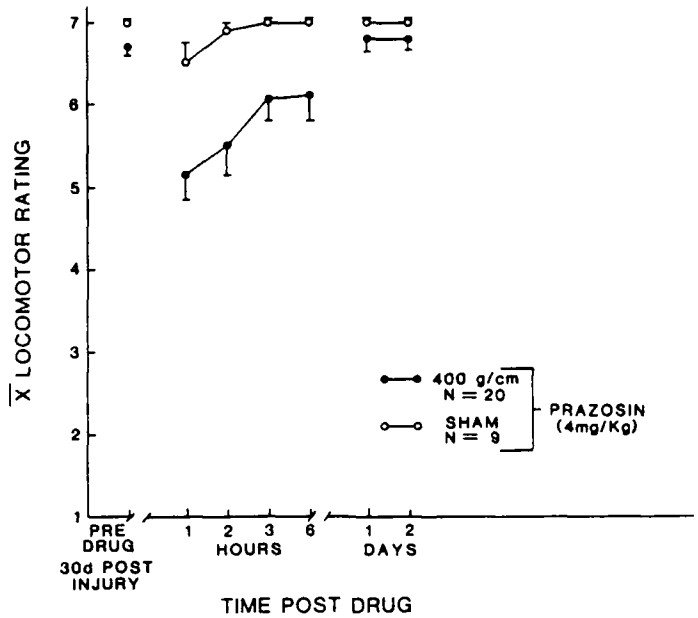

Figure 12. Mean ratings and SEM of beam-walk locomotor ability 30 day post injury, for sham control and 400 g/cm contusion groups. Both groups received a single injection of prazosin (4 mg/kg; i. p.).

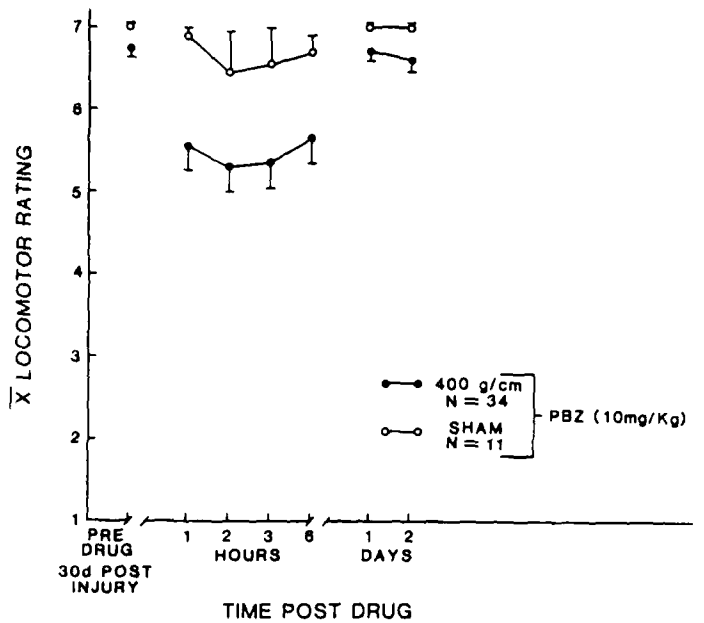

Figure 13. Mean ratings and SEM of beam walk locomotor ability 30 days post injury, for sham control and 400 g/cm contusion groups. Both groups received a single injection of phenoxybenzamine (10mg/kg; i. p.).

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