Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 3, pp. 773-779, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0060-U

Methylphenidate Treatment Following Ablation-Induced Hemiplegia in Rat: Experience During Drug Action Alters Effects on Recovery of Function

ANTHONY E. KLINE,*§ MICHAEL J. CHEN,† DOREEN Y. TSO-OLIVAS* AND DENNIS M. FEENEY*‡[1]

*Department of Psychology, University of New Mexico, Albuquerque, NM 87131-1161
†National Center for the Design of Molecular Function, Utah State University, Logan, UT 84322-4630
‡Department of Physiology, University of New Mexico, Albuquerque, NM 87131-1161
§Department of Psychology, Muenzinger Psychology Building, Campus Box 345, University of Colorado at Boulder, Boulder, CO 80309-0345

Received 12 July 1993

KLINE, A. E., M. J. CHEN, D. Y. TSO-OLIVAS, AND D. M. FEENEY. *Methylphenidate treatment following ablation-induced hemiplegia in rat: Experience during drug action alters effects on recovery of function.* PHARMACOL BIOCHEM BEHAV **48**(3) 773-779, 1994.—Two experiments examined the effects of single or multiple administrations of methylphenidate (MPH; Ritalin) and differing amounts of beam-walking trials (symptom relevant experience) during the period of drug action on recovery from hemiplegia following unilateral sensorimotor cortex ablation in rat. The first study tested multiple doses of MPH (10 mg/kg) or sterile saline given once daily, followed by four beam-walk (BW) trials at 1, 2, 3, and 6 h on 3 consecutive days. A significant and enduring enhancement of recovery was only observed 24 h after the third administration of MPH, compared to saline controls. In the second study, a single dose of MPH (10 mg/kg) or saline was administered 24 h after ablation, followed by 12 BW trials beginning 1 h and continuing at 15-min intervals until 3 h after MPH or saline administration. A significant and enduring facilitation of BW ability was produced by this single MPH treatment regimen. These data further support the importance of an interaction between symptom-relevant experience and drugs that increase norepinephrine transmission to enhance functional recovery after brain damage.

Methylphenidate Functional recovery Hemiplegia Symptom relevant experience (SRE) Brain injury Catecholamines Norepinephrine

PHARMACOLOGICAL and biochemical studies of functional recovery after cerebral cortex injury in several species, including human stroke patients, suggest an important role for norepinephrine (NE) released from projections of the nucleus locus coeruleus (LC) [for reviews, see (9,12,13,15)]. Most of these investigations examined effects of a single administration of drugs affecting NE release on recovery from hemiplegia in rat [for review see (14)]. Treatment was given 1 day after unilateral sensorimotor cortex (SMCX) ablation and recovery assessed using a beam-walk (BW) task. The initial studies using this paradigm reported that a single low dose of *d*-amphetamine (AMPH) produced an enduring (i.e., a significant difference on BW recovery for the AMPH group compared to the saline group 24 h after administration) improvement of BW performance following cortical injury. Importantly, BW trials [symptom relevant experience (SRE)] during the period of drug action is necessary for the AMPH facilitation of recovery from hemiplegia (10,16,17,20).

Recovery of BW (24) or restoration of binocular depth perception (11,25) by AMPH plus SRE is also produced in

[1] Requests for reprints should be addressed to Dr. Dennis M. Feeney, Department of Psychology, Logan Hall, University of New Mexico, Albuquerque, NM 87131.

cats even when treatment is delayed for 10 days after SMCX ablation or bilateral visual cortex ablation, respectively. The importance of the drug and SRE combination in facilitating functional recovery is most striking after visual cortex injuries because the loss of binocular depth perception is permanent, if untreated, and does not recover in either saline-treated cats provided SRE or those given AMPH and kept in darkness for 8 h after drug administration (11).

Using the same single-dose paradigm, drugs that increase NE release, such as the NE alpha$_2$ receptor antagonists yohimbine (1,43,47) and idazoxan (16) produce enduring BW recovery after SMCX ablation. Additionally, the AMPH analogs phentermine and phenylpropanolamine (12), which increase catecholamine (CA) transmission, also promote an enduring recovery of BW ability. However, in a previous dose-response study using methylphenidate (MPH; Ritalin; 3–15 mg/kg) an increase in BW performance was only seen for 1 to 3 h after administration followed by a return to saline control group performance levels at 24 h (29). This transient effect of MPH on BW recovery is unusual in that it has not been seen with any of the numerous drugs affecting CA action in this paradigm (14).

Methylphenidate is a well-characterized mild central nervous system (CNS) psychostimulant that has been successfully utilized in the treatment of attention deficit disorder in children (37) and adults (54) and in the alleviation of cognitive (8,22,30) and motor (53) functions in brain injured patients. Additionally, MPH has been reported to have pharmacological properties similar to AMPH, but without the undesirable sympathomimetic effects (27,41) and evokes similar behavioral responses (26). The reasons for the lack of an enduring enhancement of functional recovery by MPH in our previous study (29) is unclear. Several investigations have shown that MPH, like AMPH, increases brain CA levels, but by different mechanisms (32,33,39). For the stimulant class exemplified by MPH, the increased dopamine (DA) is blocked by reserpine pretreatment and is unaffected by pretreatment with alpha-methyl-p-tyrosine, which inhibits CA synthesis. The other class, exemplified by AMPH, is unaffected by reserpine, but is blocked by pretreatment with alpha-methyl-p-tyrosine. Although originally based on studies of the DAergic system (39), recent in vitro work suggests a similar distinction of mechanisms for the effects of MPH and AMPH on NE (35,36,46). Methylphenidate also differs from AMPH in its elimination half life, which is thought to be approximately 2 h (31) compared to approximately 5–7 h for AMPH (34).

Given the demonstrated importance of SRE during the period of drug action for enhancement of functional recovery [for review see (9)], it was hypothesized that the shorter half life, or duration of action, of MPH may have been the limiting factor for its previous failure to produce an enduring influence on recovery of BW. To test this hypothesis, we reexamined its effects on BW recovery in the rat ablation model of hemiplegia in two separate experiments. In the first experiment, we altered the treatment regimen from a single administration of MPH to one injection each day for 3 consecutive days. The second experiment examined the effects of a single administration of MPH coupled with an increased number of BW trials (SRE) during the period of drug action.

GENERAL METHOD AND PROCEDURES

Subjects

Forty-nine male Sprague-Dawley albino rats (Harlan-Gibco, Indianapolis, IN), weighing 300–350 g on the day of surgery, were used in these experiments. Animals were housed individually in standard steel, wire-mesh cages, allowed access to food and water ad lib, and maintained on a 12L : 12D cycle (lights on at 0700 h).

Presurgical Training

Presurgical training procedures have been described in detail elsewhere (15,48) and, therefore, will only be briefly discussed. The rats were trained to traverse a 122 cm long, 2.5 cm wide, elevated (36 cm) wooden beam and to enter a dark goal box, resembling their home cage, to escape aversive stimuli, which consisted of a 60 watt light and 62 dB white noise. Animals were trained by successive approximations on the first day, followed by a single BW trial daily until able to traverse the beam with a score of 7 (see Table 1) on 3 consecutive days. The BW training was almost always accomplished in 4 days. Beam-walk ability was independently rated by two observers, one uninformed regarding treatment conditions. There was a 99.4% agreement in BW ratings between the informed experimenter and the uninformed experimenter. Once training was complete, animals were prepared for surgery.

Surgery

Each rat was administered 60 mg/kg ketamine HCl (Ketalar) combined with 0.08 ml atropine (IM) followed 5 min later by 21 mg/kg sodium pentobarbital (Nembutal; IP) for general anesthesia. When a surgical level of anesthesia was achieved, the rat was placed in a stereotaxic apparatus (David Kopf Instruments), a craniotomy performed over the right hemisphere, (2 mm anterior to 4 mm posterior from bregma and 2 mm lateral of the saggital ridge), and the underlying cortex removed by aspiration until the white matter was visualized. The wound was lightly packed with gelfoam and the scalp closed with wound clips. Sham-operated control rats underwent a similar surgical procedure, but the skull was only lightly drilled and not penetrated, as the craniotomy itself may produce symptoms of brain injury (23,40). All surgery was performed using aseptic conditions.

Postsurgical Testing

Twenty-four hours following surgery all animals received a baseline trial to assess postsurgical BW deficits. Immediately

TABLE 1

BW RATING SCALE FOR RATS

7. Rat traverses the beam with no more than two footslips.
6. Rat traverses the beam using the affected hindlimb to aid more than 50% of its steps on the beam.
5. Rat traverses the beam using the affected hindlimb to aid less than 50% of its steps on the beam.
4. Rat traverses the beam, placing the affected hind foot on the horizontal surface of the beam without using the affected hindlimb to aid in forward locomotion.
3. Rat traverses the beam while dragging the affected hindlimb or showing treading/stepping motions with the affected hindlimb, but does not place the affected hind foot on the horizontal surface of the beam during traversal.
2. Rat fails to traverse the beam, but places the affected hind foot on the horizontal surface of the beam.
1. Rat fails to traverse the beam and does not place the affected hind foot on the horizontal surface of the beam.

thereafter the rats were administered comparable volumes of either MPH (10 mg/kg) or 0.9% physiological saline (IP). Postdrug BW testing began 1 h later, with different BW test schedules for Experiments 1 and 2 (see procedures of Experiments 1 and 2 for BW regimens). Animals making no attempt to traverse the beam within a few seconds were encouraged by prodding, which consisted of a gentle tap on the tail or rump with a wooden pencil (15). If the animal still did not locomote across the beam after 90 s had elapsed, the trial was terminated and the rat returned to its home cage and the appropriate score assigned [(10) and Table 1].

Histology

Following completion of behavioral testing (16 or 18 days postsurgery) animals were killed with an overdose of sodium pentobarbital, intracardially perfused with 0.9% physiological saline followed by 10% formalin, and the brains extracted and postfixed in the perfusate for 1 week before being transferred to a 10% formalin/20% sucrose solution. After sinking in the formalin/sucrose solution, the brains with SMCX ablation were blocked and frozen at −21 °C, sectioned through the injury at 40 μm on a Harris microtome, and every fifth section thaw-mounted onto gelatinized glass slides then stained with thionin. Extent of cortical injury was determined by tracing these coronal sections with tissue damage on a computer-assisted image enhancer (Olympus microscope, model BH-2; interfaced with an image analysis system, Southern Microinstruments; software, MicroComp Integrated Image Analysis System). Area (mm^2) of the lesion in each section was calculated by measuring the cortical area contralateral to the SMCX ablation and subtracting the cortical tissue remaining in the ipsilateral ablated area. The sum of the lesioned areas was divided by the total number of sections to obtain an average area of lesion. To estimate volume (mm^3) of lesion, this average area was multiplied by the distance (in mm) of the anterior-posterior extent of the lesion.

Only two lesion parameters have been related to recovery of BW function after SMCX ablation, extent of medial cortex damage, and lesion depth (19). Therefore, these were specifically calculated for sections containing the striatum and for those containing the hippocampal formation, by measuring sections selected at seven planes, relative to bregma, in the atlas of Paxinos and Watson (44), (1 = +2.2 mm; 2 = +1.2 mm; 3 = −0.26 mm, 4 = −2.12 mm; 5 = −4.16 mm; 6 = −5.6 mm; 7 = −6.04 mm) and in accordance with the method of Goldstein and Davis (19).

EXPERIMENT 1—REPEATED ADMINISTRATIONS OF METHYLPHENIDATE

This experiment tested the hypothesis that increasing the number of administrations of MPH from one to three and using our standard BW test protocol (BW trials at 1, 2, 3, and 6 h postadministration) would produce an enduring enhancement of locomotor recovery following ablation of the right SMCX.

Procedures

Seventeen rats received the BW training and surgical procedures described above. Ablation or sham surgery animals were randomly assigned to drug (ablated = 8; sham = 2) or saline (ablated = 5; sham = 2) groups. Beginning 24 h postsurgery, following a pretreatment baseline BW test, MPH (10 mg/kg) or a comparable volume of sterile saline was administered IP followed by BW trials at 1, 2, 3, and 6 h after administration. This procedure was repeated for 3 consecutive days followed by a single BW trial every other day for 18 days postsurgery. This dosage of MPH was selected because lower doses (3–8 mg/kg) and higher doses (12–15 mg/kg) in the prior dose-response study did not transiently facilitate recovery as well as 9 and 10 mg/kg (29).

Results

Three important results from this experiment are illustrated in Fig. 1: first, there was no effect of the sham surgeries on BW ability for rats given MPH or saline. Second, as in our previous report (29), after SMCX ablation, the first and second administrations of MPH (10 mg/kg) produced a significant, but transient improvement of BW. Finally, an enduring enhancement of BW recovery was produced after three doses of MPH. This is indicated by the significant difference between the MPH and saline-control group BW scores 24 h after the last MPH or saline administration.

These conclusions regarding the effects of a single administration of MPH on BW during the first 6 h posttreatment were statistically analyzed using orthogonal polynomials to assess the significance of the apparent linear trend over the course of three treatments and the apparent quadratic (curvilinear) appearance of the BW data after each MPH treatment [see (28), p. 22 for details on calculation]. During the 6-h test period following the first MPH treatment there was a significant quadratic trend as exemplified by an increase in BW performance followed by a significant decrease, $F(1, 7) = 5.59$, $p < 0.05$. Following the second and third administrations of MPH, there was again a similar, significant quadratic trend, $F(1, 7) = 12.62$. $p < 0.01$, and $F(1, 7) = 13.13$, $p < 0.01$, respectively. These results confirm the previous report that MPH produces a transient facilitation of BW recov-

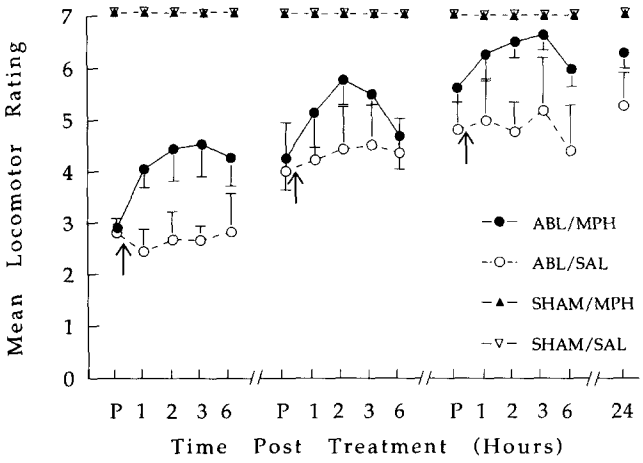

FIG. 1. Mean (±SEM) BW scores prior to and after three administrations (indicated by arrows) of methylphenidate (MPH; 10 mg/kg; IP) or saline (SAL) on 3 consecutive days beginning 1 day after SMCX ablation or sham surgery. The Ps correspond to pretreatment scores at 24, 48, and 72 h postsurgery. The hour time marks indicate the times of single BW trials. Sham surgery (SHAM/SAL) or MPH given to sham operates (SHAM/MPH) did not affect BW performance. Note the transient facilitation of BW performance after the first and second MPH administrations. An enduring facilitation, i.e., significantly higher BW scores for ABL/MPH compared to ABL/SAL groups 24 h after injection, was only observed after the third treatment (last arrow).

ery during the drug action period (29). There were no significant trends for the saline-control rats within this time period.

Analysis of the BW scores at 24 h after the third administration of MPH, using a one-way analysis of variance (ANOVA) and comparing the ablated-MPH group to the ablated-saline group showed a statistically significant group difference, $F(1, 12) = 4.74$, $p < 0.05$. This indicates that three MPH administrations with our standard BW test regimen produced an enduring enhancement of recovery from hemiplegia.

Histological analysis revealed no significant differences on extent of medial cortical necrosis, nor lesion depth between the saline and MPH treatment groups, as indicated by a oneway ANOVA (all $p > 0.05$, two-tailed). There was also no difference in mean volume of the lesion between the two groups (38.7 mm^3 for saline group vs. 37.4 mm^3 for the MPH group), $t(10) = 0.30$, $p = 0.774$. This ablation volume is remarkably similar to the volume of cortical necrosis in the trauma model used to screen drugs affecting BW recovery (14).

Discussion

The data indicates that following unilateral SMCX ablation three administrations of MPH (when providing four BW test trials over a 6-h period after each administration) were required to produce an enduring facilitation of recovery, i.e., significantly better BW performance than saline controls when tested 24 h after injection. The first and second administrations of MPH produced a transient enhancement of BW performance and replicated our previously reported finding in a dose response study (29). At 24 h after the second treatment the BW scores of the MPH group were better than the saline controls (see Fig. 1), but this was not statistically different. The significantly better effect of three compared to a single MPH administration in the hemiplegic rat is similar to that reported for AMPH in the hemiplegic cat. Repeated AMPH administration facilitates recovery significantly better than a single treatment after unilateral (24) or bilateral (49) frontal cortex ablation in the cat.

There are important differences between the effects of MPH and AMPH on functional recovery from hemiplegia. The MPH dose response study suggested that regardless of the dosage, a single administration of MPH only produces a transient facilitatory effect on BW recovery after unilateral SMCX ablation (29), whereas a single dosage of AMPH produces an enduring enhancement of BW performance (10,24). However, the BW test regimen for MPH was the same as for AMPH, but MPH has a much shorter half life than AMPH. This may require earlier and/or more SRE after a single dose of MPH to produce an enduring effect on functional recovery. The enduring effect observed after the third MPH dose may be a cumulative result of the SRE given during the period of drug action. The hypothesis that increasing SRE early after a single injection of MPH will cause an enduring enhancement of BW recovery after SMCX ablation was tested in Experiment 2.

EXPERIMENT 2—INCREASED BW EXPERIENCE AFTER A SINGLE ADMINISTRATION OF METHYLPHENIDATE PRODUCES ENDURING LOCOMOTOR RECOVERY

This experiment tested the hypothesis that the amount of SRE determines whether a single dose of MPH has a significant effect on recovery of function after SMCX injury. The design of Experiment 2 is based on two observations from Experiment 1. First, after unilateral SMCX ablation a transient facilitation of BW ability occurred primarily during the first 3 h following the first MPH injection (10 mg/kg), indicating an optimal period of drug action on this behavior. Second, an enduring facilitation of BW followed the third MPH administration, or a total of 12 BW trials distributed over the 6 h after each of the three MPH administrations. Therefore, in this experiment a single dose of MPH (10 mg/kg) or saline was followed by 12 BW trials beginning 1 h and continuing to 3 h after administration.

Procedures

Thirty-two rats received the BW training and surgery described in Experiment 1. In this experiment, a single dose of MPH or sterile saline was administered to two groups of SMCX ablated rats ($n = 10$ for each group) and two sham operate groups ($n = 6$ for each group). All animals received a BW trial every 15 min beginning 1 h postadministration until a total of 12 BW trials were provided. A single trial was also provided at 6 and 24 h posttreatment as well as every other day for 16 days following surgery.

Results

The data from Experiment 2 are summarized in Fig. 2, which illustrates that enduring recovery of BW follows a single administration of MPH when SRE is increased from 3 to 12 BW trials during the first 3 h after drug administration. Recall that in Experiment 1 and in our prior dose–response study (29) that only a transient effect of BW recovery was observed with the same dose of MPH and three BW trials during the first 3 h after drug administration. There was no effect of sham surgery or MPH on BW performance in the sham operates as indicated by the virtually perfect BW scores at all test points. A repeated measures ANOVA indicated that the BW data from the group given MPH were significantly better than

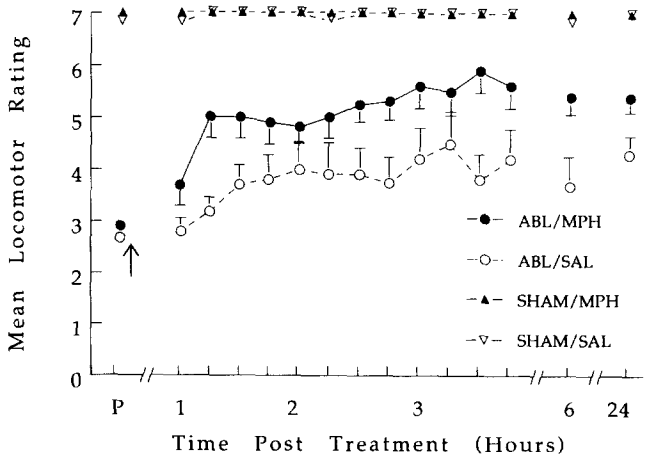

FIG. 2. Mean (±SEM) BW scores prior to and following a single MPH administration (10 mg/kg; IP) or SAL but with an increased number of BW trials after treatment compared to the protocol depicted in Fig. 1. Note the enduring and statistically significant facilitation of BW recovery after a single dose produced by increasing the number of BW trials given during the maximal period of drug action (1–3 h following MPH administration). Beginning 1 h after treatment, a single BW trial was conducted every 15 min for 3 h and also at 6 and 24 h. In contrast to the data depicted in Fig. 1 and in a previous dose–response study (29), this increased SRE during the period of maximal drug action produced a significant facilitation of recovery from hemiplegia that endured 24 h after a single administration of MPH.

those administered saline at several time points during the MPH action period as well as at 6 h and 24 h after administration, $F(1, 19) = 6.52$, $p < 0.05$. Specifically, MPH-treated rats performed significantly better than saline-treated rats at BW trials 2, 3, 7, 8, 11, and 12, and 6 and 24 h (all $p < 0.05$, two-tailed).

As in Experiment 1, the two lesion parameters important for spontaneous recovery, medial cortex damage, and lesion depth (19), were not significantly different for saline nor MPH groups (all $p > 0.05$, two-tailed). However, the mean volume of the lesion was significantly different between the two groups (51.4 mm^3 for MPH group vs. 36.8 mm^3 for the saline group) $t(18) = 2.34, p = .031$.

The mean lesion extent for all animals from Experiment 1 and Experiment 2 combined for MPH (45.6 mm^2) and saline (37.5 mm^2) treatments was not statistically different, $t(30) = 1.80, p > 0.05$. There was no significant relationship between the extent of cortical ablation and the pretreatment (24 h post ablation) BW score ($r = -0.25$). Additionally, there was no correlation ($r = -0.10$) between the extent of the cortical ablation and the response to MPH (BW score 24 h after MPH minus pretreatment BW score). A similar lack of a simple relationship between SMCX lesion volume and BW recovery rate in response to AMPH treatment has been reported by Goldstein and Davis (19).

Discussion

In animals with unilateral SMCX ablation, increasing the number and timing of BW trials following a single administration of MPH changed a transient improvement of BW performance observed in Experiment 1 to an enduring recovery. The increased SRE alone had no detectable effect on BW recovery as noted by the lack of any improvement of performance in the saline group. The BW scores of the MPH-treated group were significantly better than those of the saline-treated group at 24 h following treatment. The faster recovery in the MPH group occurred despite significantly larger lesions in these animals compared to saline controls. While lesion size was not related to functional recovery in this study, recent work by Nishino et al. found that lesion size was an important factor in BW recovery. Specifically, it was reported that the effectiveness of yohimbine in facilitating BW recovery was decreased if the lesion was larger than 35 mm^2 (43). This indicates the importance of histological confirmation of lesion extent in studies of functional recovery.

GENERAL DISCUSSION

These two experiments indicate that methylphenidate can produce an enduring facilitation of recovery from hemiplegia after unilateral SMCX ablation in the rat. Furthermore, the results clearly show that the amount of SRE provided during the first 3 h after drug administration determines whether or not MPH enhances BW recovery. The timing and number of BW trials used in Experiment 1 were adapted from the paradigm successfully used to measure beneficial effects of a single administration of AMPH on recovery of function. Drugs that have produced a significant and enduring enhancement on recovery using that single administration paradigm include AMPH (48) which, among its actions, releases and blocks NE reuptake, yohimbine (1,43,47), and idazoxan (16), $alpha_2$ noradrenergic receptor antagonists, and desipramine (4), which blocks NE reuptake. Importantly, desipramine lacks psychostimulant effects, indicating that this action of drugs increasing functional recovery is not critical. However, the amount of SRE allowed with the standard paradigm was inadequate to produce enhanced recovery after a single administration of MPH. Only by increasing the number of BW trials during the drug action period did MPH produce an enduring enhancement of recovery with a single administration. The initial lack of an enduring effect by MPH was puzzling, and we reported that the data from a dose-response study indicated MPH had no effect (29) in this model considered useful for predicting effects on functional recovery in man after cortical stroke or trauma (19). It is unclear why an increase of SRE is necessary for a single dose of MPH to produce an enduring enhancement of BW recovery. Perhaps, as with some other compounds (48,52), the short half life of MPH prevented sufficient SRE during its period of action to alter the rate of BW recovery. The data from the two experiments reported here underscore the importance of caution in interpreting negative data.

The results further indicate that after cortical injury, the presence and amount of SRE provided during drug-evoked NE synaptic release determines the endurance of effects on functional recovery. This general topic has received little attention until the use-dependent changes in neuronal responsiveness and its modulation by NE were described (21). The most persuasive evidence implicating NE in mediating this functional recovery is that intraventricular infusion of NE, but not DA, (2,3) nor serotonin (unpublished observations) enhances BW recovery after SMCX injury. Furthermore, only NE infusion into the contralateral (to the injury) cerebellar hemisphere, but not ipsilateral to SMCX injury, produces AMPH-like enhanced functional recovery after SMCX ablation (5,6). This suggests that the site of the interaction between NE and SRE for recovery from hemiplegia is within the cerebellum. This is hypothesized to involve an alleviation of functional depression (9) with a central role for $alpha_1$-adrenoceptors (15). Pertinent to the current experiments is the report (38) that 2 h after a single low dose of MPH there is an increased affinity and downregulation of $alpha_1$-adrenoceptors in rat brain. Data from receptor binding studies in brain-injured animals support the hypothesized central role for $alpha_1$ NA in recovery of function (14,15). There is a decrease in $alpha_1$-NAergic receptor binding after cerebral ischemia (42) and also a decrease in $alpha_1$-NAergic receptors following cortical traumatic brain injury (45). Such changes could be involved in the MPH altered response to SRE which enhances locomotor recovery.

The importance of demonstrating an effect of MPH on recovery of function in this model has both clinical and scientific significance. Methylphenidate is currently used for attention deficit disorder (37,54) and reportedly improves cognitive (8,22,30) and motor (53) functions in brain-injured patients. Preliminary double-blind placebo controlled studies report that AMPH combined with physical therapy significantly improved functional recovery in small samples of hemiparetic (7,50) and aphasic (51) stroke patients. Perhaps MPH, which has weaker cardiovascular effects than AMPH (41), may also be useful in promoting recovery from stroke or traumatic brain injury in human beings.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation to T. Flores and T. Rolland for excellent technical work. For assistance with statistical analyses, we thank Dr. V. Westerberg and P. Barela. Our gratitude also to Ciba-Geigy for their generous donation of methylphenidate HCL (Ritalin).

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