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Short-Term and Medium-Term Effects of Spinal Cord Tract Transections on Soleus H-Reflex in Freely Moving Rats

XIANG YANG CHEN, KUO CHING FENG-CHEN, LU CHEN, DAYNA M. STARK, and JONATHAN R. WOLPAW

ABSTRACT

Spinal cord function is normally influenced by descending activity from supraspinal structures. When injury removes or distorts this influence, function changes and spasticity and other disabling problems eventually appear. Understanding how descending activity affects spinal cord function could lead to new means for inducing, guiding, and assessing recovery after injury. In this study, we investigated the short-term and medium-term effects of spinal cord bilateral dorsal column (DC), unilateral (ipsilateral) lateral column (LC), bilateral dorsal column ascending tract (DA), or bilateral dorsal column corticospinal tract (CST) transection at vertebral level T8-T9 on the soleus H-reflex in freely moving rats. Data were collected continuously for 10–20 days before and for 20–155 days after bilateral DC (13 rats), DA (10 rats), CST (eight rats), or ipsilateral LC (seven rats) transection. Histological examination showed that transections were 98(±3 SD)% complete for DC rats, 80(±20)% complete for LC rats, 91(±13 SD)% complete for DA rats, and 95(±13)% complete for CST rats. LC, CST, and DA transections produced an immediate (i.e., first-day) increase in H-reflex amplitude. LC transection also produced a small decrease in background activity in the first few posttransection days. Other than this small decrease, none of the transections produced evidence for the phenomenon of spinal shock. For all transections, all measures returned to or neared pretransection values within 2 weeks. DA and LC transections were associated with modest increase in H-reflex amplitude 1–3 months after transection. These medium-term effects must be taken into account when assessing transection effects on operant conditioning of the H-reflex. At the same time, the results are consistent with other evidence that, while H-reflex rate dependence and H-reflex operant conditioning are sensitive measures of spinal cord injury, the H-reflex itself is not.

Key words: corticospinal tract; dorsal column; dorsal column ascending tract; lateral column; soleus activity; spinal cord injury; rat

INTRODUCTION

SPINAL CORD REFLEX PATHWAYS normally operate under the control of descending pathways from supraspinal structures. When spinal cord injury disrupts or abolishes this control, reflex pathways undergo a series of acute and chronic changes that contribute to the development of spasticity and other functional abnormalities (Fujimori et al., 1966; Ashby and Verrier, 1975; Davis, 1975; Henneman, 1980; Little and Halar, 1985; Dimitrijevic et al., 1988; Boorman et al., 1992; Shefner et al., 1992; Calancie et al., 1993; Doyle et al., 1993; St.

Wadsworth Center, New York State Department of Health and State University of New York, Albany, New York.

George, 1993; Stein et al., 1993; Hechman, 1994; Young, 1994; Nozaki et al., 1996; Thomas and Ross, 1997; Faist et al., 1999). Improved understanding of how descending pathways control spinal reflex function and of the mechanisms underlying the changes that occur after spinal cord injury impairs this descending control could lead to new methods for inducing, guiding, and assessing recovery after injury.

Operant conditioning of the H-reflex, the electrical analog of the spinal stretch reflex, is an experimental model for defining mechanisms underlying acute and chronic descending control of spinal cord reflex function (Wolpaw, 1987; Chen and Wolpaw, 1995, 1996, 1997; Chen et al., 1996, 1999b; Wolpaw, 1997). The H-reflex is mediated largely by the two-neuron monosynaptic arc consisting of the Ia primary afferent fiber from the muscle spindle, the motoneuron, and the synapse between them (Matthews, 1972; Brown, 1984). When exposed to a task in which reward depends on H-reflex amplitude, both monkeys and rats can modify activity in descending control pathways so that H-reflex amplitude changes appropriately. Like the reflex changes that develop after spinal cord injury, operantly conditioned H-reflex change develops over days and weeks. Recent physiological and anatomical studies indicate that it is associated with plasticity at several sites in the spinal cord (Wolpaw and Lee, 1989; Carp and Wolpaw, 1994, 1995; Feng-Chen and Wolpaw, 1996; Wolpaw, 1997).

We are trying to determine which descending pathways are responsible for H-reflex conditioning by transecting specific pathways and observing the effects of these transections on conditioning (e.g., Chen and Wolpaw, 1997). In rats, the dorsal column contains the main corticospinal tract as well as an ascending tract carrying input from proprioceptors and skin receptors (Chung et al., 1987; Smith and Bennett, 1987; Cliffer and Giesler, 1989; Patterson et al., 1989, 1990; Tracey, 1995); and the lateral column contains the rubrospinal, vestibulospinal, and reticulospinal tracts and a variety of ascending tracts (Zemlan et al., 1978, 1979; Holstege and Kuypers, 1987; Tracey, 1995).

As an essential prerequisite for assessing the effects of specific pathway transections on H-reflex conditioning, we assessed the effects of these transections on the naive (i.e., unconditioned) H-reflex in the absence of exposure to the H-reflex conditioning protocol. The present study analyzes the short-term (within 20 days posttransection) and medium-term (1–5 months posttransection) effects of dorsal column (DC), lateral column (LC), dorsal column corticospinal tract (CST), or dorsal column ascending tract (DA) transection on the soleus H-reflex in freely moving rats. The use of "medium-term" is intended to recognize that the effects of spinal cord injury may continue to develop over many months and years. A small part of the data have been briefly summarized elsewhere (Chen and Wolpaw, 1997; Chen et al., 1999a).

METHODS

Subjects were 38 female Sprague-Dawley rats weighing 200–300 g at the beginning of study. All procedures satisfied the "Guide for the Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (National Academy Press, Washington, DC, 1996) and had been reviewed and approved by the Institutional Animal Care and Use Committee of the Wadsworth Center. The H-reflex recording methodology, described in detail elsewhere (Chen and Wolpaw, 1994, 1995, 1996, 1997; Chen et al., 1996, 1999b, Wolpaw and Herchenroder, 1990), is summarized here. The pathway transection methods are described fully.

Measurement of H-Reflex, M Response, and Background Electromyogram

Each rat was implanted under general anesthesia (ketamine HCl, 80 mg/kg; xylazine, 10 mg/kg; both intraperitoneal [i.p.]) with chronic stimulating and recording electrodes in the right leg. To elicit the H-reflex, a silicone rubber nerve cuff containing a pair of stainless steel multi-stranded fine-wire electrodes was placed on the posterior tibial nerve just above the triceps surae branches. To record soleus electromyogram (EMG) activity, a pair of fine-wire electrodes, with the final 0.5 cm bare, were placed in the right soleus muscle. The Teflon-coated wires from the nerve cuff and the muscle traveled subcutaneously to a connector plug mounted on the skull with stainless steel screws and dental cement. Seven to 10 days after implantation surgery, each rat was tested with nerve-cuff stimulation to ensure that an H-reflex was present at M response (i.e., direct muscle response) threshold.

Data collection began at least 20 days after electrode implantation. Throughout data collection, the animal lived in a standard rat cage with a 40-cm flexible cable attached to the skull plug. The cable, which allowed the animal to move freely about the cage, carried the wires from the electrodes to an electronic swivel above the cage, from whence they passed to an EMG amplifier and a nerve-cuff stimulation unit. All animals had free access to food and water. Animal well-being was carefully checked several times each day, and body weight was measured weekly. Laboratory lights were dimmed from 2100 to 0600 each day.

Soleus EMG was monitored continuously by com-

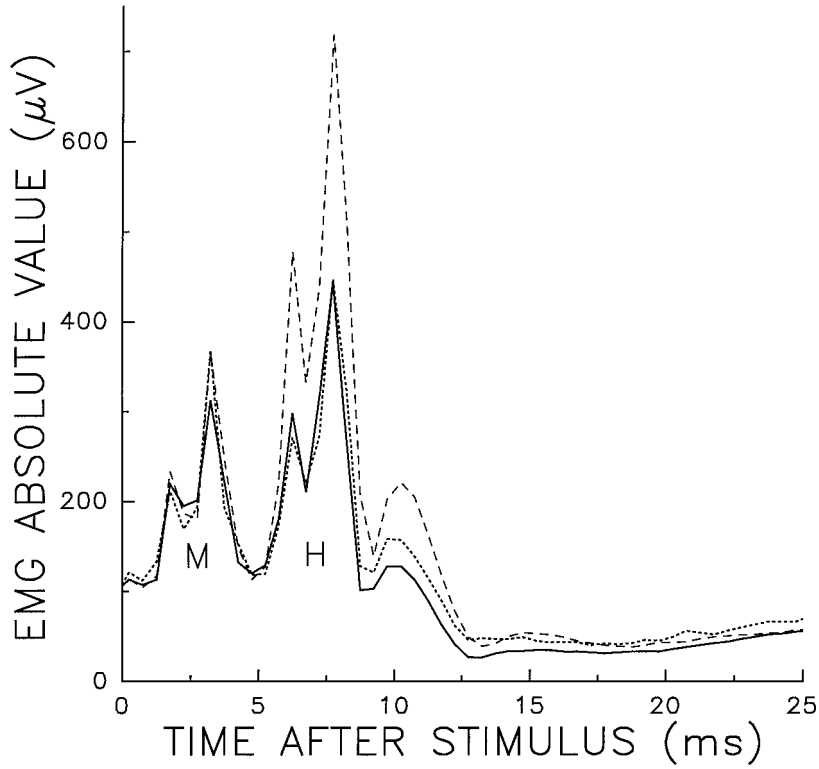

FIG. 1. Daily average absolute value of EMG activity for 25 ms after stimulation from an LC rat for a day before LC transection (solid line) and for day 1 (dashed line) and day 18 (dotted line) after transection. The transient rise in H-reflex amplitude after LC transection is apparent. H, H-reflex; M, M response. Background EMG is indicated by the level at zero time.

puter. If the absolute value of background (i.e., ongoing) EMG (i.e., equivalent to the full-wave rectified value) remained within a defined range for a randomly varying 2.3–2.7-s period, a stimulus pulse (typically 0.5 ms in duration) just above M response threshold was delivered by the nerve cuff. Pulse amplitude was automatically adjusted after each trial so as to maintain a constant M response amplitude throughout data collection. The computer digitized soleus EMG and stored its absolute value for 50 ms following the stimulus. In the course of its daily activity, the animal normally satisfied the background EMG requirement (which was about 10% of maximum voluntary EMG), and therefore received nerve cuff stimulation, 2,500–8,800 times per day. H-reflex amplitude was measured as average absolute EMG amplitude in the H-reflex interval (typically 5.5–9.0 ms after stimulation) minus background EMG amplitude, and M response amplitude was measured as average absolute EMG amplitude in the M response interval (typically 1.5–4.0 ms after stimulation) minus background EMG amplitude. Background EMG was measured as average absolute EMG amplitude in the background interval, which was the 50 ms immediately prior to stimulation. Figure 1 shows average daily poststimulus EMG responses to the nerve cuff stimulation from a representative animal. Data were collected from each rat for 10–22 days to determine the animal's initial (i.e., pretransection) H-reflex amplitude. Then the dorsal column (DC), the right lateral column (LC), the dorsal column corticospinal tract (CST), or the dorsal column ascending tract (DA) was transected as described below. Data collection started as soon as the animal recovered from the anesthesia and continued for at least 20 days. For some animals it continued longer (i.e., up to 155 days after the transection) to evaluate the medium-term effects of the transection. An extensive body of normative data indicates that, in the absence of spinal cord lesions or other interventions, background EMG, M response, H-reflex, and stimulus amplitude remain stable over such prolonged periods.

Spinal Cord Transections

After collection of pretransection control data, each rat was subjected to a bilateral DC transection (13 DC rats), a right LC transection (seven LC rats), a bilateral CST transection (eight CST rats), or a bilateral DA transection (10 DA rats) of the thoracic spinal cord. The rat was anesthetized with an i.p. injection of ketamine HCl (80 mg/kg) and xylazine (10 mg/kg). A one-vertebrate dor-

sal laminectomy was performed at T8-T9 with minimal disturbance of the dural envelop, and the rat was immobilized with ear bars and rubber-band retraction.

The cord was visualized under a dissection microscope. All transections were produced by electrocautery (small vessel cauterizer; Fine Science Tools, Foster City, CA). The cauterizer was mounted in a micromanipulator (DC, CST, and DA rats) or hand-held (LC rats), and was activated in brief pulses to minimize thermal damage to adjacent tissue. For DC rats, transection extended 0.4 mm to either side of the midline and 1.1 mm into the spinal cord from the dorsal surface. For CST rats, the tip of the cautery was positioned 1.0 mm left of the midpoint of the dorsal surface of the spinal cord, pointed medially at an angle of 45° from vertical, and advanced 1.7 mm. This was calculated to produce a transection track that was 1.5 mm long and about 0.5 mm wide in the transverse plane and involved the dorsal horn of the left side and the dorsal column CST of both sides. As previously noted, this is the main CST in the rat (Chung et al., 1987; Smith and Bennett, 1987; Cliffer and Giesler, 1989; Patterson et al., 1989, 1990; Tracey, 1995). For DA rats, transection extended 0.4 mm to either side of the midline and 0.7 mm into the spinal cord from the dorsal surface. For LC rats, the lateral half of the right side of the spinal cord was transected. The site was then rinsed with normal saline and covered with Durafilm to minimize connective tissue adhesions to the dura, and the muscle and skin were sutured in layers. DC, CST, and DA transections were bilateral because a transection that was both complete and exclusively ipsilateral was not technically feasible. LC transection was ipsilateral because we wished to avoid the considerable disability likely to be associated with a bilateral LC transection (which would have destroyed about two-thirds of the white matter). At the thoracic level, the major descending tracts (i.e., rubrospinal, vestibulospinal, and reticulospinal tracts in the LC and the main CST in the DC) and the DA ascending tract are mainly or exclusively ipsilateral to the leg they innervate (Tracey, 1995). Thus, for the present purpose, that is, evaluation of effects on the H-reflex, ipsilateral and bilateral transections are probably comparable.

Immediately after transection, the rat was placed under a heat lamp and given an analgesic (Demerol, 0.2 mg, i.m.). Once awake, it received a second dose of analgesic, and was returned to its cage to continue data collection. Until spontaneous voiding returned, the bladder was expressed at least twice per day, and antibiotics (Gentocin, gentamicin sulfate, 0.25 mg, b.i.d., i.m., Flo-Cillin, sterile penicillin G benzathine and penicillin G procaine, 15,000 units, q.o.d., i.m.) and lactated Ringer's solution (5 mL, b.i.d., s.c.) were given. The time of return of bladder function was defined as the time between (a) injury and (b) a point midway between the last time the bladder was found to be distended and was manually expressed, and the next time manual expression was attempted and the bladder was found to be empty (as noted, expression was attempted at least twice per day). The animal was given a piece of apple (>10 g) each day from before the transection until the end of the study, and for each of the first 5 posttransection days, it was given a soft mash of water-soaked rat chow, with vitamin C (about 8 mg/kg/day) added to keep the urine acidic and thereby help prevent urinary tract infections. Until body weight regained its pretransection level, weight was measured daily and the animal received a high-calorie dietary supplement (Nutri-Cal; 2–4 mL/day, p.o.).

At the end of study, which for some rats was after subsequent exposure to the H-reflex operant conditioning protocol (e.g., Chen and Wolpaw, 1997), each rat was given an overdose of sodium pentobarbital (i.p.) and perfused through the heart with saline followed by 4% paraformaldehyde (or 3% paraformaldehyde and 1% glutaraldehyde) in 0.1 M phosphate buffer (pH 7.3). The placement of the EMG electrodes and the nerve cuff and the integrity of the tibial nerve were verified, and the soleus muscles of both sides were removed and weighed.

The spinal cord was removed and blocks encompassing the transection were embedded in paraffin. Transverse 20-μm-thick serial sections were cut from the paraffin-embedded blocks and stained with Luxol fast blue (for myelinated fibers) and 0.1% cresyl violet (for Nissl substance). Sections encompassing the transection were assessed to determine the location and size of the transection. Camera lucida drawings were made at a magnification of $\times$50. Remaining white matter was identified at a magnification of $\times$200 by the presence of normal Luxol fast blue staining. The tracings were enlarged and then digitized (Summagraphics Corp. digitizing pad and Jandel Scientific Sigmascan program), and the tissue remaining at the epicenter of the transection was measured according to the method of Olby and Blakemore (1996). For DC, CST, and DA rats, the area of DC, CST, or DA remaining was measured as percent of the area of that structure 2–5 mm rostral to the rostral limit of the lesion. (In accord with Olby and Blakemore [1996], the structure at a level rostral to the rostral limit of the lesion was found to be comparable in area to the structure in normal rats.) For LC rats, the area of right LC remaining was measured as percent of the left LC. (Nearly identical values were obtained when LC area was calcu-

lated as percent of the right LC rostral to the rostral limit of the lesion.) Thus, for example, a value of 20% indicates that, at the transection epicenter, 80% of the LC was damaged or absent. The border between the LC and the ventral column was defined according to Paxinos and Watson (1986).

Data Analysis

Each rat's daily values for H-reflex, background EMG, stimulus amplitude, and number of trials were expressed as percent of the average value for the final 10 pretransection days. To evaluate the short-term transection effect for each measure for each animal group (i.e., DC, LC, CST, and DA) for the first 20 posttransection days, a repeated measures ANOVA was used to detect a transection effect at the $p < 0.05$ level. If an effect was found, Dunnett's multiple comparisons method was used to determine which posttransection days differed significantly from the pretransection data. In addition, the average values for posttransection days 1–10 and the average values for posttransection days 11–20 were compared with the average values for the final 10 pretransection days by paired *t* test. Finally, to evaluate medium-term transection effects, data collections in some rats were continued for 30–155 days posttransection, and the average values for the final 10 days of data were compared with the average values for the final 10 pretransection days by paired *t* test.

RESULTS

Prior to spinal cord transection, H-reflexes, background EMG, and M responses were very similar to those of other normal rats (Chen and Wolpaw 1994, 1995, and unpublished data). Average values (±SD) were 105 (±51) μV for the H-reflex, 103 (±13) μV for background EMG, and 138 (±47) μV for the M response. Trials/day averaged 4,809 (±1,758).

Body weight fell 2–13% in the first week after the transection and recovered to its pretransection level in 1–7 weeks. For all rats, weight increased from 253–444 g at time of transection to 270–475 g at time of perfusion.

Bladder function (i.e., spontaneous voiding), which was absent immediately after injury, returned over 0–8 days. One-way analysis of variance (ANOVA) revealed a statistically significant difference among the four groups in the time to return of bladder function ($p < 0.05$). Pairwise multiple comparisons with the Newman-Keuls method indicated that the time was significantly shorter for DA rats than for DC rats ($p < 0.05$). No other significant intergroup differences were detected.

After perfusion, soleus muscle weights (measured as percent of body weight) were symmetrical and did not differ significantly from those of normal rats. As illustrated in Figure 2, tissue damage at the lesion epicenter was largely confined to the targeted area (except for CST rats, in which the contralateral dorsal horn or dorsal LC

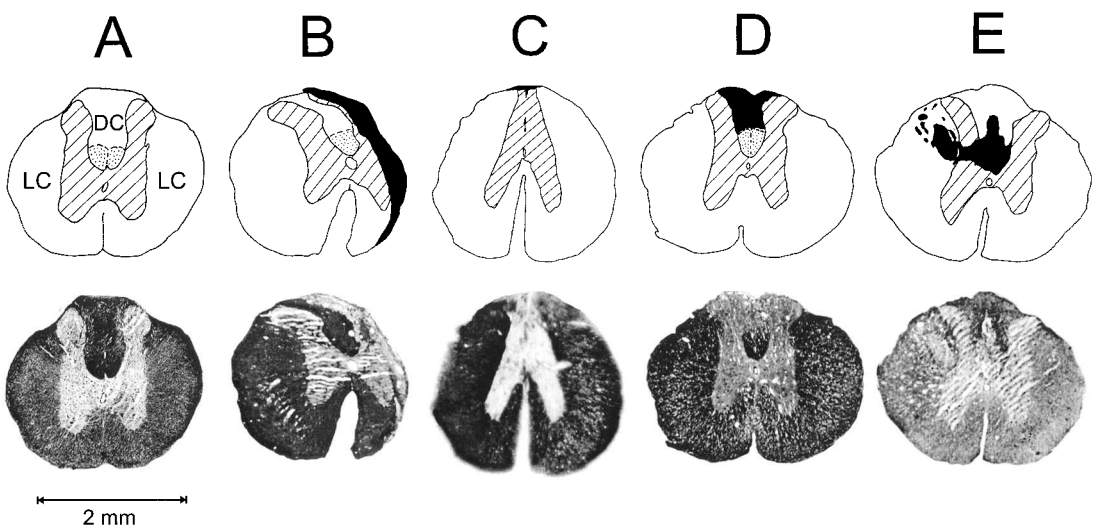

FIG. 2. Camera lucida drawings (top) and photomicrographs (bottom) of transverse sections of T8 spinal cord from a normal rat (**A**), an LC rat (**B**), a DC rat (**C**), a DA rat (**D**), and a CST rat (**E**). In lesioned rats, the section shown is at the transection epicenter. The lateral (LC) and dorsal (DC) columns are labeled in A. In the camera lucida drawings, hatching indicates gray matter, stippled areas (A,B,D) are the main corticospinal tract, and black areas (B–E) are necrotic debris, cystic cavities, or fibrous septa.

was often involved). Examination of the transverse serial sections indicated that the region of tissue loss had a total rostrocaudal length of 1.5–4.5 mm.

Lateral Column Transection

Immediately after LC transection, rats showed right hindlimb paralysis which lasted 1–3 days and then slowly recovered to the point where locomotion looked normal or nearly normal. Bladder function, absent after injury, returned over 1–4 days (2.7 ± 1.0 days [mean ± SD]). In the seven LC rats, the percentage of right LC remaining averaged 20(±20 SD)% (range, 0–50%). Figure 2B shows a transverse spinal cord section from an LC rat at the level of the transection.

Figure 3A shows average (±SE) daily H-reflex, background EMG, stimulus amplitude, and trials/day for 10 days before and 20 days following transection for the seven LC rats. LC transection had significant effects on H-reflex and background EMG ($p < 0.01$ and $p < 0.001$, respectively, by repeated measures ANOVA). H-reflex amplitude was significantly increased on day 1 ($p < 0.05$ by Dunnett's test) and slightly but not significantly decreased in the subsequent 10 days. It regained its pretransection value by day 15. Background EMG was significantly reduced on days 1 and 3 ($p < 0.01$) and regained its pretransection level by about 1 week. Stimulus amplitude appeared to decrease in the first few days after transection, but no significant difference was detected by repeated measures ANOVA ($p = 0.07$). Finally, no significant effects were detected on trials/day ($p > 0.4$).

Figure 1 shows daily average absolute value of EMG activity for 25 ms after stimulation from an LC rat for a day before LC transection and for days 1 and 18 after transection. The brief rise in H-reflex amplitude in the first day after LC transection is apparent.

As Table 1 shows, average background EMG was significantly decreased for posttransection days 1–10, but not for posttransection days 11–20. No significant differences were detected for the other measures ($p > 0.15$ for each).

Four rats with short-term data similar to those of the

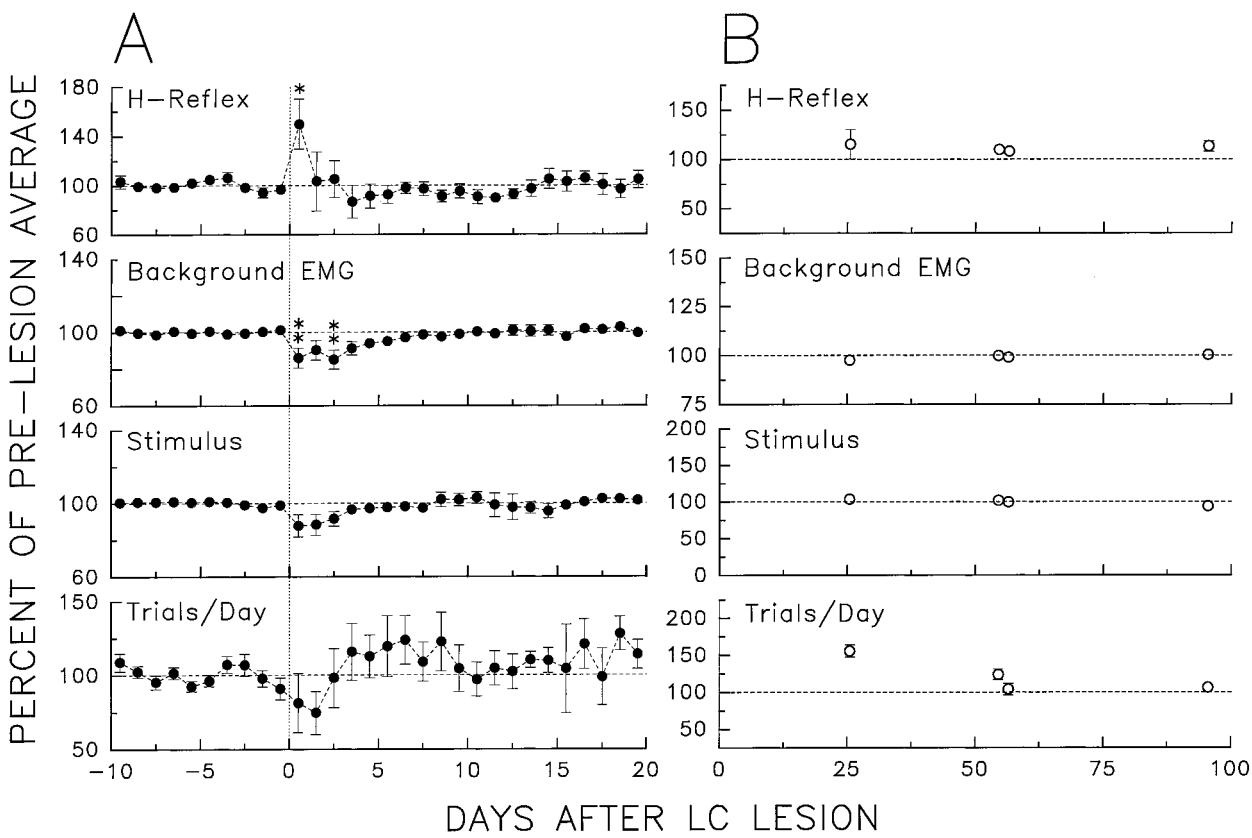

FIG. 3. (**A**) Average (±SE) daily H-reflex amplitude, background EMG, stimulus amplitude, and trials/day for 7 rats for 10 days before and 20 days after LC transection (in percent of pretransection average). Days marked by asterisks are significantly different from pretransection days (i.e., $**p < 0.01$; $*p < 0.05$). (**B**) Final posttransection values (i.e., average ± SE of final 10 days) for H-reflex amplitude, background EMG, stimulus amplitude, and trials/day for 4 rats followed for 30–101 days after LC transection (in percent of pretransection average).

Table 1. Average (SD) Short-Term (Posttransection Days 1–10 and 11–20) and Medium-Term (Final 10 Posttransection Days) Values for H-Reflex Amplitude, Background EMG, Stimulus Amplitude, and Trials/Day for LC, DC, DA, and CST Rats in Percent of Average Pretransection Values

		Posttransection days 1–10	*Posttransection days 11–20*	*Final 10 posttransection days*
LC rats	H-reflex	101 ± 25	96 ± 14	111 ± 3**
(7 short-term,	Background EMG	93 ± 6*	100 ± 6	99 ± 1
4 medium-term)	Stimulus amplitude	99 ± 6	100 ± 6	99 ± 4
	Trials/day	106 ± 36	113 ± 29	122 ± 24
DC rats	H-reflex	104 ± 25	101 ± 21	104 ± 19
(13 short-term,	Background EMG	95 ± 8*	97 ± 2**	99 ± 4
7 medium-term)	Stimulus amplitude	99 ± 6	100 ± 3	108 ± 16
	Trials/day	102 ± 22	93 ± 19	107 ± 33
DA rats	H-reflex	112 ± 18	108 ± 23	148 ± 46*
(10 short-term,	Background EMG	97 ± 4	97 ± 10	99 ± 1
5 medium-term)	Stimulus amplitude	100 ± 5	99 ± 1	101 ± 2
	Trials/day	109 ± 28	93 ± 13	107 ± 21
CST rats	H-reflex	109 ± 15	109 ± 25	97 ± 12
(8 short-term,	Background EMG	99 ± 2	101 ± 5	101 ± 4
4 medium-term)	Stimulus amplitude	100 ± 6	99 ± 5	96 ± 4*
	Trials/day	103 ± 21	101 ± 14	93 ± 17

*$p < 0.05$, **$p < 0.01$ compared with pretransection value by paired t test.

entire LC group were followed for 30–101 days after LC transection. Figure 3B displays the final values (average of final 10 days in percent of pretransection control, i.e., average for the final 10 pretransection days) for H-reflex, background EMG, stimulus amplitude, and trials/day for each of the four rats. As shown in Table 1, H-reflex amplitude showed a small (i.e., 11%) but significant ($p < 0.01$) increase over its pre-transection value. No other significant differences were detected ($p > 0.2$ for each of the other measures).

Dorsal Column Transection

Immediately after transection, DC rats showed bilateral hindlimb paralysis that lasted 2–3 days and then slowly abated over 1–2 weeks to the point where locomotion looked normal or nearly normal. Bladder function, absent immediately after injury, returned over 1–8 days (3.6 ± 2.5 days [mean ± SD]). DC transection was complete or nearly complete in all 13 animals: 2(±3 SD)% (range, 0–8%) remained. Figure 2C shows a transverse section from a DC rat.

Figure 4A shows average (±SE) daily H-reflex, background EMG, stimulus amplitude, and trials/day for 10 days before and 20 days following DC transection for the 13 DC rats. H-reflex amplitude increased for the first three days, background EMG fell slightly for days 4–13, and trials/day increased in the first day. However, none of these changes was significant by repeated measures ANOVA (i.e., $p > 0.2$ for each).

The average values for posttransection days 1–10 and 11–20 were compared with those for the final 10 pretransection days by paired t test. Average background EMG for posttransection days 1–10 and 11–20 was slightly but significantly ($p < 0.05$ and $p < 0.01$, respectively) decreased after DC transection. No significant differences were detected for the other measures ($p > 0.3$ for each). Table 1 summarizes the results.

Seven rats with short-term data similar to those of the entire DC group were followed for 30–155 days after DC transection. Figure 4B displays the final values (i.e., average of final 10 days in percent of pretransection control) for H-reflex, background EMG, stimulus amplitude, and trials/day for each of the seven rats. As Table 1 shows, final values were very similar to control values, and no significant changes were detected by paired t test ($p > 0.2$ for each comparison).

Dorsal Column Ascending Tract Rats

Immediately after transection, the 10 DA rats showed bilateral hindlimb paralysis which lasted for several hours only. Locomotion usually recovered to normal or nearly normal in 1–3 days. Bladder function returned over 0–2 days (0.7 ± 0.6 days [mean ± SD]). DA transection was usually complete or nearly complete: 9(±15)% (range, 0–31%) remained. Figure 2D shows a transverse section from a DA rat.

Figure 5A shows average (±SE) daily H-reflex, background EMG, stimulus amplitude, and trials/day for 10

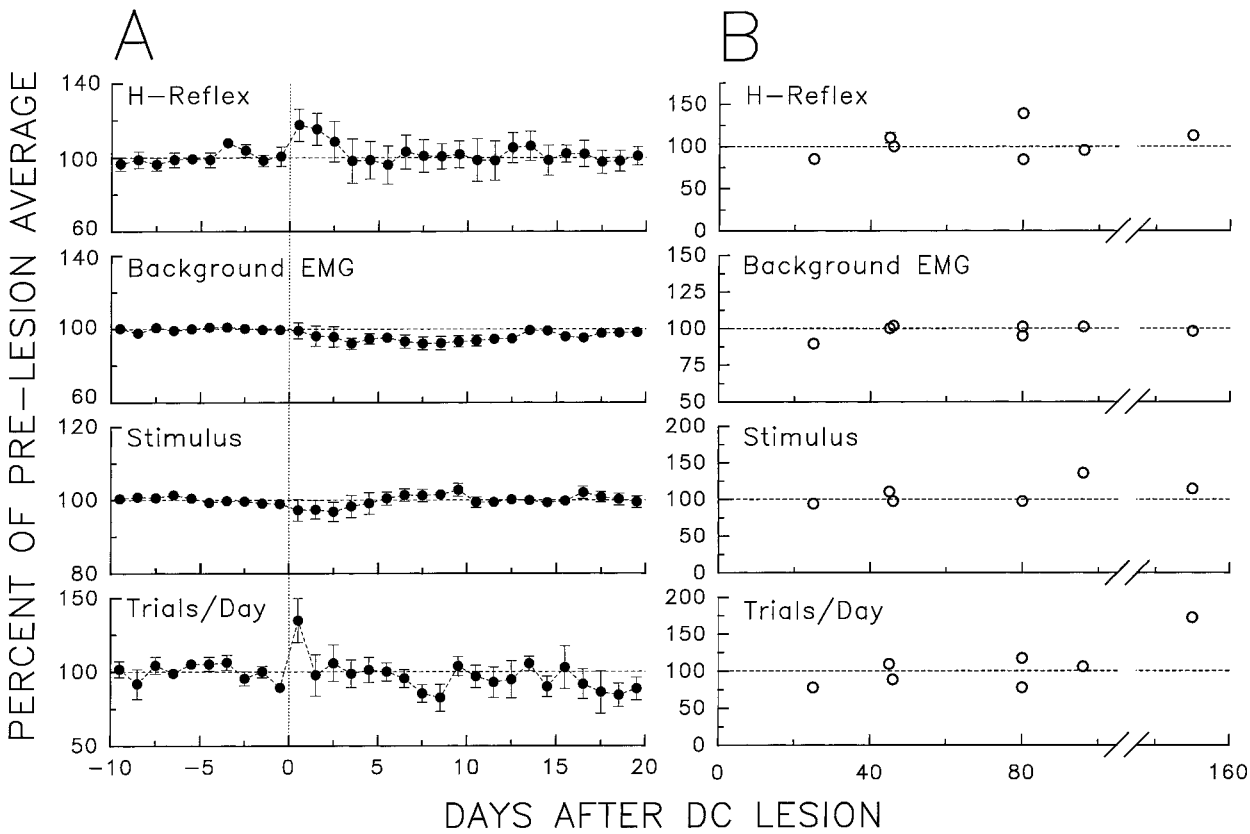

FIG. 4. (**A**) Average (±SE) daily H-reflex amplitude, background EMG, stimulus amplitude, and trials/day for 13 rats for 10 days before and 20 days after DC transection (in percent of pretransection average). (**B**) Final posttransection values (i.e., average ± SE of final 10 days) for H-reflex amplitude, background EMG, stimulus amplitude, and trials/day for 7 rats followed for 30–155 days after DC transection (in percent of pretransection average). (For one rat, a change in the stimulus delivery unit precluded comparison of pretransection and final posttransection stimulus amplitudes.)

days before and 20 days following transection for the 10 DA rats. DA transection had significant effects on H-reflex amplitude and daily trial number ($p < 0.001$ for both by repeated measures ANOVA). H-reflex amplitude increased significantly on day 1 ($p < 0.01$ by Dunnett's test) and returned to its pretransection value by day 3. Daily trial number increased significantly on day 1 ($p < 0.01$) and returned to its pretransection level by day 4. Background EMG and stimulus amplitude showed no significant short-term transection effects. As Table 1 shows, values for posttransection days 1–10 and 11–20 were not significantly different from pretransection values ($p > 0.06$ for each measure by paired t test).

Five rats with short-term data similar to those of the entire DA group were followed for 30–155 days after DA transection. Figure 5B displays the final values (i.e., average of final 10 days in percent of pretransection control) for H-reflex, background EMG, stimulus amplitude, and trials/day for each of the five animals. As Table 1 shows, final values for H-reflex amplitude averaged 148(±46 SD)% of their pretransection value. While the increase was large for only one rat, it was evident in each of the five rats and was significant ($p < 0.05$ by paired t test). Background EMG, stimulus amplitude, and trials/day in these animals did not change significantly ($p > 0.2$ for each by paired t test).

Dorsal Column Corticospinal Tract Rats

Immediately after transection, the eight CST rats showed bilateral hindlimb paralysis, which decreased over 1–2 days. Locomotion returned to normal or nearly normal by 10 days. The deficit lasted longer for the left leg than for the right, probably due to collateral damage to the posterior part of the left lateral column caused by the passage of the cauterizer on its way to the CST. Bladder function returned over 1–3 days (2.2 [±0.9] days [mean ± SD]). CST transection was usually nearly complete: 7(±19)% (range, 0–54%) of the right CST and 3(±7)% (range, 0–20%) of the left CST remained. On

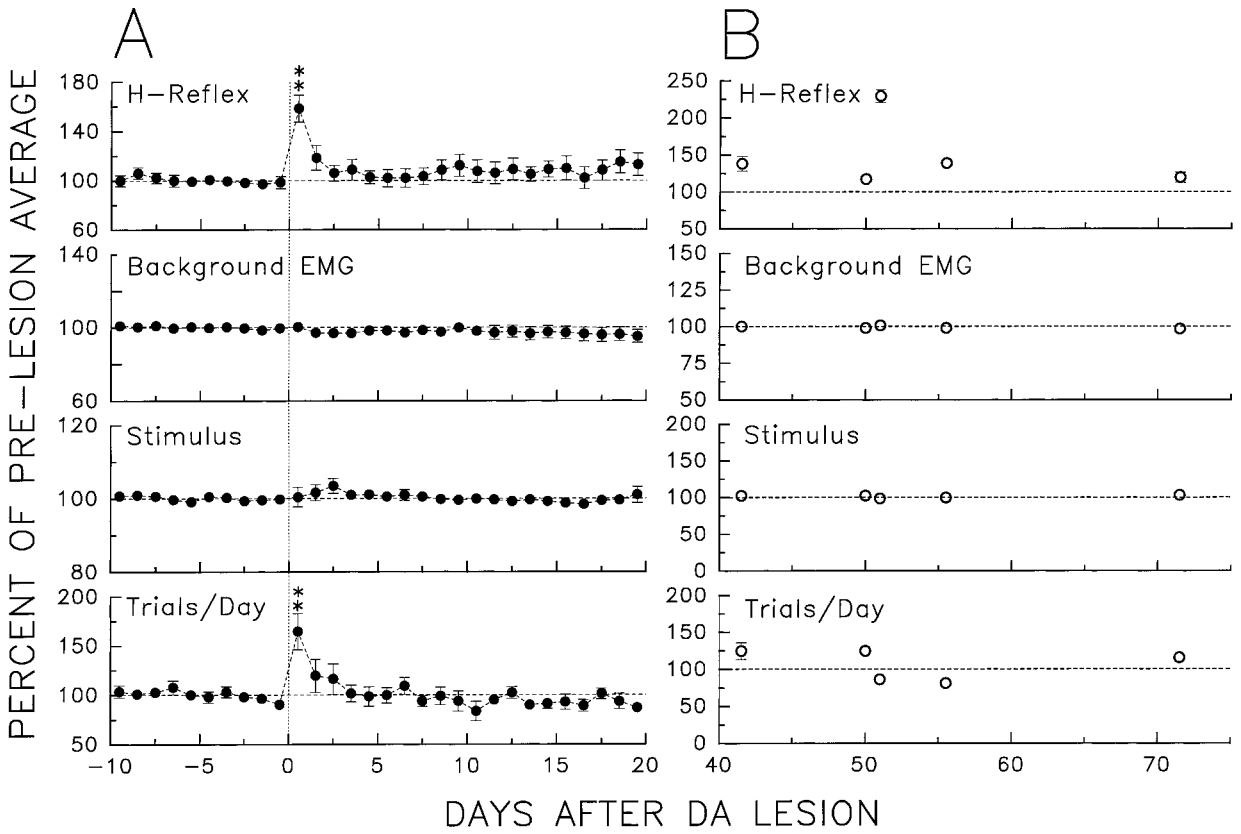

FIG. 5. (**A**) Average (±SE) daily H-reflex amplitude, background EMG, stimulus amplitude, and trials/day for 10 rats for 10 days before and 20 days after DA transection (in percent of pretransection average). Days marked by asterisks are significantly different from pretransection days (i.e., $^{**}p < 0.01$). (**B**) Final posttransection values (i.e., average ± SE of final 10 days) for H-reflex amplitude, background EMG, stimulus amplitude, and trials/day for 5 rats followed for 46–76 days after DA transection (in percent of pretransection average).

the other hand, the transections also involved the left LC and the right and left DA to varying extents: 65(±27)% (range, 32–100%) of the left LC, 51 (±22)% (range, 18–78%) of the right DA, and 29(±40)% (range, 0–98%) of the left DA remained. Figure 2E shows a transverse section from a CST rat.

Figure 6A shows average (±SE) daily H-reflex, background EMG, stimulus amplitude, and trials/day for 10 days before and 20 days following transection for the eight CST rats. CST transection had significant effects on the H-reflex ($p < 0.02$ by repeated measures ANOVA). H-reflex amplitude increased significantly on day 1 ($p < 0.01$ by Dunnett's test) and returned to its pretransection value by day 3. Daily trial number appears to be increased in the first day after transection. However, repeated measures ANOVA indicated that the posttransection days were not significantly different from the pretransection days ($p = 0.07$; although a significant increase was found on day 1 by Dunnett's test [$p < 0.05$]). No change was found for background EMG or stimulus amplitude ($p > 0.1$ by repeated measures ANOVA). For all measures, average values for post-transection days 1–10 and 11–20 (Table 1) did not differ significantly from pre-transection values ($p > 0.1$ for each comparison).

Four rats with short-term data similar to those of the whole CST group were followed for 50–85 days after CST transection. Figure 6B displays the final values (i.e., average of final 10 days in percent of pretransection control) for H-reflex, background EMG, stimulus amplitude, and trials/day for each of the four animals. As Table 1 indicates, only stimulus amplitude shows a significant change, and it was very small (4%).

DISCUSSION

This study investigated the short-term effects (i.e., first 20 days posttransection) and medium-term effects (i.e., from 1–5 months posttransection) of specific spinal cord pathway transections on the H-reflex of the rat soleus

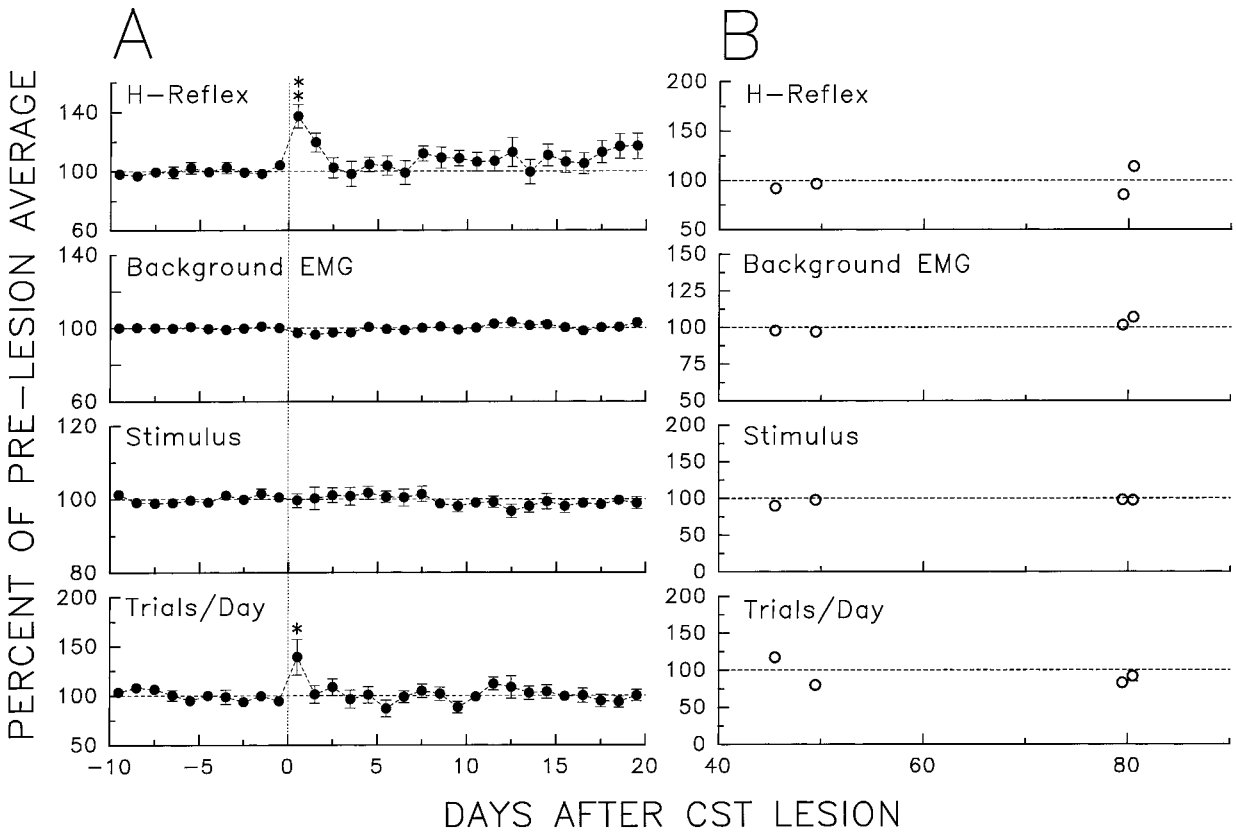

FIG. 6. (**A**) Average (±SE) daily H-reflex amplitude, background EMG, stimulus amplitude, and trials/day for 8 rats for 10 days before and 20 days after CST transection (in percent of pretransection average). Days marked by asterisks are significantly different from pretransection days (i.e., $**p < 0.01$; $*p < 0.05$). (**B**) Final posttransection values (i.e., average ± SE of final 10 days) for H-reflex amplitude, background EMG, stimulus amplitude, and trials/day for 4 rats followed for 50–85 days after CST transection (in percent of pretransection average).

muscle. The study had several distinctive and important features in addition to the anatomical specificity of the transections. First, the H-reflex was measured before and after the transection, so that each rat could be compared to itself. Second, it was measured in the awake behaving animal, so that the confounding effects of concurrent anesthesia were absent. Third, the H-reflex was elicited only when background (i.e., ongoing) EMG activity was in a certain range, and the amplitude of the eliciting stimulus was kept constant in relation to M response threshold. Thus, the potentially profound effects of change in motoneuron background activity or in effective stimulus strength were greatly reduced. While several short-term and medium-term transection effects were observed, and are discussed in this section, the most striking finding was that all these effects were modest.

Histological analysis showed that the DC, DA, and LC transections were complete or nearly complete and were limited mainly to the targeted pathways. Furthermore, collateral damage to adjacent areas of mid-thoracic gray matter would have been unlikely to affect the function of soleus motoneurons and their associated lumbosacral segmental pathways. The CST transections were more problematic because, while the CST itself was largely destroyed, the adjacent DA and left LC pathways often sustained significant damage. The left DA and LC damage was probably not important, since these pathways are largely ipsilateral. The substantial right DA damage might have affected results, but this possibility is reduced by the fact that the medium-term increase in H-reflex amplitude noted in the DA rats was not found in the CST rats.

Short-Term Effects of Transections

For all four transection types, H-reflex amplitude was larger for the first 1–2 days immediately after the transection. This effect was significant in the LC, CST, and DA rats, and evident, though not significant, in the DC rats. It could arise through one or more of several mech-

anisms. The first is a direct effect on the Ia synaptic terminal. Ia excitatory postsynaptic potentials in cat medial gastrocnemius and soleus motoneurons increase dramatically within hours of thoracic spinal cord transection (Nelson et al., 1979; Nelson and Mendell, 1979; Cope et al., 1988). Transection of the ascending collaterals of Ia afferents might contribute to this effect (Decima and Morales, 1983; Decima et al., 1986), and account for the brief H-reflex increase in DC and DA rats. A second possible mechanism is change in presynaptic inhibition of the Ia terminal (Faist et al., 1994). Interruption of descending control clearly affects presynaptic inhibition (Ashby and Verrier, 1975; Roby-Brami and Bussel, 1990; Calancie et al., 1993; Stein et al., 1993; Faist et al., 1999). This effect is presumably due to change in the activity of the mediating spinal cord interneurons. The third mechanism is also interneuronal: transections might affect interneurons in the oligosynaptic homonymous group I excitatory and/or inhibitory pathways that might contribute to the H-reflex (Baldissera et al., 1981; Burke et al., 1984; Fournier et al., 1986; Jankowska, 1992). The fourth mechanism is change in motoneuron excitability (Taylor et al., 1984). In cats, dorsal hemisection of the thoracic spinal cord causes an acute decrease in firing threshold and changes the minimum firing rate of lumbar motoneurons (Powers and Rymer, 1988; Carp et al., 1991). While in the present study overall motoneuron excitation as assessed by background EMG showed little or no change, it is possible that transection-induced change in the slope or order of motoneuron recruitment could account for the transient H-reflex increases. However, this seems less likely because the motoneurons responsible for background EMG prior to the transections, and thus most susceptible to excitation by the H-reflex stimulus, are presumably the motoneurons most responsive to Ia input. Thus, change in recruitment order would be more likely to account for an H-reflex decrease than for the increase actually observed. Finally, whatever the neuronal or synaptic mechanism of the transient increase, the fact that it occurred with all four types of transection suggests that it could be a nonspecific effect of the laminectomy and/or the anesthesia. In this regard, it should be noted that Cope et al. (1980) found that spinal cord transection in cats could influence synaptic transmission via mechanisms (perhaps humoral) operating outside the spinal cord.

Another immediate effect was the increase in trial number on the first posttransection day. This was most prominent in DA and CST rats but was also evident in DC rats. The fact that it was most prominent in DA rats, combined with the fact that CST rats had substantial DA damage, suggests that it was an effect of DA transection. Given the structure of the protocol, i.e., that trials occurred only when background EMG was in a certain range, this finding suggests that DA transection transiently increased soleus background activity. On the other hand, the absence of discernible concurrent change in background EMG (which the broad background EMG limits [e.g., 40–200 μV] of the H-reflex protocol would have allowed) implies that the change was an increase in the amount of time during which background activity was present, rather than an increase in the level of that activity. The third immediate change was the drop in background EMG in the several days immediately following LC transection. This was accompanied by a slight drop in trials/day. The rat LC contains rubrospinal, vestibulospinal, and reticulospinal tracts and a variety of ascending tracts (Zemlan et al., 1978, 1979; Holstege and Kuypers, 1987; Tracey, 1995). At this point, it is unclear whether more limited transections confined to one or more specific pathways would produce the effects noted in Figure 4A. Beyond these three immediate changes, the only other change discernible in the first 2 weeks was a slight decrease in background EMG after DC transection.

In the several days immediately after transection, rats showed a bilateral (DC, CST, and DA rats) or unilateral (LC rats) decrease in spontaneous hindlimb movement. This observation is consistent with the early decrease in background EMG in LC rats, but not with the delayed and more modest decrease in DC rats or the lack of change in background EMG in CST and DA rats. It is possible that DC, CST, or DA transection reduced movement without affecting soleus muscle activation, perhaps by producing cocontraction or poorly coordinated contractions of agonists and antagonists. Comprehensive data from multiple hindlimb muscles would be needed to address this question.

One notable feature of the short-term data was the lack of substantial evidence for spinal shock, the profound depression of segmental function that is traditionally associated with substantial spinal cord trauma (Mountcastle, 1980; Atkinson and Atkinson, 1996). Indeed, the most prominent finding was a transient increase in H-reflex amplitude. The drops in background EMG with LC and DC transections, and in trial number with LC transections, were modest. The duration of spinal shock is greatest in man and other primates and declines sharply with species level. Spinal shock in rats, measured by nociceptive reflexes, wanes rapidly in the first few hours after injury and is gone by 6–8 h (Schouenborg et al., 1992). In the present study, data collection did not begin for several hours (i.e., until the animal awoke and began to produce the required background EMG), and the first posttransection data point encompassed the entire 24 h of the first day. Thus, most of the data comprising this first point were probably obtained after the effects of spinal shock

on oligosynaptic spinal reflexes had largely dissipated. Four other factors also help to explain why the H-reflex and the background EMG were not profoundly depressed during this first day. First, the H-reflex is not dependent, as the tendon jerk is, on muscle spindle function, and thus is not susceptible to decrease by reduction in gamma motoneuron background activity. Second, in contrast to most previous studies, H-reflexes were elicited only when background EMG was in a certain range, so that alpha motoneuron background activity was comparable to its pretransection level. Third, the transections studied here were limited to specific pathways, so that they differed substantially from the much larger and/or less specific lesions most often studied. Fourth, the present data were obtained from awake freely moving animals, rather than from anesthetized animals. The last three factors may account for the difference between the results described here and those of Thompson et al. (1992, 1993), who noted that the H-reflex was depressed at 6 days after a contusion injury.

Medium-Term Effects of Transections

The increase in H-reflex amplitude months after DA transections was the most prominent medium-term effect noted in the present study. It is consistent with studies (Decima and Morales, 1983; Decima et al., 1986) showing that transection of the ascending branches of muscle spindle primary afferent fibers increases the strength of the synaptic connections made by their remaining segmental branches. It is interesting that the same effect was not evident after DC transections, which included both DA and CST transection. This suggests that the increase produced by the DA transection alone might have been mediated supraspinally and conveyed to the segmental pathway of the H-reflex by the CST. This would explain why the increase failed to occur when both the DA and CST were destroyed. It is conceivable that the H-reflex increase reflects a compensatory reaction by sensorimotor cortex to the loss of ascending input from muscle proprioceptors.

LC transections also produced a small medium-term increase in H-reflex amplitude. It is not clear which of the several LC descending and ascending pathways was important in this regard. This medium-term effect and the greater medium-term effect of DA transections are in general consistent with clinical and laboratory observations of the effects of spinal cord injury. Spinal cord injury in humans often results in the gradual development of hyperreflexia and other manifestations of spasticity (Davis, 1975; Taylor et al., 1984; Little and Halar, 1985; Dimitrijevic et al., 1988; St. George, 1993; Stein et al., 1993). Thompson et al. (1992) found that spinal cord contusion reduced the sensitivity of the H-reflex to rate depression, perhaps due to decrease in the presynaptic inhibition produced by homonymous group I stimulation (Thompson et al., 1996). In the present study, the required 2.3–2.7-s period of background EMG maintenance prior to stimulation, combined with the time necessary for poststimulus recording (and computer oversight of the other online rats), ensured that the maximum stimulation rate for each rat was only 0.3 Hz. Thus, change in rate-dependent depression should not have affected our data. Thompson et al. (1992) also noted a decrease in H-reflex threshold not seen in the present data. (The small medium-term drop in stimulus amplitude after CST transection seen in the present study [Table 1] is a drop in the strength of stimulation needed to elicit the target M response. It does not imply a drop in the strength of afferent input needed to elicit the H-reflex.) It is possible that the threshold effect noted by Thompson et al. (1992) was due to change in motoneuron background activity, which probably did not occur in the present study because the protocol permitted only minimal change in average background EMG. Studies in cats indicate that spinal cord transection increases triceps surae EPSPs measured several months later (Nelson and Mendell, 1979; Munson et al., 1986; Hochman and McCrea, 1994a,b). However, this effect appears to depend largely on transection occurring just above the motoneurons, and thus would not be expected to be prominent in the present study, in which transection was at T8-T9, well above the L4-L6 level of the soleus motoneurons.

CONCLUSION

The lack of medium-term effects of CST transection on H-reflex amplitude is important for studies aimed at defining the contributions of the CST to operant conditioning of the H-reflex. It indicates that data collection and interpretation should not be complicated by changes in H-reflex amplitude caused by CST transection itself. For example, the apparent failure of CST rats to decrease the H-reflex with conditioning (Chen et al., 1998) can be ascribed to a transection effect on conditioning capacity, because the present data indicate that such failure is not due to a transection-induced H-reflex increase that obscures an operantly conditioned decrease. On the other hand, the existence of modest medium-term H-reflex increase after DA or LC transection must be taken into account in studies aimed at defining contributions of these tracts to H-reflex conditioning. The direct effects of the transection on the H-reflex must be distinguished from any effects on H-reflex conditioning.

Finally, the results have broader implications in regard

to assessment of the functional effects of spinal cord injuries and assessment of the efficacy of therapeutic interventions. They are consistent with previous data (Blight, 1983; Bresnahan et al., 1987; Chen et al., 1996, 1999b) in showing that locomotion is not a sensitive measure of the lasting effects of mild or moderate spinal cord contusion injuries in rats. Furthermore, they indicate that the H-reflex itself, elicited from the awake behaving rat at a defined level of background EMG, is also a relatively insensitive measure of the effects of spinal cord injury. On the other hand, other measurement protocols based on the H-reflex, such as H-reflex rate dependence and H-reflex operant conditioning, do seem to be sensitive measures of injury (Thompson et al., 1992; Chen et al., 1996, 1999b). Indeed, recent studies indicate that operant conditioning of the H-reflex in rats depends on the corticospinal tract and does not depend on other major descending tracts (Chen and Wolpaw, 1997; Chen et al., 1998). Thus, it appears to provide a specific measure of corticospinal tract function.

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Address reprint requests to:
Xiang Yang Chen, Ph.D.
Wadsworth Center
New York State Department of Health
P.O. Box 509
Albany, NY 12201-0509

E-mail: chenx@wadsworth.org