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Corticospinal Tract Transection Permanently Abolishes H-Reflex Down-Conditioning in Rats

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ABSTRACT

Previous studies have shown that corticospinal tract (CST) transection, but not transection of other major spinal cord tracts, prevents down-conditioning of the H-reflex, the electrical analog of the spinal stretch reflex. This study set out to determine whether the loss of the capacity for H-reflex down-conditioning caused by CST transection is permanent. Female Sprague-Dawley rats received CST, lateral column (LC), or dorsal column ascending tract (DA) transection at T8–9; 9–10 months later, they were exposed to the H-reflex down-conditioning protocol for 50 days. In the LC and DA rats, H-reflex size fell to 60 (± 9 SEM)% and 60 (± 19)%, respectively, of its initial size. This down-conditioning was comparable to that of normal rats. In contrast, H-reflex size in the CST rats rose to 170 (± 42)% of its initial size. A similar rise does not occur in rats exposed to down-conditioning shortly after CST transection. These results indicate that CST transection permanently eliminates the capacity for H-reflex down-conditioning and has gradual long-term effects on sensorimotor cortex function. They imply that H-reflex down-conditioning can be a reliable measure of CST function for long-term studies of the effects of spinal cord injury and/or for evaluations of the efficacy of experimental therapeutic procedures, such as those intended to promote CST regeneration. The results also suggest that the role of sensorimotor cortex in down-conditioning extends beyond generation of the essential CST activity.

Key words: H-reflex conditioning; spinal cord injury; corticospinal tract; plasticity; rat

INTRODUCTION

SINCE THE LANDMARK STUDY of Fritsch and Hitzig (1870), numerous laboratory and clinical studies have explored the role of sensorimotor cortex and its most prominent output, the corticospinal tract (CST), in motor control. Nevertheless, the precise contribution of the CST to motor function remains elusive (Cheney et al., 1991; Darian-Smith et al., 1999; Davidoff, 1990; Porter and Lemon, 1993). The CST is clearly important for fine motor control, but there is as yet no reliable measure of CST function. Such a measure would be extremely valuable for assessing the extent and nature of spinal cord injuries and could contribute to the evaluation of new therapeutic approaches.

Although most work has focused on the short-term interactive role of the CST in motor function, recent studies show that the brain also exerts long-term tonic control over

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spinal cord pathways. Descending activity from the brain gradually modifies the spinal cord during development, after supraspinal trauma, and during skill acquisition (Chen and Wolpaw, 1997, 2002; Chen et al., 2002; see review, Wolpaw and Tennissen, 2001). Operant conditioning of the H-reflex, the electrical analog of the spinal stretch reflex (SSR), is a fruitful model for studying this long-term control (Carp and Wolpaw, 1994, 1995; Carp et al., 2001; Chen and Wolpaw, 1997, 2002, 2005; Chen et al., 2002, 2003; Feng-Chen and Wolpaw, 1996; Pillai et al., 2004; Wang et al., 2004, 2006; Wolpaw and Chen, 2001; Wolpaw and Lee, 1989). The SSR (or "tendon jerk") is the initial response to sudden muscle stretch and is the simplest behavior of the vertebrate central nervous system (Brown, 1984; Henneman and Mendell, 1981; Magladery et al., 1951; Matthews, 1972). It is mediated largely by a monosynaptic pathway, consisting of the Ia afferent neuron from the muscle spindle, its synapse on the alpha motoneuron in the spinal cord, and the motoneuron itself. Monkeys, humans, rats, and mice can increase or decrease SSR or H-reflex size in response to a reward contingency (Carp et al., 2006; Chen and Wolpaw, 1995; Evatt et al., 1989; Wolf et al., 1995; Wolpaw, 1987; Wolpaw et al., 1983). Reflex increase (i.e., up-conditioning) or decrease (i.e., down-conditioning) occurs gradually over days and weeks and is accompanied by plasticity in spinal cord motoneurons, in the synaptic terminals on them, and probably in spinal interneurons as well (Carp and Wolpaw, 1994, 1995; Carp et al., 2001; Feng-Chen and Wolpaw, 1996; Pillai et al., 2004; Wang et al., 2004, 2006).

Recent studies indicate that H-reflex conditioning depends on the CST, not on other major spinal cord tracts: transection of the main CST prevents conditioning, while transection of the ipsilateral lateral column (LC), which contains the rubrospinal, vestibulospinal, and reticulospinal tracts and several ascending tracts, or the dorsal column ascending tract (DA) does not do so (Chen and Wolpaw, 1997, 2002; Chen et al., 2002). These results suggest that H-reflex conditioning is a specific measure of CST function and could be used to assess the functional integrity of the CST after spinal cord injury and to evaluate the effectiveness of new therapies. It could provide a crucial addition to anatomic methods for quantifying CST regeneration and physiological methods (e.g., focal cortical stimulation) that can detect CST connections to spinal cord neurons but cannot determine whether these connections are functioning properly.

The previous studies tested H-reflex conditioning only during the first several months after tract transection (Chen et al., 1996, 1999, 2002; Chen and Wolpaw, 1997, 2002), but spinal cord function continues to change much longer after injury (Liverman et al., 2005). Therefore, before H-reflex conditioning can be used as a specific measure of CST function, it is essential to determine: (1) whether the dependence of H-reflex conditioning on the CST is permanent (i.e., if the CST is destroyed, is the loss of the capacity for conditioning permanent or does it eventually return?); and (2) whether the lack of dependence on other major descending tracts is also permanent. The present study addresses these important questions and thereby contributes to establishing H-reflex conditioning as a valuable new method for assessing CST function. It also provides new insight into the supraspinal mechanisms that produce the spinal cord plasticity that directly underlies H-reflex conditioning.

METHODS

Subjects were 14 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* from the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (National Academy Press, Washington, D.C., 1996) and had been reviewed and approved by the Institutional Animal Care and Use Committee of the Wadsworth Center. The protocols for the spinal cord tract transections and for H-reflex conditioning are presented in detail elsewhere (Chen and Wolpaw,1995, 1997, 2002; Chen et al., 2001b, 2002, 2003) and summarized here.

Under general anesthesia, each rat received one of the three transections (i.e., bilateral CST, ipsilateral LC, or bilateral DA transection) at T8–9 with an electrocautery (small vessel cauterizer, Fine Science Tools, Foster City, CA). For CST transection (5 rats), the cauterizer was mounted in a micromanipulator, and the tip was positioned 1.0 mm left of the midline of the dorsal surface of the spinal cord, pointed medially at an angle of 45° from vertical, and advanced 1.7 mm. For LC transection (6 rats), the lateral half of the right side of the spinal cord was transected. (LC transection was unilateral to avoid the considerable disability likely to be associated with bilateral LC transection [which would have destroyed about two-thirds of the white matter], and because, at the thoracic level, the major descending tracts in the LC [i.e., rubrospinal, vestibulospinal, and reticulospinal tracts] are mainly or exclusively ipsilateral to the leg they serve [Tracey, 2004].) For DA transection (3 rats), transection extended 0.4 mm to either side of the midline and 0.7 mm into the spinal cord from the dorsal surface.

After transection, the site was 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. As previously described in detail (Chen and Wolpaw, 1997, 2002; Chen et al., 2001b, 2002,

2003), care in the days immediately after transection included analgesia, antibiotics, food supplementation, and bladder expression until bladder function fully returned. Locomotion returned to normal or nearly normal (i.e., BBB for both hindlimbs were 20–21 [Basso et al., 1995]) within 2 weeks after the transection.

After tract transection, the rats were singly housed and maintained for 9–10 months. They were then implanted under general anesthesia with chronic stimulating and recording electrodes in the right leg. To elicit the H-reflex, a nerve cuff was placed on the right posterior tibial nerve just above the triceps surae branches. To record soleus EMG activity, fine-wire electrodes were inserted in the right soleus muscle. The Teflon-coated wires from the nerve cuff and the muscle passed subcutaneously to a connector plug mounted on the skull.

Data collection began at least 4 weeks after the implantation. Throughout this period, each animal continued to live in a standard rat cage, with a 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 a commutator above the cage and from there to an EMG amplifier and a nerve-cuff stimulator. All animals had free access to water and food, except that during H-reflex down-conditioning they obtained food mainly as a reward (as described below).

A computer system continuously monitored soleus EMG and controlled the nerve-cuff stimulus. If the absolute value of background EMG stayed within a defined range for a randomly varying 2.3–2.7 sec period, a stimulus pulse (usually 0.5 msec in duration) was delivered by the nerve cuff. Pulse amplitude was continuously adjusted so that it remained just above M-response threshold. Background EMG level, M-response size, and stimuli per day remained stable throughout data collection. In the control mode, the computer simply measured the absolute value of soleus EMG for 50 msec following the stimulus. In the down-conditioning mode, it gave a food reward 200 msec after nerve stimulation if EMG amplitude in the H-reflex interval (typically 5.5–9.0 msec after stimulation) was below a criterion value.

In the course of its normal activity, the animal usually satisfied the background EMG requirement and thus received nerve-cuff stimulation 5,000–10,000 times per day. H-reflex size was calculated as average EMG amplitude in the H-reflex interval minus average background EMG amplitude at the time of stimulation and was expressed in units of average background EMG amplitude. Data were collected under the control mode for 20 days to determine the initial size of the animal's H-reflex. It was then exposed to the down-conditioning mode for 50 days. To determine the final effect of down-conditioning on H-reflex size, average H-reflex size for the final 10 days of exposure was calculated as percent of initial H-reflex size (i.e., average of final 10 control-mode days). As in the past, successful down-conditioning was defined as a decrease of at least 20% from initial H-reflex size (Chen and Wolpaw, 1995; Wolpaw et al., 1993).

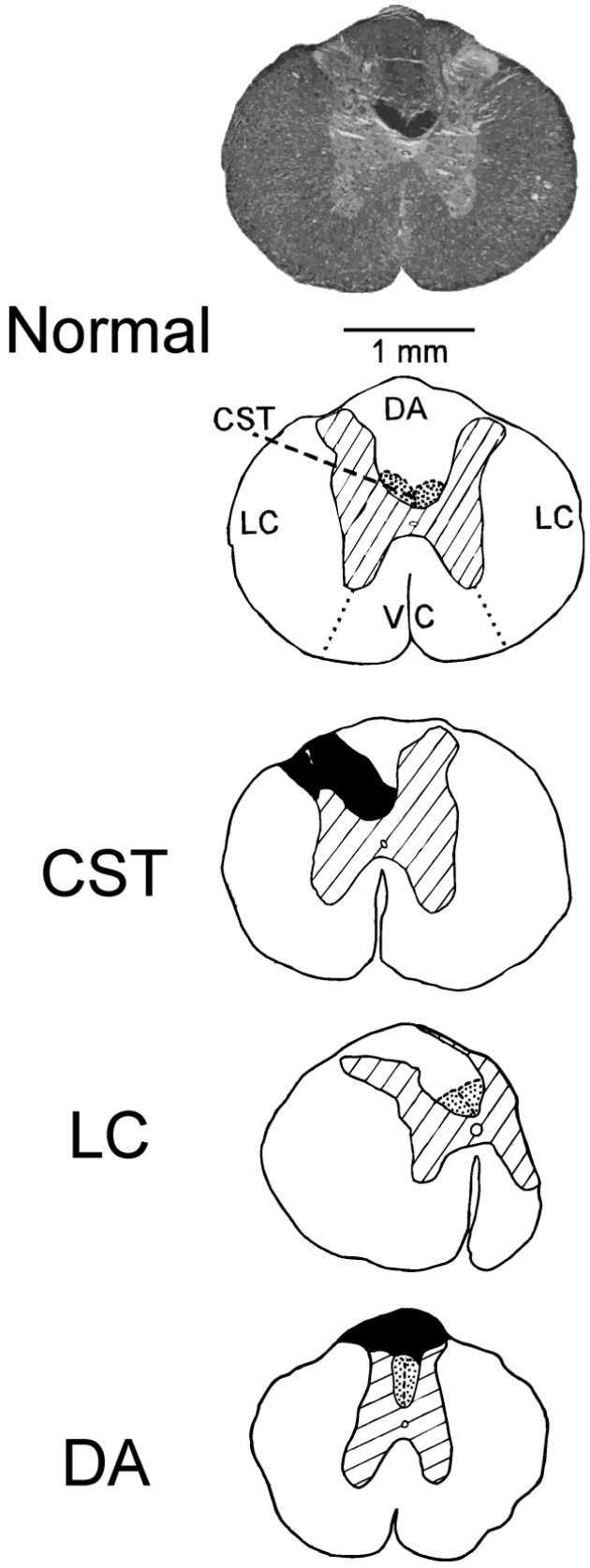
At the end of the study period, each rat was sacrificed by an overdose of sodium pentobarbital and perfused through the heart with saline followed by 3% paraformaldehyde and 1% glutaraldehyde in 0.1 M phosphate buffer (pH 7.3). The EMG electrodes, nerve cuff, and posterior tibial nerve were examined and the soleus muscles of both sides were removed and weighed. Soleus weights (as percent of body weight) were symmetrical and did not differ significantly from those of normal rats (Chen and Wolpaw, 1995, 1997, 2002; Chen et al., 1996, 1999, 2001a, 2002, 2003; Wolpaw and Chen, 2001; and unpublished data).

The spinal cord was removed, and blocks encompassing the transection were embedded in paraffin. Transverse 10–20 μm-thick serial sections were cut and stained with Luxol fast blue (Aldrich Chemical Company, Milwaukee, WI). For CST or DA transection, the area remaining was measured as percent of the area of that structure 2–5 mm rostral to the rostral limit of the lesion. For LC transection, the area of right LC remaining was measured as percent of the left LC.

In the five CST rats, 90 ($\pm$ 22 SD)% (range 51–100%) of the right CST and 99 ($\pm$ 2 SD)% (range 95–100%) of the left CST were destroyed. In the six LC rats, 77 ($\pm$ 21)% (range 47–100%) of the right LC was destroyed. In the three DA rats, 83 ($\pm$ 12)% (range 71–100%) of the right DA and 83 ($\pm$ 13)% (range 70–100%) of the left DA were destroyed. The CST transections also involved the left LC and the right and left DA to varying extents: 48 ($\pm$ 34)% (range 11–100%) of the left LC, 30 ($\pm$ 26)% (range 0–61%) of the right DA, and 88 ($\pm$ 13)% (range 70–100%) of the left DA were destroyed. Since CST, DA, and the major descending LC tracts are almost exclusively ipsilateral at T8–9, since DA transection alone has no effect on conditioning (Chen and Wolpaw, 1997, 2002; Chen et al., 2002; and see below), and since the extent of left LC or DA loss in CST rats did not correlate with final H-reflex size ($p > 0.1$), this contralateral collateral damage does not account for the effects of CST transection that are described below. Figure 1 shows a T8–9 transverse section and corresponding camera lucida drawings from normal, CST, LC, and DA rats.

RESULTS

All rats recovered quickly from CST, LC, or DA transection. They remained active and continued to gain



weight steadily throughout the 1-year course of the study (i.e., tract transection, 9–10 month interval, implantation, down-conditioning protocol, perfusion). Body weight increased from 267 g (± 35 SD, range 229–327 g) at the time of transection to 409 g (± 71 SD, range 282–526 g) at the time of perfusion.

The control-mode values for background EMG level, M-response size, and H-reflex size from the CST, LC, and DA rats of this study did not differ significantly ($p > 0.1$ for each measure) from those of 53 normal female rats studied to date (Chen and Wolpaw, 1995, 1997, 2002; Chen et al., 1996, 1999, 2001a, 2002, 2003; Wolpaw and Chen, 2001; and unpublished data). At the same time, H-reflex size tended to be larger than normal (i.e., by 44, 38, and 39% for CST, LC, and DA rats, respectively). Previous data suggest that LC or DA transection might have contributed to these high values (Chen et al., 2001b). However, the fact that similarly high values occurred in CST rats as well suggests that they may reflect a nonspecific age-related change.

Figure 2 summarizes the long-term effects of the tract transections on down-conditioning and includes for comparison earlier data on the short-term effects and data from normal rats. It shows average final H-reflex sizes (in percent of initial size) as follows: for the LC, CST, and DA rats of this study, that were exposed to the down-conditioning protocol nearly 1 year after transection (designated "late"); for the LC, CST, and DA rats that were exposed to down-conditioning shortly after transection (i.e., within 30 days, designated "early") (Chen and Wolpaw, 1997, 2002; Chen et al., 2002); and for normal rats exposed to down-conditioning (Chen and Wolpaw, 1995, 1997, 2002; Chen et al., 1996, 1999, 2001a, 2002, 2003; Wolpaw and Chen, 2001; and unpublished data).

The seven groups differ significantly ($p < 0.001$ by ANOVA) in final H-reflex size. The effects of down-conditioning were very similar in the normal rats, the early and late LC rats, and the early and late DA rats: final values were 67 (± 3)%, 72 (± 8)%, 60 (± 9)%, 66 (± 6)%, and 60 (± 19)% of initial size, respectively; and 75%, 71%, 67%, 83%, and 67%, respectively, reached the criterion for successful down-conditioning (i.e., H-reflex

FIG. 1. Photomicrograph of the T8–9 spinal cord from a normal rat and T8–9 camera lucida drawings from a normal rat, a rat with bilateral transection of the corticospinal tract (CST rat), a rat with transection of the right lateral column (LC rat), and a rat with bilateral transection of the dorsal ascending tract (DA rat). Hatch marks indicate gray matter; stippled areas indicate the main corticospinal tract; and blackened areas indicate necrotic debris or cystic cavities.

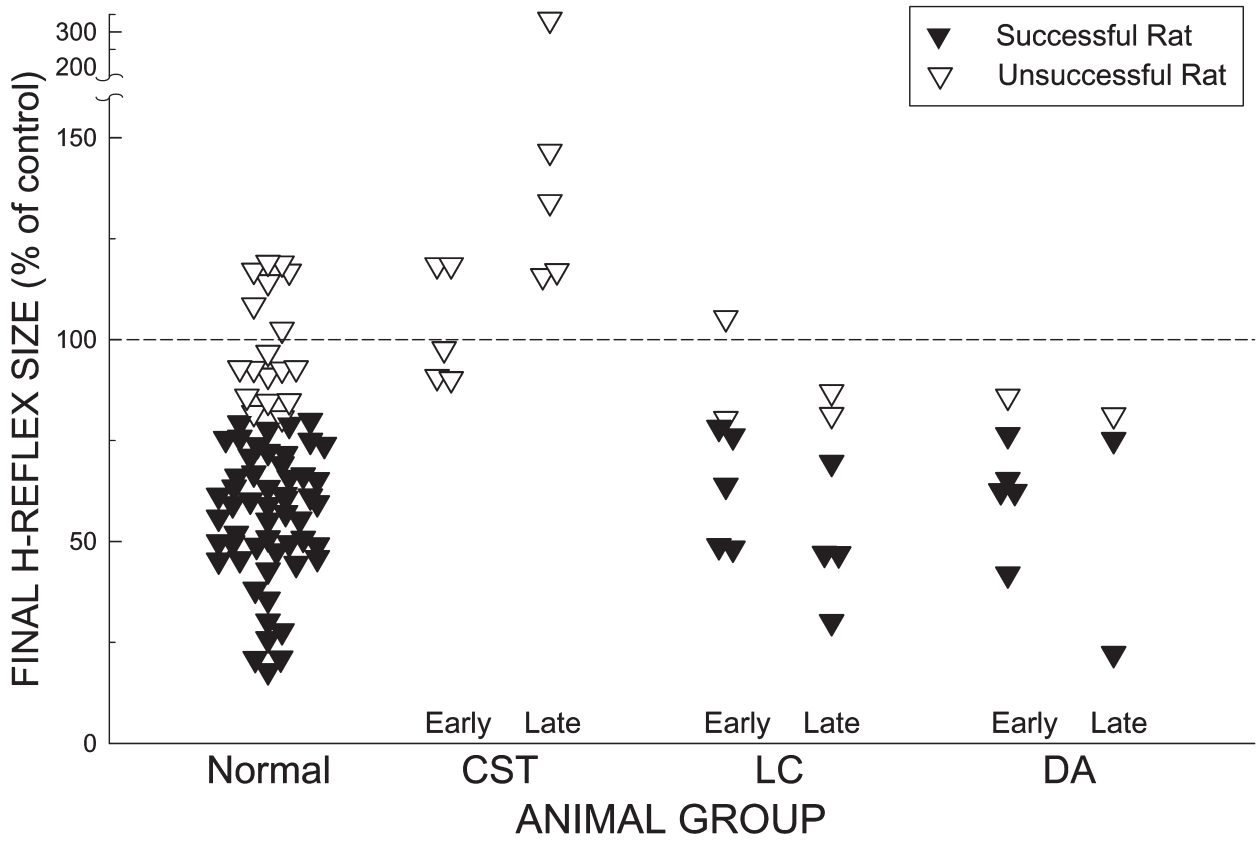


FIG. 2. Effects of tract transections on H-reflex down-conditioning. Final H-reflex sizes for normal, LC, CST, and DA rats. Each down triangle represents one rat's final H-reflex value (i.e., average H-reflex size for the final 10 days of down-conditioning). Down-conditioning was similarly effective in normal rats and early and late LC and DA rats. In contrast, down-conditioning did not occur in early or late CST rats, and late CST rats actually increased the H-reflex in response to the down-conditioning protocol. See text for full discussion. Early, rats conditioned shortly after transection; late, rats conditioned nearly 1 year after transection; ▼, successful rat (decrease $\geq$ 20%); ▽, unsuccessful rat (decrease $<$ 20%). The late LC, CST, and DA rat data are from the present study. The early LC, CST, and DA rat data are from Chen and Wolpaw, 1997, 2002. The extensive normal rat data are from numerous previous studies (Chen and Wolpaw, 1995, 1997, 2002; Chen et al., 1996, 1999, 2001a, 2002, 2003; Wolpaw and Chen, 2001; and unpublished data).

decreased at least 20%) (Chen and Wolpaw, 1995; Wolpaw et al., 1993). In contrast, final H-reflex size in the five early and five late CST rats averaged 103 ($\pm$ 6)% and 170 ($\pm$ 42)% of initial size, respectively; none of these CST rats reached the criterion for successful H-reflex down-conditioning.

Figure 3 shows average poststimulus EMG from a normal rat, an early CST rat, and a late CST rat for representative days before down-conditioning and near the end of down-conditioning. With exposure to down-conditioning, the normal rat decreased the H-reflex. In contrast, the early CST rat showed no change, and the late CST rat actually increased the H-reflex. For each rat, background EMG and M-response remained the same throughout data collection.

DISCUSSION

The results demonstrate that the loss of the capacity for H-reflex down-conditioning produced by CST transection is permanent or, more precisely, persists for at least 1 year. This duration is a very long period in the 2–3 year normal life span of a Sprague-Dawley rat and would be sufficient to encompass the duration of a wide variety of long-term studies evaluating new therapeutic methods aimed at restoring function after spinal cord injury. Furthermore, the lack of effect of LC or DA transection on down-conditioning also persists for this period.

The close similarities between H-reflex and SSR conditioning in monkeys, rats, mice, and humans (Carp et

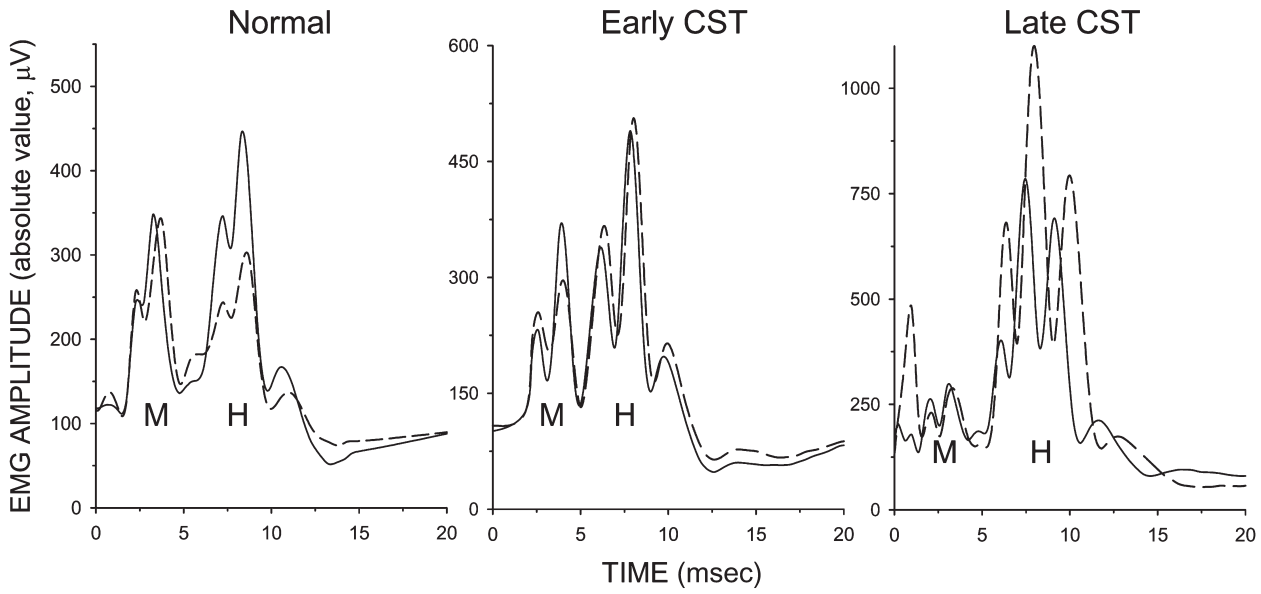


FIG. 3. Average poststimulus EMG from a normal rat, an early CST rat, and a late CST rat for representative days before down-conditioning (solid lines) and at the end of down-conditioning (dashed lines). With exposure to down-conditioning, the normal rat decreased the H-reflex. Neither the early nor the late CST rat decreased the H-reflex. The H-reflex in the late CST rat increased with exposure to the down-conditioning exposure. (A small stimulus artifact is evident in the postconditioning trace of the late CST rat.) In each rat, background EMG (represented by the value at 0 msec) and M-response remained the same throughout data collection.

al., 2006; Chen and Wolpaw, 1995; Evatt et al., 1989; Wolf et al., 1995; Wolpaw, 1987; Wolpaw et al., 1983; see review, Wolpaw, 1997) and the evidence that strokes involving sensorimotor cortex prevent SSR conditioning in humans (Segal, 1997) suggest that the CST has a similarly unique role in supporting H-reflex conditioning in humans and thus could serve as a good measure of CST function. At the same time, it is not clear whether H-reflex conditioning can still occur when the CST is damaged but not totally destroyed. Restoration of H-reflex conditioning may require complete or only partial regeneration of the relevant portion of the CST. The answer to this question will significantly affect the practical usefulness of the new measure. Certainly, the ability to detect partial regeneration would be a valuable attribute.

The H-reflex increase seen in late CST rats exposed to H-reflex down-conditioning is a surprising finding. It is paradoxical in that it occurs under the down-conditioning mode (i.e., when the rat is being rewarded for a smaller H-reflex). While the underlying mechanism of this paradoxical H-reflex increase is still unclear, a similar paradoxical H-reflex increase occurs when rats with recent contralateral sensorimotor cortex (cSMC) ablation are exposed to the down-conditioning protocol (Chen et al., 2004). It is possible that by 10 to 12 months after CST transection, the cSMC of the late CST rats has undergone retrograde degeneration that mimics the effect of cSMC ablation on down-conditioning (Belhaj-Saif and Cheney, 2000; Curt et al., 2002; Raineteau and Schwab, 2001).

The paradoxical H-reflex increase seen in cSMC rats and in late CST rats when they are exposed to down-conditioning could be related to similarly unexpected increases found in other reflex conditioning studies. In normal rats that have decreased the H-reflex in response to down-conditioning, either CST transection or ablation of cerebellar output nuclei leads to a similar increase: the H-reflex becomes larger than it was prior to down-conditioning (Chen and Wolpaw, 2002; Wolpaw et al., 2005). In down-conditioned monkeys, general anesthesia and spinal cord transection produce reflexes that are larger than expected on both the down-conditioned and unconditioned sides (even though the asymmetry in reflex size created by down-conditioning remains evident) (Wolpaw and Lee, 1989; Wolpaw et al., 1989). These earlier results and the increase found in this study imply that cSMC has a role in H-reflex conditioning that goes beyond the production of appropriate CST activity and are consistent with other data indicating that this conditioning is associated with a complex pattern of spinal and supraspinal plasticity (Carp and Wolpaw, 1994, 1995; Carp et al., 2001; Chen and Wolpaw, 1997, 2002, 2005; Chen et al., 2002, 2003, 2005; Feng-Chen and

Wolpaw, 1996; Pillai et al., 2004; Wang et al., 2004, 2006; Wolpaw, 1997; Wolpaw and Tennissen, 2001 for review).

In sum, the present study indicates that the loss of the capacity for H-reflex down-conditioning after CST transection is permanent and, thus, that H-reflex down-conditioning provides a potentially valuable new method for measuring CST function in long-term studies of the effects of spinal cord injury and/or of the efficacy of new therapeutic methods, such as those intended to promote CST regeneration. It also provides new information that broadens the role of sensorimotor cortex in H-reflex conditioning.

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