Conditioned H-Reflex Increase Persists After Transection of the Main Corticospinal Tract in Rats

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Chen, Xiang Yang, Lu Chen, and Jonathan R. Wolpaw. Conditioned H-reflex increase persists after transection of the main corticospinal tract in rats. J Neurophysiol 90: 3572–3578, 2003. First published August 13, 2003; 10.1152/jn.00264.2003. The brain shapes spinal cord function throughout life. Operant conditioning of the H-reflex, the electrical analog of the spinal stretch reflex (SSR), is a relatively simple model for exploring the spinal cord plasticity underlying this functional change and may provide a new method for modifying spinal cord reflexes after spinal cord injury. In response to an operant conditioning protocol, rats can gradually increase (i.e., up-training mode) or decrease (i.e., down-training mode) the soleus H-reflex. This study explored the effects of midthoracic transection of the ipsilateral lateral column (LC) [rubrospinal, vestibulospinal, and reticulospinal tracts], the dorsal column corticospinal tract (CST), or the dorsal column ascending tract (DA) on maintenance of an H-reflex increase that has already occurred. Rats were implanted with EMG electrodes in the right soleus muscle and a nerve-stimulating cuff on the right posterior tibial nerve. After initial (i.e., control) H-reflex size was determined, the rats were exposed for 50 days to the up-training mode, in which reward was given when the H-reflex was above a criterion value. H-reflex size gradually rose to 168 ± 12% (mean ± SE) of its initial value. Each rat then received an LC, CST, or DA transection and continued under the up-training mode for 50 more days. None of the transections abolished the H-reflex increase. H-reflex size increased further to 197 ± 19% of its initial value and did not differ significantly among LC, CST, and DA rats (P > 0.78 by ANOVA). Although earlier studies show that the main CST is needed for acquisition of H-reflex up-training and down-training and for maintenance of down-training, this study shows that it is not needed for maintenance of up-training. It adds to the evidence that H-reflex conditioning changes the spinal cord and that the spinal cord plasticity associated with up-training is different from that associated with down-training.

INTRODUCTION

Descending activity from the brain regulates spinal cord function during development and throughout life (Wolpaw and Tennissen 2001). When injury or disease impairs this long-term control, reflex patterns are distorted and spasticity and other disabling problems arise. The descending spinal cord pathways and segmental mechanisms through which the brain induces and maintains spinal cord plasticity are largely unknown. Better understanding would elucidate the acquisition of motor skills and could lead to novel methods for inducing, guiding, and assessing recovery of function after spinal cord injury and for treating other disorders associated with spasticity and other abnormalities of spinal cord reflex function.

The H-reflex is the electrical analogue of the simplest behavior of the vertebrate CNS, the spinal stretch reflex (SSR). Both are mediated by a wholly spinal and largely monosynaptic pathway composed of the primary afferent neuron, the alpha motoneuron, and the synapse between them (Brown 1984; Matthews 1972). Motivated by a conditioning protocol in which reflex size determines whether reward occurs, rats and monkeys can gradually increase or decrease the SSR or H-reflex (Chen and Wolpaw 1995; Wolpaw 1987; Wolpaw and Lee 1989; Wolpaw et al. 1983, 1993). A comparable phenomenon occurs in humans (Evatt et al. 1989; Wolf and Segal 1990, 1996; Wolf et al. 1995). In these studies, conditioning has been demonstrated for the biceps brachii SSR in monkeys and humans, for the triceps surae H-reflex in monkeys, and for the soleus H-reflex in rats. In both primates and rats, the conditioned reflex increase or decrease develops over days and weeks (Chen et al. 2001a; Wolpaw and O’Keefe 1984). This reflex change is associated with plasticity in the spinal cord itself (Carp and Wolpaw 1994, 1995; Carp et al. 2001; Feng-Chen and Wolpaw 1996; Wolpaw 1997, 2001).

Studies showing that midthoracic spinal cord contusion injury impairs conditioning of the rat soleus H-reflex and that the impairment correlates with the severity of the injury confirmed that acquisition of an H-reflex increase or decrease depends on descending activity from the brain (Chen et al. 1996, 1999). We are exploring the dependency of the acquisition and maintenance of H-reflex change on specific spinal cord pathways and supraspinal regions. Studies to date report that midthoracic transection of the dorsal column corticospinal tract (CST) [i.e., the main CST (Holstege and Kuypers 1987; Kennedy 1990; Kuypers 1981; Tracey 1995)] prevents acquisition of H-reflex increase or decrease, whereas transection of the ipsilateral lateral column (LC) [containing rubrospinal, vestibulospinal, and reticulospinal tracts and several ascending tracts (Holstege and Kuypers 1987; Kennedy 1990; Kuypers 1981; Tracey 1995)] or transection of the dorsal column ascending tract (DA) has no apparent effect on the acquisition of an H-reflex increase or decrease (Chen and Wolpaw 1997, 2002; Chen et al. 2002). Furthermore, if the CST is transected after an H-
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reflex decrease has been achieved, the decrease disappears within 10 days. In contrast, if the LC or DA is transected after an H-reflex decrease has been achieved, the decrease does not disappear (Chen and Wolpaw 2002). In summary, rats with CST transection lose the ability to increase or decrease the H-reflex, and they also lose the ability to maintain a decrease achieved before the transection. In contrast, rats with LC or DA transection can increase or decrease the H-reflex as well as normal rats, and they can maintain a decrease achieved before the transection. These results indicate that the main CST is essential for acquisition of H-reflex up- and down-training and for maintenance of H-reflex down-training, whereas the ipsilateral LC and the DA are not.

The purpose of this study was to determine the effect of CST, LC, or DA transection on the maintenance of an H-reflex increase in the soleus muscle. Rats that had increased the H-reflex over a 50-day exposure to the up-training protocol were given an LC, CST, or DA transection and then continued under the up-training protocol for another 50 days to determine whether the H-reflex increase persisted or disappeared. The fact that the CST is needed for acquisition of an increase or a decrease and for maintenance of a decrease, and that the LC and DA are not needed, suggested that only the CST would prove essential for maintenance of an increase. On the other hand, behavioral, physiological, and anatomical data indicate that up- and down-training are not mirror images of each other, but rather depend on different mechanisms (reviewed in Wolpaw 1997, 2001). This suggested that maintenance of an H-reflex increase might not show the same dependency on descending spinal cord pathways as does maintenance of an H-reflex decrease.

METHO DS

Subjects were 22 female Sprague-Dawley rats weighing 200–300 g at the beginning of the study. All procedures followed 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 protocols for chronic electrode implantation, H-reflex conditioning in freely moving rats, and spinal cord pathway transections are described in detail elsewhere (Chen and Wolpaw 1995, 1997, 2002; Chen et al. 2001b, 2002) and are only summarized here.

Each rat was placed under general anesthesia [ketamine HCl, 80 mg/kg, administered intraperitoneally (ip); xylazine, 10 mg/kg, ip] and implanted with long-term nerve-stimulating and EMG recording electrodes in the right leg. To elicit the soleus H-reflex, a nerve-stimulating cuff encircled the right posterior tibial nerve just above the branches to the triceps surae muscles. To record soleus EMG activity, a pair of fine-wire electrodes were placed in the right soleus muscle. The Teflon-coated wires from the cuff and the muscle passed subcutaneously to a connector plug on the skull.

Data collection began ≥25 days later. Throughout data collection, each animal lived in a standard rat cage with a flexible cable attached to the skull plug. The cable, which allowed the animal to move freely in the cage, carried the wires from the electrodes to an electronic commutator above the cage, from which they passed to an EMG amplifier and a stimulator. All animals had free access to water and to food, except that during H-reflex up-training they obtained food primarily as described below. A computer monitored soleus EMG continuously and triggered the nerve cuff stimulus. If the absolute value (i.e., equal to the full-wave rectified value) of background (i.e., ongoing) EMG remained in a defined range for a randomly varying 2.3- to 2.7-s period, a 0.5-ms stimulus pulse was given through the cuff. Its amplitude was initially set just above the M-response threshold, and from then on was automatically adjusted after each stimulus to maintain stable M-response size (typically about 2–3% of Mmax) throughout data collection. During its normal activities, the animal typically fulfilled the background EMG requirement, and thus received the nerve cuff stimulus, 2,600–9,000 times per day. Each trial’s H-reflex size was calculated as the average EMG amplitude (measured as absolute value) for the H-reflex interval (typically 5.5–9.0 ms after the stimulus) minus the average background EMG amplitude, and was expressed in units of average background EMG amplitude. In the control mode, the computer simply measured EMG for 50 ms after stimulation and determined H-reflex size. In the HRup (i.e., up-training) mode, it also gave a reward (a 20-mg food pellet) 200 ms after the stimulus if the EMG amplitude in the H-reflex interval exceeded a criterion value (Chen and Wolpaw 1995).

Spinal cord pathway transection was performed by electrocautery as previously described in detail (Chen and Wolpaw 1997, 2002; Chen et al. 2001b, 2002). Briefly, the rat was anesthetized as for electrode implantation, a one-vertebra dorsal laminectomy at T9 exposed the dura, the rat was placed in a stereotaxic frame, and the cord was visualized with a dissection microscope. Each rat received one of three transections: right lateral column (i.e., including rubrospinal, vestibulospinal, and reticulospinal tracts) (LC rats); bilateral main CST (i.e., located in the base of the dorsal column) (CST rats); or bilateral DA (i.e., located in the dorsal column dorsal to the main CST) (DA rats) (Chung et al. 1987; Cliffer and Giesler 1989; Holstege and Kuypers 1987; Patterson et al. 1989, 1990; Paxinos and Watson 1986; Smith and Bennett 1987; Tracey 1995; Zemlan et al. 1978, 1979). The cauterizer was activated in brief pulses to minimize thermal damage to adjacent tissue. For LC rats, the lateral half of the right side of the spinal cord was transected. For CST rats, 2 approaches were used. In the lateral approach (4 rats), the cauterizer was mounted in a micro-manipulator 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. This was calculated to produce a transection track 1.5 mm long and about 0.5 mm wide in the transverse plane and including the dorsal horn of the left side and the main CST of both sides. In the dorsal approach (3 rats), transection extended 0.4 mm to either side of the midline and 1.1 mm into the spinal cord dorsal surface, and thus included both the DA and the CST on both sides. 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, and thus cut the DA bilaterally while sparing the CST. At T9, the descending tracts in the LC, the main CST, and the DA are mainly or exclusively ipsilateral to the leg they innervate (Tracey 1995), so that the effects on H-reflex conditioning of ipsilateral and bilateral transections should be comparable. CST and DA transections were bilateral because a transection that was both complete and exclusively ipsilateral was not technically feasible.

After transection, the site was rinsed with saline and covered with Durafilm to minimize connective tissue adhesions to the dura, and the muscle and skin were sutured in layers. The rat was put under a heating lamp and given an analgesic (Demerol, 0.2 mg, administered intramuscularly). Once awake, it received a 2nd dose of analgesic and returned to its cage to continue data collection. Care in the days immediately after transection included analgesia, antibiotics, bladder expression, and food supplementation as previously described in detail (Chen and Wolpaw 1997, 2002; Chen et al. 2001b, 2002). Bladder function returned within several days, and locomotion returned to normal or nearly normal within 10 days.

Figure 1A shows the experimental protocol. Rats were first exposed to the control mode for 20 days to determine control H-reflex size. They were then exposed to the HRup mode for 50 days. Rats that achieved an H-reflex increase [defined as an increase of ≥20% over initial size for days 41–50 of HRup exposure (Chen and Wolpaw...
1995; Chen et al. 2002; Wolpaw et al. 1993] then received an LC (5 LC rats), a CST (7 CST rats), or a DA (5 DA rats) transection and continued up-training for another 50 days (i.e., days 51–100 of HRup exposure). Initial H-reflex size (i.e., final 10 days in control mode) did not differ significantly among the 3 groups \( P > 0.91 \) by ANOVA. In all 3 rat groups, background EMG amplitude and M-response size remained stable over the entire period of study.

To determine the effects of LC, CST, and/or DA transection and of continued up-training on the H-reflex increase, we compared the final H-reflex sizes (i.e., average H-reflex sizes for days 91–100) of the rats in the 3 groups (i.e., LC rats, CST rats, and DA rats) to their H-reflex sizes just before transection (i.e., H-reflex size for days 41–50) by one-way ANOVA. H-reflex results are presented as means ± SE.

At the end of study, each rat was killed with an overdose of sodium pentobarbital (ip) and perfused through the heart with saline followed by 4% paraformaldehyde in 0.1 M phosphate buffer. 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 excised and weighed. The spinal cord was removed, and blocks encompassing the spinal cord were embedded in paraffin and weighed. The spinal cord was removed, and blocks encompassing the spinal cord were embedded in paraffin and weighed. The spinal cord was removed, and blocks encompassing the spinal cord were embedded in paraffin and weighed.

**RESULTS**

**Up-training of the H-reflex**

Over the initial 50 days of up-training, 17 of the 22 rats (i.e., 77%) achieved an H-reflex increase [i.e., defined as an increase to ≥120% of the initial value for days 41–50 of up-training (Chen and Wolpaw 1995; Chen et al. 2002)]. In the remaining 5 rats, the H-reflex remained within 20% of its initial value. This success rate is comparable to that of our previous studies in which up-training was successful in 35 out of 43 normal rats (i.e., 81%) (Carp et al. 2001; Chen and Wolpaw 1995, 1996; Chen et al. 1999, 2002) \( P > 0.7 \), Fisher exact test). In these 17 rats, H-reflex size for days 41–50 was 168 ± 12% of its initial value. These rats were then given an LC (5 LC rats), a CST (7 CST rats), or a DA (5 DA rats) transection. All 17 then continued under the HRup mode for another 50 days.

**Spinal cord pathway transections**

As in previous studies (Chen and Wolpaw 1997, 2002; Chen et al. 2001b, 2002), rats showed a transient hindlimb paralysis immediately after transection (both hindlimbs for CST and DA rats and right only for LC rats). This deficit abated over several days. For all rats, locomotion about the cage appeared normal or nearly normal within 3–13 days. Body weight fell 3–11% in the 1st wk after transection and then regained its pret transection level over 1–5 wk. For all rats, weight increased from 268 ± 33 g (mean ± SD) at the time of transection to 380 ± 56 g at the time of perfusion. Soleus muscle weights (measured as percentage of body...
TABLE 1. Average percentage of right LC, CST, and DA remaining in LC, CST, and DA transected rats

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<tr>
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<th>LC Rats</th>
<th>CST Rats</th>
<th>DA Rats</th>
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<tr>
<td>Right LC</td>
<td>4 (0–11)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Right CST</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Right DA</td>
<td>85 (25–100)</td>
<td>18 (0–80)</td>
<td>20 (0–48)</td>
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For those values that differ across the rats in the group, the range is shown in parenthesis. Transections: CST, corticospinal tract; DA, dorsal column ascending tract; LC, lateral column.

weight) were symmetrical and did not differ significantly from those of intact rats.

As Fig. 1B illustrates, tissue loss at the lesion epicenter in LC and DA rats was largely confined to the targeted tracts, whereas tissue loss in CST rats included much of the right DA in addition to the entire right CST. Table 1 summarizes the ipsilateral results for each rat group. LC rats retained none or very little of the right LC, all of the right CST, and, except for one rat, all of the right DA; CST rats retained all of the right LC, none of the right CST, and a small amount of the right DA; and DA rats retained all of the right LC and CST and a small amount of the right DA. [Contra]laterally, as expected from the transection method, CST rats retained none of the left CST and DA rats retained all of the right LC and CST and a small amount of the right DA; whereas tissue loss in CST rats included much of the right DA in addition to the entire right CST. Table 1 summarizes the remaining in LC, CST, and DA transected rats.

Figure 2A summarizes the H-reflex results for the LC (5 rats), CST (7 rats), and DA (5 rats) groups. At the end of the first 50 days of up-training (i.e., days 41–50) just before transection, H-reflex size had reached 168 ± 12% of its initial value (156 ± 15% for LC rats, 171 ± 18% for CST rats, and 177 ± 30% for DA rats). After transection and 50 more days of training (i.e., days 91–100), H-reflex size was 197 ± 19% of its initial value (191 ± 26% for LC rats, 185 ± 33% for CST rats, and 219 ± 44% for DA rats). At neither time did H-reflex size differ significantly among LC, CST, and DA rat groups (P > 0.78 for effect of group by ANOVA).

As the Fig. 2A expansion shows, H-reflex size in all 3 groups increased in the first 1 to 2 days after transection (P values of <0.01, <0.05, and <0.01 for LC, CST, and DA rats, respectively, for day 51 vs. day 50 by paired t-test) and returned to its pretransection value by days 3–4 after transection. This transient increase has been noted in earlier studies after midthoracic LC, CST, DA, or combined CST and DA transection in naive or conditioned rats. It appears to be a nonspecific effect of the surgery and/or general anesthesia (Chen and Wolpaw 2002; Chen et al. 2001b).

Beyond this transient effect, neither LC, CST, nor DA transection seemed to have any impact on H-reflex size. The H-reflex increase achieved in the first 50 days remained and even grew larger through the 2nd 50-day period of up-training. This further increase from the values for days 41–50 was
Discussion

None of the 3 transections—LC, main CST, or DA—abolished an H-reflex increase achieved in response to the up-training protocol. Although the LC and DA transections were quite specific, involving little damage to other ipsilateral pathways, the CST transections also destroyed 20–100% of the ipsilateral DA. Nevertheless, in light of the finding that none of the transections abolished the H-reflex increase, the implication is still clear: once an H-reflex increase has been achieved, the main CST, like the LC or DA, is not needed to maintain it. Furthermore, the fact that the increase persisted in those CST rats that also lost much or all of the left (i.e., contralateral) LC suggests that the left LC, which may project to right soleus motoneurons (Jankowska et al. 2003), is also not needed for maintenance of an increase.

The data also suggest that the H-reflex continues to increase during the 50 days after the transection. Although continued up-training is not surprising in LC or DA rats, given that these transections do not impair up-training, it is unexpected in CST rats, in that CST transection does prevent up-training (Chen et al. 2002). However, the continued increase has an alternative explanation in the CST rats, and in the LC and DA rats as well. LC or DA transection in naive (i.e., unconditioned) rats is associated with a modest long-term increase in the H-reflex (Chen et al. 2001b). Whereas CST transection itself has no long-term effect on H-reflex size (Chen et al. 2001b), the CST transections of the present study included most or all of the DA. Thus in all 3 groups, the slight increase over days 51–100 could represent a direct effect of LC or DA transection. However, the modest amplitude and gradual development (i.e., over 3–4 wk) of this direct effect (Chen et al. 2001b) imply that it cannot account for the preservation of the H-reflex increase achieved in the 1st 50 days of up-training. This preserved increase was much larger than the increase associated with DA or LC transection in naive rats. Furthermore, it was present immediately after LC, CST, or DA transection; it did not take 3–4 wk to develop.

Previous studies of the effects of pathway transections showed that the main CST is needed for acquisition of an H-reflex increase or decrease and for maintenance of an H-reflex decrease, whereas the ipsilateral LC and the DA are not needed (Chen and Wolpaw 1997, 2002; Chen et al. 2002). These studies are consistent with evidence that conditioning of the SSR is impaired in cerebrovascular accidents that damage the sensorimotor cortex (Segal 1997). They imply that the CST, in addition to its well-recognized role in the immediate fine control of distal movements (Cheney et al. 1991; Darian-Smith et al. 1999; Davidoff 1990; Porter and Lemon 1993), exerts long-term adaptive control over spinal reflex strength. In the context of these findings, the present results are unexpected because they show that a conditioned H-reflex increase, once established, no longer requires the main CST. It remains possible that maintenance of an H-reflex increase requires pathways in the ventral column, such as the minor CST (Brosamle and Schwab 1997), but this possibility has not yet been evaluated.

The contrast between the maintenance requirements of H-reflex increase and decrease adds to the evidence that up-training and down-training are not mirror images of each other but rather depend on different spinal mechanisms. H-reflex conditioning causes plasticity at multiple sites in the spinal cord (Wolpaw 1997; Wolpaw and Tennissen 2001). Although the relationship of some of these changes to H-reflex change is uncertain, it appears that H-reflex decrease is associated with motoneuron and motor unit plasticity and reflects a positive shift in motoneuron firing threshold, whereas H-reflex increase is associated with plasticity elsewhere in the spinal cord and may reflect changes in interneurons conveying group I homonymous (and synergist) input to the motoneuron (Carp and Wolpaw 1994, 1995; Feng-Chen and Wolpaw 1996; Halter et al. 1995; Wolpaw and Tennissen 2001).

The present results should also be considered in the context of other data concerning the persistence of conditioning. In monkeys, the reflex asymmetry produced by up-training or down-training persists under deep anesthesia for ≥3 days after complete spinal cord transection (Wolpaw and Lee 1989). This relatively short-term result is consistent with the results in up-trained or down-trained rats at a similar point after transection of the ipsilateral LC, the CST, or the DA. In rats and monkeys switched from up-training to down-training or vice versa, the reflex change induced by the 2nd training mode occurs gradually, following a course comparable to that found when that mode follows the control mode in a previously unconditioned rat (Chen and Wolpaw 1996; Wolpaw 1983). The extensive evidence that up-training and down-training have different mechanisms implies that reversal of training by switching to the opposite mode reflects the addition of new plasticity rather than the elimination of previous plasticity. In this light, the reversal data are also compatible with the present finding that maintenance of up-training, unlike maintenance of down-training (Chen and Wolpaw 2002), does not require the main CST.

Perhaps most interesting is the apposition of these new data with the effects in monkeys of simply discontinuing up-training or down-training of the SSR once it has occurred (Wolpaw et al. 1986). When this is done, SSR increase gradually disappears with a half-life of about 17 days, whereas SSR decrease persists unchanged for ≥4 wk. These results were considered consistent with extensive clinical and laboratory evidence that the normal long-term effect of cortical influence is suppression of spinal reflexes (Brodal 1981; Joynt and Griggs 2000). In this light, up-training might be expected to disappear gradually when the reward contingency is removed. The fact that it does not disappear in the LC and DA rats of the present study is most probably attributable to the continuation of the reward contingency and the preservation of the main CST. In contrast, the fact that it does not disappear in the CST rats could be attributed to the fact that the loss of an increase is not a passive phenomenon, but rather depends on an active process of reflex suppression (comparable to the process responsible for down-training) that requires the CST.

The fact that acquisition of H-reflex up- or down-training appears to require only the CST implies that H-reflex training might be used to modify reflex function in patients with spinal cord injuries (or other supraspinal or spinal disorders) that
spare the CST. It might thereby contribute to restoration of function. Furthermore, once methods for promoting regeneration of injured spinal cord pathways are available, H-reflex conditioning might be particularly useful as a means for reeducating reconnected spinal cord circuitry, that is, for reestablishing satisfactory spinal reflex patterns. To evaluate these exciting possibilities, current studies are exploring the effects of H-reflex conditioning on locomotion in normal rats and in rats with spinal cord injuries (Chen L et al. 2003a; Chen XY et al. 2003b; Chen Y et al. 2003c).

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DISCLOSURES
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