Plasticity in the Distribution of the Red Nucleus Output to Forearm Muscles After Unilateral Lesions of the Pyramidal Tract

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Belhaj-Saīf, Abderraouf and Paul D. Cheney. Plasticity in the distribution of the red nucleus output to forearm muscles after unilateral lesions of the pyramidal tract. J. Neurophysiol. 83: 3147–3153, 2000. It has been hypothesized that the magnocellular red nucleus (RNm) contributes to compensation for motor impairments associated with lesions of the pyramidal tract. To test this hypothesis, we used stimulus triggered averaging (StTA) of electromyographic (EMG) activity to characterize changes in motor output from the red nucleus after lesions of the pyramidal tract. Three monkeys were trained to perform a reach and prehension task. EMG activity was recorded from 11 forearm muscles including one elbow, five wrist, and five digit muscles. Microstimulation (20 μA at 20 Hz) was delivered throughout the movement task to compute StTAs. Two monkeys served as controls. In a third monkey, 65% of the left pyramidal tract had been destroyed by an electrolytic lesion method five years before recording. The results demonstrate a clear pattern of postlesion reorganization in red nucleus–mediated output effects on forearm muscles. The normally prominent extensor preference in excitatory output from the RNm (92% in extensors) was greatly diminished in the lesioned monkey (59%). Similarly, suppression effects, which are normally much more prominent in flexor than in extensor muscles (90% in flexors), were also more evenly distributed after recovery from pyramidal tract lesions. Because of the limited excitatory output from the RNm to flexor muscles that normally exists, loss of corticospinal output would leave control of flexors particularly weak. The changes in RNm organization reported in this study would help restore function to flexor muscles. These results support the hypothesis that the RNm is capable of reorganization that contributes to the recovery of forelimb motor function after pyramidal tract lesions.

INTRODUCTION

The direct pyramidal projection from motor cortex to motoneurons in primates is most well-developed for control of distal muscles (e.g., Hepp-Reymond 1988; Porter and Lemon 1993; Wiesendanger 1981). In fact, many early studies of motor behavior after pyramidal tract lesions revealed severe deficits in movements at distal joints (Chapman and Wiesendanger 1982; Hepp-Reymond et al. 1974; Lawrence and Kuypers 1968a; Schwartzman 1978; Tower 1944). Distal movement impairment is most severe when the pyramidal tract lesion is complete (Chapman and Wiesendanger 1982; Lawrence and Kuypers 1968a; Schwartzman 1978). However, several weeks postlesion, monkeys showed considerable recovery although digit movements remained clumsy. On the basis of their studies, Lawrence and Kuypers (1968a,b) suggested that this recovery could be mediated by rubrospinal neurons. Supporting this view was the fact that arm and hand movements in monkeys with combined lesions of the pyramidal tract and the rubrospinal tract were severely impaired and there was little recovery even after extensive postoperative training.

There are a number of similarities between corticospinal and rubrospinal neurons (Cheney et al. 1991a; Fetz et al. 1989). Anatomic and electrophysiological studies show that in primates corticospinal and rubrospinal neurons make monosynaptic connections with motoneurons of the cervical and lumbar spinal cord (Holstege et al. 1988; Humphrey et al. 1984; Mewes and Cheney 1991; Phillips and Porter 1977; Porter and Lemon 1993; Ralston et al. 1988; Shapovalov et al. 1971). The axons of both the lateral corticospinal and rubrospinal systems travel in the lateral funiculus of the spinal cord and influence both distal and proximal muscles of the forelimb, although the strongest effects are on distal muscles (Belhaj-Saīf et al. 1998; Horn et al. 1993; McKiernan et al. 1998; Miller et al. 1993). Moreover, nearly half of the cortical neurons tested in relation to a reach and prehension task simultaneously facilitated both distal (wrist and digits) and proximal (elbow and shoulder) muscles (McKiernan et al. 1998). These similarities, together with the work of Lawrence and Kuypers (1968a,b) lend support to the notion that the red nucleus may be capable of restoring motor function lost as a result of damage to the corticospinal system associated with lesions of the pyramidal tract.

However, if the rubrospinal system is involved in recovery of motor function that was lost as a result of damage to the corticospinal system, rubrospinal neurons should show appropriate changes in synaptic output organization and/or functional activity during movement. This is particularly true in view of the fact that, despite the similarities of the two systems, the rubrospinal system exhibits a very prominent extensor preference in the distribution of excitatory output effects that is not characteristic of the corticospinal system (Belhaj-Saīf et al. 1998; Gibson et al. 1985; Mewes and Cheney 1991, 1994; Miller et al. 1993). Our goal in this study was to examine the organization of red nucleus output after unilateral pyramidalotomy in the monkey. We were most interested in identifying changes in organization that might underlie motor recovery.
Our results revealed a remarkable reorganization of rubrospinal output after recovery from pyramidal tract lesions in which the normal extensor preference was largely lost in favor of a distribution more closely matching that of the corticospinal system.

METHODS

Data were collected from three male rhesus monkeys (*Macaca mulatta*, age 6–10 yr). At the time of recording, the control animals weighed 11 and 11.2 kg and the lesioned animal weighed 11.5 kg. The animals were placed in a primate chair with a padded restraint for the left forearm. The right arm was allowed freedom of movement. Each monkey was trained to perform a reach and prehension task. During this task, the monkey begins by resting its hand on a home-plate device. After a variable time delay, the monkey reaches forward to a cylindrical well positioned at eye level. The monkey retrieves a food pellet (94 mg) from the well, carries the pellet to its mouth, and then returns its hand to home plate. The task could be made more or less difficult by changing the diameter of the target cylinder (16 to 47 mm). This task was selected because it engages the activity of both distal and proximal muscles as functional synergies for producing coordinated multijoint movements.

After training was complete, a recording chamber and EMG electrodes were implanted in each monkey. For all implant surgeries, the monkeys were tranquilized with ketamine (10 mg/kg) and anesthetized with isoflurane gas. Surgeries were performed using full sterile procedures in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. Postoperatively, monkeys received prophylactic antibiotics and analgesic medication. All work involving the monkeys conformed to the procedures outlined in the Guide for the Care and Use of Laboratory Animals published by the U.S. Department of Health and Human Services, National Institutes of Health. Aspects of the methods used for EMG implants, chamber implants, localization of the red nucleus, and the methods for stimulus-triggered averaging and data analysis have been detailed in Belhaj-Saif et al. (1998).

Circular stainless steel recording chambers (22 mm inside diameter) were implanted in all three monkeys. The position of this chamber was at anterior 7 and angled at 30° from the sagittal plane as described in Belhaj-Saif et al. (1998). In one monkey, an additional medial chamber (14 mm inside diameter) was centered at anterior 3.5 and lateral 1.9. The position of this chamber allowed electrode penetrations into the pyramidal tract and the red nucleus. EMG activity was recorded from a total of eleven forearm muscles including an elbow flexor (brachioradialis, BR), five wrist muscles (extensor carpi radialis, ECR; extensor carpi ulnaris, ECU; flexor carpi radialis, FCR; flexor carpi ulnaris, FCU; and palmaris longus, PL), and five digit muscles (extensor digitorum communis, EDC; extensor digitorum 2.3, ED23; extensor digitorum 4.5, ED45; flexor digitorum superficialis, FDS; and flexor digitorum profundus, FDP).

Stimulus-triggered averaging procedures

Microstimuli (20 μA at 20 Hz) were applied during all phases of the movement. EMGs from 11 muscles of the forearm were rectified and digitized at a rate of 4 kHz and averages were compiled over a 60-ms epoch (20 ms before the trigger to 40 ms after it). Stimuli were counted only if the EMG activity in that epoch was ≥5% of the full scale of a given signal. This criterion was chosen to avoid counting epochs containing little or no EMG activity (McKiernan et al. 1998). Each average was based on at least 500 trigger events. Our stimulus triggered averaging (StTA) technique is further documented in Belhaj-Saif et al. (1998) and Cheney et al. (1991b).

Lesion procedure

With the monkey under ketamine anesthesia, a lesion electrode penetration was made through the medial chamber. The penetration followed a vertical trajectory running parallel to the midline. The pyramidal tract lesion was made electrolytically using a radio frequency lesion maker (RFG4-A, KOPF Instruments). Two sets of lesions were made 26 days apart. The first set consisted of three lesions and the second set consisted of two lesions at a site ~1 mm rostral to the first set of lesions. Each lesion was made at a different depth. At each site, electrical stimulation was applied to confirm the position of the electrode in the pyramidal tract. Evoked movements of the digits and/or wrist were considered to be evidence of placement in the pyramidal tract. Once proper placement was confirmed, electrode tip temperature was raised to 65–70° Celsius and maintained for 1 min. After each lesion, the response to electrical stimulation was retested. After the first set of lesions, no response was obtained even with an intensity 19× the prelesion threshold. On day 26, a second set of lesions was made. The extent of damage was evaluated by stimulation after the second lesion. Weak movements of the wrist and digits were evoked at 15× the prelesion threshold.

Histology and behavioral data

In the monkey used for pyramidotomy, the lesion of the left pyramidal tract was 65% complete. Some fibers in both the medial and lateral parts of the tract were spared (Fig. 1A). Figure 1B shows camera lucida drawings that characterize the extent of degeneration of pyramidal tract axons at different levels of the medulla. The pre- and postpyramidal lesion behavioral data are presented in Fig. 1C. After the first set of lesions (day 0), we observed a clear impairment in arm movement with a large increase in performance time. However, the monkey showed relatively rapid recovery during the first seven days postlesion, achieving 75% of prelesion performance. This was followed by a more gradual recovery lasting for a period of three weeks after which performance was at prelesion control levels. An additional lesion introduced at this time produced only a small deficit in performance which was 80% of full recovery in 62 days. The final outcome was that the monkey recovered functional use of its hand, but finger movements during retrieval of food pellets remained clumsy and independent use of the digits was somewhat impaired. This is evident from Fig. 1D, which compares final postlesion performance (5 yr after the lesions) from the left hand (unlesioned) with that from the right hand (lesioned) for three different food well (cylinder) diameters. Pellet retrieval from cylinder 4 did not require independent use of the digits. In contrast, efficient pellet retrieval from cylinder 6 did require independent use of two digits. Pellet retrieval from cylinder 6 with the right hand required twice as much time as retrieval with the left hand (*P* < 0.001).

RESULTS

Data were collected from the left red nucleus in three monkeys (*Macaca mulatta*). Two were used as controls and one had a unilateral lesion of the left pyramidal tract. StTA data were collected five years after the lesion. Some of the data from the control monkeys was described in Belhaj-Saif et al. (1998). A total of 733 output effects on forearm muscle activity were obtained from 172 microstimulation sites in the magnocellular red nucleus (RNm) of the control monkeys; 555 (76%) were poststimulus facilitation effects (PSF) and 178 (24%) were poststimulus suppression effects (PSStS). In the lesioned monkey, 104 RNm microstimulation sites were tested yielding a total of 902 output effects; 753 (83%) were PSF effects and 149 (17%) were PSStS effects.

In the control monkeys, a large fraction of the stimulation...
sites (73%) produced a PSTF in at least one wrist muscle and one digit muscle, 25% of the sites produced effects in only digit muscles, and 2% in only wrist muscles. In contrast, the monkey with the pyramidal tract lesion showed a substantial increase in the number of stimulation sites that facilitated at least one digit and one wrist muscle (94%), and a decrease in the number of sites that facilitated only digit muscles (3%). The number of sites producing effects in only wrist muscles remained the same (3%).

Distribution of the poststimulus effects

Figure 2 shows the differences in distribution of PSTF and PSTS for the recorded muscles in the lesioned and control monkeys. This distribution shows that some muscles that were only weakly facilitated by the RNm in control monkeys became strongly facilitated in the lesioned monkey. This applies primarily to BR and flexor muscles of the digits and wrist. In fact, in control monkeys, <1% (4) of all PSTFs were in BR, 38% (210) in wrist muscles, and 61% (341) in digit muscles. The lesioned monkey showed a somewhat different distribution of PSTF effects: 9% (66) were in BR, 44% (332) in wrist muscles, and 47% (355) in digit muscles.

Most notable, however, were the changes in distribution related to flexors and extensors. In control monkeys, the number of PSTFs obtained in extensor muscles was much higher than that found in flexor muscles. Totaling all forelimb muscles, 92% of PSTFs were in extensor muscles whereas only 8% were in flexors (Fig. 3C). This bias in favor of extensors was similar for both wrist and digit muscles; 92% of wrist PSTFs (excluding BR) and 91% of digit PSTFs were in extensor muscles. If the analysis is limited to moderate and strong PSTFs (excluding weak PSTFs), the difference
in the number of PStFs between flexor and extensor muscles is even greater. In the lesioned monkey, this disparity in number of extensor and flexor PStF effects was greatly diminished; 54% of digit muscle PStFs and 63% of wrist muscle PStFs were in extensors (Fig. 3A). If only moderate and strong PStFs were considered, the number of PStF effects in extensors (58 and 69% in digit and wrist extensors, respectively) versus flexors (42 and 31% in digit and wrist flexors, respectively) showed a slightly greater extensor preference that was still less than in control monkeys (92 and 96% in digit and wrist extensors, respectively; 8 and 4% in flexors).

The distribution of PStS effects showed lesion-related changes in distribution that were the inverse of changes in PStF effects. In control monkeys, 90% of all PStS were in flexor muscles and only 10% were in extensor muscles (Fig. 3D). However, in the lesioned monkey, 65% of PStS were in flexor muscles; 35% were in extensor muscles.

**FIG. 2.** Distribution of poststimulus effects in pyramidal tract lesioned (left) and control (right) monkeys. Each graph represents the distribution of poststimulus facilitation effects (PStF; right) and poststimulus suppression effects (PStS; left) obtained from 11 muscles of the forearm. Diagonally filled bars on the right of each graph represent weak PStFs. BR, brachioradialis; PL, palmaris longus; FCU, flexor carpi ulnaris; FCR, flexor carpi radialis; ECU, extensor carpi ulnaris; ECR, extensor carpi radialis; FDS, flexor digitorum superficialis; FDP, flexor digitorum profundus; EDC, extensor digitorum communis; ED23, extensor digitorum 2,3; ED45, extensor digitorum 4,5.

**FIG. 3.** Distribution of PStF (A and C) and PStS (B and D) in extensor and flexor muscles of the wrist and digits in a monkey with unilateral pyramiotomy (A and B) and in control monkeys (C and D). Diagonally filled bars, flexor muscles; white bars, extensor muscles. Frequency of PStFs is higher in extensor muscles of control monkeys and reduced in the lesioned monkey; frequency of PStS is higher in flexor muscles of control monkeys and reduced in the lesioned monkey.
muscles and 35% were in extensor muscles (Fig. 3).

**TABLE 1. Latency and magnitude of PSTF effects**

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<tr>
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<th>Control Monkeys</th>
<th>PT Monkey</th>
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<tr>
<td></td>
<td>Onset latency</td>
<td>Magnitude</td>
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<td></td>
<td>(ms)</td>
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<tr>
<td>Wrist Flexors</td>
<td>7.5 ± 1.3*</td>
<td>30.9 ± 12.1</td>
</tr>
<tr>
<td>Wrist Extensors</td>
<td>8.3 ± 1.3*</td>
<td>32.6 ± 16.8*</td>
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<tr>
<td>Digit Flexors</td>
<td>9.2 ± 4.0</td>
<td>30.5 ± 10.1</td>
</tr>
<tr>
<td>Digit Extensors</td>
<td>7.8 ± 0.8</td>
<td>37.2 ± 22.3*</td>
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Data are based on moderate and strong Poststimulus facilitation effects (PStF). Values are means ± SD. PT, pyramidal tract. * Significantly different from the PT monkey values (P ≤ 0.05).

The results of this study demonstrate a reorganization, associated with unilateral lesion of the pyramidal tract, in the pattern of red nucleus–mediated output effects to forearm muscles. After recovery from a lesion that destroyed 65% of the pyramidal tract unilaterally, the strong extensor preference, which is a prominent characteristic of normal RNm output, was greatly diminished, leaving a more equal distribution of extensor and flexor facilitation. This change in RNm output organization is reflected in the following results: 1) in the pyramidal tract–lesioned monkey, 59% of PStF effects were in extensor muscles compared with 92% in unlesioned monkeys; 2) in the pyramidal tract–lesioned monkey, 65% of PStS effects were in flexor muscles compared with 90% in unlesioned monkeys; and 3) the number of facilitation effects in flexor muscles was increased. The increase in facilitation effects on flexor muscles was associated with a large increase in the number of RNm sites producing cofacilitation of extensors and flexors and a similar reduction in the number of sites producing facilitation of extensors only. Therefore, the transformation of RNm sites into sites that only facilitate flexors does not seem to occur; rather, it is most likely that sites previously yielding only extensor effects expanded their muscle fields to include effects on flexors. This pattern of reorganization may reflect the nature of the task the monkeys performed during recovery of motor function. Reach-and-prehension involves substantial periods of extensor and flexor muscle coactivation, which may have shaped the reorganization process in favor of cofacilitation.

The fact that the pyramidal tract lesion was incomplete may have contributed to the relatively rapid functional recovery of the contralateral hand. However, Chapman and Wiesendanger (1982) showed that the extent of digit function recovery 2–4 wk postlesion was not different in two monkeys in which the pyramidal tract sizes were 66 and 87%. In our study, it is noteworthy that even with one-third of the pyramidal tract spared, permanent deficits remained for digit function (Fig. 1D); this was evident when the monkey was required to use one or two digits to remove a food pellet from the smallest cylinder. It should also be pointed out that CNS plasticity probably occurs for lesions that are far from complete and that, in fact, this plasticity presumably contributes to recovery of function. Our results certainly support this point of view.

Why is an increase in facilitation effects on flexor muscles important to the recovery process after loss of corticospinal neurons? It is important to remember that normal corticospinal output is relatively evenly distributed between extensors and flexors, although the magnitude of postspike facilitation effects on extensor muscles from cortical cells is slightly greater than on flexor muscles (Cheney and Fetz 1985; Fetz et al. 1989; Kasser and Cheney 1985). On the other hand, output from the red nucleus shows a very heavy bias favoring extensor muscles. If the red nucleus was involved in compensating for loss of corticospinal neurons, this sparse capability for facilitation of flexor muscles might seriously limit the extent of functional recovery in flexor muscles. However, our results in fact demonstrate that motor recovery from pyramidal tract lesions is...
associated with an increase in the number of effects on flexor muscles. This plasticity presumably strengthens the output to flexor muscles in a way that contributes to recovery of motor function in these muscles and compensates for loss of corticospinal input. However, we cannot rule out a possible contribution of ipsilateral corticospinal axons and/or spared contralateral corticospinal axons to the recovery process. This interpretation is supported by the findings of Lawrence and Kaypers (1968a,b) that show that after lesions of the red nucleus in monkeys that had recovered from bilateral pyramidotomy, the fingers of the contralateral hand were held extended and the monkeys could not use their flexor muscles to grasp a piece of food.

The site of plasticity mediating the changes we observed is unclear at this time. Reorganization of the terminals of rubrospinal axons in the spinal cord is one possibility. Precedent for such plasticity exists in the work of Wolpaw (1987) and Wolpaw et al. (1993), who showed that the monosynaptic H-reflex could be modulated by operant conditioning techniques. In fact, monkeys could increase or decrease the amplitude of the H-reflex in the absence of any change in background EMG activity. In addition, Feng-chen and Wolpaw (1996) showed that H-reflex conditioning is accompanied by changes in motoneuron physiological properties as well as changes in synaptic terminals. However, some of the facilitation effects we observed, and all of the suppression effects, are probably mediated by spinal interneurons and the potential for plasticity in these circuits would certainly be greater.

The nature of neuronal activation that is caused by microstimulation raises an alternative possibility for the site of plasticity. It is likely that the predominant mode of neuronal excitation caused by cortical microstimulation is through synaptic inputs rather than direct stimulation of neuronal cell bodies (Cheney 1996; Porter and Lemon 1993). There is also evidence to support indirect activation of rubromotoneuronal (RM) cells by microstimulation (Cheney et al. 1991b). If microstimulation activates RM cells synaptically, the output effects observed in stimulus-triggered averages will reflect not only the muscle fields of the activated RM cells but also the distribution of activated afferent terminals within the red nucleus. Plasticity of the type found in the present study could result from a redirection of afferent inputs toward the RM cells that facilitate flexor muscles. Because the increase in flexor effects that we observed is largely due to an increase in sites producing cofacilitation of flexors and extensors and a reduction in sites producing facilitation of extensors only, the branching of axon terminals from extensor RM cells to flexor RM cells would provide the best explanation of our results. Such a reorganization of afferent input is supported by the work of Tsukahara (1985), who showed that corticorubral excitatory postsynaptic potentials (EPSPs) increased in association with lesions of the contralateral interpositus nucleus or upon a reversal of the nerves leading to extensor and flexor muscles. These changes were accompanied by the sprouting of axodendritic synapses from distal to proximal dendrites. Therefore, afferent inputs to the red nucleus are certainly capable of substantial feats of plasticity.

However, the large disparity between extensor and flexor facilitation that normally exists in the red nucleus demonstrates a paucity of flexor RM cells and places a limit on what a simple rearrangement of afferent input to RM cells could achieve. It seems unlikely that the plasticity of afferent inputs to RM cells, in the absence of any other changes, could fully explain our results. Testing the output of individual RM cells with spike-triggered averaging after recovery from pyramidal tract lesions should provide some insight into this issue.

Finally, it is important to emphasize that the observations in the present study were based on comparing data from two control monkeys with that from one monkey with a unilateral pyramidal tract lesion. We believe the data from the lesioned monkey are important in revealing, for the first time, a remarkable degree of reorganization in red nucleus output associated with pyramidal tract lesions.

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