Developmental plasticity of descending motor pathways

Hsiu-Ling Li1 and Curtis O. Asante2

1Department of Neuroscience, Columbia University, and 2Department of Physiology, Pharmacology and Neuroscience, The City College of The City University of New York, New York City, New York

Submitted 17 December 2010; accepted in final form 25 January 2011

JUVENILE ANIMAL BRAINS ARE HIGHLY PLASTIC BECAUSE REFINEMENT AND MATURATION OF THE CNS CONTINUES AFTER BIRTH. Thus, juvenile brain injury often triggers remodeling of the CNS, which may lead to functional recovery if the newly formed circuits are properly wired. For instance, it has been shown that juvenile rats receiving unilateral lesions of the sensorimotor cortex (SMC) can develop fairly normal grasping and reaching movements later in adulthood (Barth and Stanfield 1990; Hicks and D’Amato 1970). This functional recovery is attributed to the remodeling of the corticospinal system from the undamaged hemisphere (Barth and Stanfield 1990). While the mature corticospinal terminations predominantly innervate the contralateral side, unilateral brain damage in neonatal rats may induce aberrant sprouting of undamaged corticofugal projections to the ipsilateral side. Moreover, these atypical circuits are functional since intracortical microstimulation of the undamaged SMC elicits responses of ipsilateral limb muscles (Kartje-Tillotson et al. 1985). Undoubtedly, large-scale reorganization of the corticospinal system occurs to compensate for the functional loss after early brain injury. However, the organization of circuits that originate from the undamaged SMC and comprise connections with the motoneurons (MNs) of ipsilateral forelimbs, is still unclear.

In a recent issue of Journal of Neurophysiology, Umeda et al. (Umeda et al. 2010) performed a series of electrophysiological recordings to identify the descending pathways that relay motor commands to the affected forelimb muscles in hemidecorticated rats. They first determined that cervical segments C5–C7 were recorded. In control rats, a single pulse of pyramidal stimulation was comparably high on both contralateral (92.5%) and ipsilateral (89.4%) sides. Together, these results suggest that compensatory circuits from the undamaged pyramid act to activate ipsilateral MNs on the affected side. Interestingly, the average segmental latencies of contralateral and ipsilateral MNs in hemidecorticated rats were comparable to each other, but significantly shorter than those of their counterparts in control rats. Moreover, a high percentage of MNs from both sides of hemidecorticated rats exhibited very rapid responses with latencies less than 3.0 ms, whereas the MNs in control rats displayed a wide range of latencies. Based on the segmental latencies, several pathways are hypothesized to mediate the activation of ipsilateral MNs in injured rats. The monosynaptic pathway between the dorsal, lateral, and ventral components of the corticospinal tracts (CSTs) and segmental spinal neurons is known to have latencies from 0.3 to 0.9 ms (Alstermark et al. 2004). Furthermore, the authors speculate that the reticulospinal pathway has faster conduction velocity compared with CSTs, which could possibly evoke the responses of MNs within 0.3 ms. In contrast, the delayed responses with latencies longer than 0.9 ms could be mediated via the oligosynaptic connections from CSTs or extra-pyramidal tracts to spinal interneurons. These data suggest that both corticospinal and cortico-reticulo-spinal pathways might play a role in activating the ipsilateral MNs in hemidecorticated rats.

The authors next investigated to what extent the pyramidal excitation of ipsilateral MNs is relayed via the reticulospinal neurons in the brain stem by transecting the dorsal column at C2 to interrupt CST transmission in hemidecorticated rats. As expected, this treatment abolished both the field potential and

The ipsilateral, side. In contrast, stimulation of the undamaged pyramid of the hemidecorticated rats evoked comparable responses bilaterally, suggesting the emergence of compensatory corticospinal circuits that might mediate the functional recovery of injured rats.

The authors next asked whether these atypical projections are able to excite the ipsilateral MNs in hemidecorticated rats. Following single or repetitive pulses of pyramidal stimulation, the intracortical responses of the MNs located in spinal segments C5–C7 were recorded. In control rats, a single pulse of stimulation was not sufficient to elicit bilateral MN responses. However, repetitive stimulation evoked significant EPSPs in a high percentage of contralateral MNs (92.5%). It is estimated that 50–60% of the recorded MNs are deep radial (DR) MNs, which control the contraction of forelimb muscles via DR nerves. In contrast, the same protocol only induced modest responses from a smaller population of ipsilateral MNs (67.2%). In hemidecorticated rats, repetitive stimulation on the undamaged pyramid evoked significant EPSPs of MNs bilaterally. Moreover, the proportions of MNs responsive to the stimulation were comparably high on both contralateral (95.2%) and ipsilateral (89.4%) sides. Together, these results suggest that compensatory circuits from the undamaged pyramid act to activate ipsilateral MNs on the affected side.

The ipsilateral, side. In contrast, stimulation of the undamaged pyramid of the hemidecorticated rats evoked comparable responses bilaterally, suggesting the emergence of compensatory corticospinal circuits that might mediate the functional recovery of injured rats.

The authors next asked whether these atypical projections are able to excite the ipsilateral MNs in hemidecorticated rats. Following single or repetitive pulses of pyramidal stimulation, the intracortical responses of the MNs located in spinal segments C5–C7 were recorded. In control rats, a single pulse of stimulation was not sufficient to elicit bilateral MN responses. However, repetitive stimulation evoked significant EPSPs in a high percentage of contralateral MNs (92.5%). It is estimated that 50–60% of the recorded MNs are deep radial (DR) MNs, which control the contraction of forelimb muscles via DR nerves. In contrast, the same protocol only induced modest responses from a smaller population of ipsilateral MNs (67.2%). In hemidecorticated rats, repetitive stimulation on the undamaged pyramid evoked significant EPSPs of MNs bilaterally. Moreover, the proportions of MNs responsive to the stimulation were comparably high on both contralateral (95.2%) and ipsilateral (89.4%) sides. Together, these results suggest that compensatory circuits from the undamaged pyramid act to activate ipsilateral MNs on the affected side.

The authors next asked whether these atypical projections are able to excite the ipsilateral MNs in hemidecorticated rats. Following single or repetitive pulses of pyramidal stimulation, the intracortical responses of the MNs located in spinal segments C5–C7 were recorded. In control rats, a single pulse of stimulation was not sufficient to elicit bilateral MN responses. However, repetitive stimulation evoked significant EPSPs in a high percentage of contralateral MNs (92.5%). It is estimated that 50–60% of the recorded MNs are deep radial (DR) MNs, which control the contraction of forelimb muscles via DR nerves. In contrast, the same protocol only induced modest responses from a smaller population of ipsilateral MNs (67.2%). In hemidecorticated rats, repetitive stimulation on the undamaged pyramid evoked significant EPSPs of MNs bilaterally. Moreover, the proportions of MNs responsive to the stimulation were comparably high on both contralateral (95.2%) and ipsilateral (89.4%) sides. Together, these results suggest that compensatory circuits from the undamaged pyramid act to activate ipsilateral MNs on the affected side.
the excitation of MNs on the contralateral side following pyramidal stimulation. In contrast, the same protocol was still able to evoke EPSPs on ipsilateral MNs, despite a smaller magnitude. The latencies to evoke these residual responses (less than 3.0 ms) are similar to those before transection. Together, these data further confirm that both corticospinal and reticulospinal pathways could account for the excitation of ipsilateral MNs in hemidecorticated rats (Fig. 1). More importantly, disruption of CST transmission further suggested that the reticulospinal pathway might activate ipsilateral MNs efficiently within 0.3 ms via monosynaptic connections or with a longer delay via oligosynaptic connections (Fig. 1B). These findings are further supported by their unpublished data that direct stimulation on the medullary reticular formation could activate ipsilateral MNs efficiently.

Here, it is noteworthy that dorsal column transection at cervical level C2 is an effective way to eliminate the main component of the CST (dorsal CST), but this treatment does not disrupt the smaller components of the CST that travel down more lateral and ventral parts of the spinal cord. In addition, apart from CSTs, other prominent descending tracts such as rubrospinal and vestibulospinal pathways are also implicated in motor function. Importantly, these pathways would not have been affected by the dorsal column transection since their route to spinal cord gray matter is not via the dorsal column. It is therefore likely that although the effects obtained may be largely attributed to cortico-reticular-spinal pathways, one cannot discount the contribution of these other pathways. In fact, the authors did explore the possible involvement of rubrospinal tracts and propriospinal circuits in the functional recovery of hemidecorticated rats. However, their results by retrograde labeling have excluded these possibilities (unpublished data). Thus, future experiments will still be needed to test the role of other aforementioned pathways in mediating the motor recovery of hemidecorticated rats. However, compared with the high conduction velocity and efficiency of the direct cortico-reticulo-spinal pathway, it is likely that these pathways may only mediate delayed, rather than fast, excitation of ipsilateral MNs.

Nonetheless, this series of experiments has clearly demonstrated the importance of direct cortico-reticulo-spinal pathways in evoking fast responses of ipsilateral motor units and thereby promoting motor recovery after juvenile brain injury. In contrast, although less characterized in this study, the indirect cortico-reticulo-spinal pathways might also contribute to slow responses of ipsilateral MNs via spinal interneurons, including commissural interneurons. In fact, these ipsilateral cortico-reticulo-spinal pathways, although minor, are normally present in control rats (Fig. 1B). However, ipsilateral pyramidal stimulation alone rarely evokes any responses of ipsilateral MNs under physiological conditions.

Fig. 1. Hemidecortication-induced plasticity of corticospinal (A) and reticulospinal (B) pathways. A: in control rats (left), mature corticospinal tract (CST) projections predominantly innervate spinal interneurons (IN) on the contralateral side. However, in juvenile hemidecorticated rats (right), undamaged CST projects bilaterally (blue) and therefore can mediate the activation of both ipsilateral (red) and contralateral (blue) motor neurons (MN) following pyramidal stimulation. B: under physiological conditions (left), the cortico-reticulo-spinal pathways are not effective enough to activate ipsilateral MNs (dashed lines). However, the effectiveness of these pathways is strengthened (thick line) after hemidecortication (right) and thereby sufficient to mediate both fast and slow excitation of ipsilateral MNs via monosynaptic (red) and oligosynaptic (black) connections, respectively.
It is therefore likely that the synaptic efficacy of these pathways is augmented in developing motor circuits after hemidecortication (Fig. 1B). One possible mechanism is that these ipsilateral corticoreticular fibers may expand their synaptic territories in the absence of their contralateral counterparts during development and thereby enhance the efficacy of transmission. Alternatively, hemidecortication may cause changes in the microenvironment of both brain and spinal cord, such as the expression levels of neurotransmitters and growth factors. Neurotransmitters, such as serotonin and nor-adrenaline, have been shown to modulate the activation of commissural interneurons and may thereby strengthen the indirect cortico-reticulo-spinal pathways (Jankowska and Edgley 2006). Moreover, it has been shown that reticulospinal tracts express high levels of TrkB and TrkC receptors and thus the outgrowth and the synaptic strength of reticulospinal tracts may be influenced by changes in the levels of BNDF and neurotrophins (King et al. 1999). Together, ipsilateral cortico-reticulo-spinal pathways may provide an alternate pathway that replaces the functions of damaged motor circuits after juvenile brain injury. In fact, treatment with the potassium channel blocker, 4-AP, has been shown to enhance the effectiveness of these cortico-reticulo-spinal pathways to activate the ipsilateral MNs (Jankowska and Edgley 2006). Clinical use of 4-AP has also been proven beneficial for the motor deficits associated with multiple sclerosis and after various spinal cord injuries (Nashmi and Fehlings 2001). For future studies, it will be of clinical importance to better understand the mechanisms underlying the enhancement of ipsilateral cortico-reticulo-spinal pathways for the treatment of motor deficits associated with early brain injury, such as cerebral palsy.

While the reticulospinal pathways are functionally important in hemidecorticated rats, CSTs appear to be the major locus of remodeling following juvenile brain damage across animal species. Developing CST projections reach the mature pattern after birth (Martin et al. 2007). This maturation is thought to be driven by primary motor (M1) cortical activity. Thus, early brain damage often leads to the rewiring of developing CSTs. Intuitively, this injury-induced plasticity would be expected to be beneficial. However, studies in both cats and humans have raised the question as to whether the anatomical or synaptic plasticity associated with early brain injury are always reparative (Eyre 2007; Martin et al. 2007). Unilateral inactivation of M1 activity in kittens leads to hemiparesis that correlates with a paucity of CST projections from the damaged hemisphere, whereas CST projections from the undamaged side send exuberant projections bilaterally (Friel and Martin 2007). Accordingly, the CSTs in hemiplegic cerebral palsy (CP) patients no longer respond to transcranial magnetic stimulation (TMS) on the plegic side, yet TMS of the intact side results in bilateral activation (Eyre 2007). The presence of bilateral CST projections in hemiplegic cats and CP patients is similar to the undamaged CST pathways, which activate bilateral MNs in hemidecorticated rats (Fig. 1A). However, the hemiplegic cats are still unable to use their forelimbs even in the presence of atypical ipsilateral CST projections in the plegic side. Moreover, clinical evidence has further suggested that these aberrant projections might aggravate the motor deficits associated with the hemiplegic CP patients. Loss of responses from the injured cortex and maintenance of fast ipsilateral projections from the unaffected cortex is strongly associated with a poor outcome in hemiplegic CP patients. A possible explanation for this discrepancy is that these aberrant projections, at the time of brain injury, fail to establish functional linkages with the cortical and subcortical network required for effective arm and hand control. Furthermore, these ipsilateral projections could even displace the surviving projections from the injured hemisphere and cause a “dominant negative” effect that leads to a gradual loss of residual motor skills. Thus, injury-induced plasticity may be reparative only if the newly formed circuits are functionally integrated into the CNS; otherwise, it may only aggravate the progression of motor impairments.

In summary, Umeda et al. (2010) demonstrate the importance of corticospinal and reticulothalamic pathways in mediating the functional recovery of reaching and grasping ability in hemidecorticated rats (Fig. 1). Of particular interest is that the authors have underscored an alternative pathway, the cortico-reticulo-spinal pathway, in mediating the fast excitation of ipsilateral MNs for functional recovery.

ACKNOWLEDGMENTS
The authors thank Drs. Kathleen Friel and Ben S. Huang for comments.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES