Systems Descending from the Cortex and Brain Stem: Functional Recovery Following Damage

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Contents

Abstract

Complex activation patterns of forelimb muscles during skilled reach and grasp movements are generated by the combined activity of a variety of descending pathways from supraspinal centers to the spinal motoneurons. The corticospinal tract originating from the primary motor cortex is directly connected to motoneurons innervating forelimb muscles and are considered to be crucial for the dexterous digit movements, while other descending inputs mediated by the brainstem nuclei such as red nucleus (rubrospinal tract), brainstem reticular formation (reticulospinal tract), and propriospinal neurons additionally contribute to various aspects of the skilled forelimb movements. These pathways are also involved in the compensation of the impaired motor functions for the recovery after injury to the corticospinal tract such as the stroke and spinal cord injury. There, these various descending pathways dynamically interact with each other depending on the location and extent of the injury.

Keywords

Corticospinal tract · Rubrospinal tract · Reticulospinal tract · Propriospinal tract · Dexterous hand movement · Recovery · Neurorehabilitation

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Brief History

Hans Kuypers made seminal series of neuroanatomical and behavioral studies in the 1960s–1970s and established the concepts of descending motor control by corticospinal tract (CST) and a variety of brainstem-spinal pathways. Notably, he classified the pathways into the ventromedial and lateral systems. His studies showed that the rubrospinal tract (RuST), which belongs to the lateral system as well as the CST, plays a major role in the compensatory process of impaired distal movements after lesion of the CST, while the reticulospinal tract (ReST) primarily controls the proximal muscles for the posture adjustment. The function of the RuST has been studied in cats and monkeys until the 1980s. In addition, after the 1990s, the roles of the (ReST) and propriospinal neurons (PNs) in compensation of the distal hand muscles after lesion of the CST have been clarified. Thus, the lateral/ventromedial system dichotomy has been updated. More recently, after the 2010s, the introduction of a variety of circuit manipulation techniques both in rodents and non-human primates revealed a novel and more detailed picture on the functions on a variety of descending motor systems.

Neural Mechanisms Underlying the Motor Recovery from CST Injuries

1. *Descending Motor Pathways for the Control of Skilled Forelimb Control*

Motor commands that drive skeletal muscle activity are transmitted from a variety of supraspinal centers to the spinal cord via several descending pathways that run in parallel. According to the location of descending axons in the spinal white matter and the target zone in the spinal gray matter, Kuypers and colleagues classified the descending pathways into two major categories: the ventromedial system and lateral system (Kuypers et al. 1962). The descending axons of the lateral system descend in the dorsolateral funiculus and terminate in the lateral part of the intermediate zone and lateral motor nuclei which innervate distal muscles of extremities. The CST and RuST belong to the lateral system. The CST originates mainly from the primary motor cortex (M1) and other motor-related cortices such as premotor and supplementary motor areas and descends through the internal capsule, cerebral peduncle, brainstem pyramid on the same side and about 90% of them crosses the midline at the most caudal part of the brainstem (pyramidal decussation), and descend in the dorsolateral funiculus of the spinal cord. In higher primates including humans, the axons from the M1 terminate mainly to the laminae VI, VII, and IX of the spinal gray matter and partly to the lamina VIII of the contralateral side after crossing the midline again. However, axons from other areas than M1 lack projection to lamina IX. The remaining 10% descend either in the ventromedial funiculus or dorsolateral funiculus ipsilateral to the cells of origin. In addition, the RuST, originating from the magnocellular subdivision of the red nucleus also terminate in laminae VI, VII, and IX in macaque monkeys. Thus, there are a number of similarities between the CST

and RuST neurons from an anatomical point of view. However, electrophysiological studies also revealed some functional differences between the two tracts; the RuST exhibits a prominent extensor preference in the distribution of excitatory output effects, which is not the case for the CST. Despite such differences, the lateral system is supposed to be primarily involved in the control of the distal portion of extremities, especially skilled forelimb movements such as reaching and grasping (Fig. 1a). In contrast, the axons of the ventromedial system descend in the ventral funiculus of the ventral portion of the lateral funiculus and terminate in the ventromedial portion of the spinal gray matter. The ReST, originating from the pontomedullary reticular formation, vestibulospinal tracts, tectospinal tract, and interstitiospinal tract which originates from the interstitial nucleus of Cajal in the mesencephalon, belong to this category. In addition, spinal projection originating from the fields of Forel [or the rostral interstitial nucleus of medial longitudinal fasciculus (riMLF)] at the mesodiencephalic junction, are also involved in this category (Isa and Sasaki 2002; Fig. 1b). All these pathways have been considered to control voluntary movements of proximal muscles such as the head, trunk and proximal part of the limbs, locomotion, and posture. However, more recent studies have revealed that the

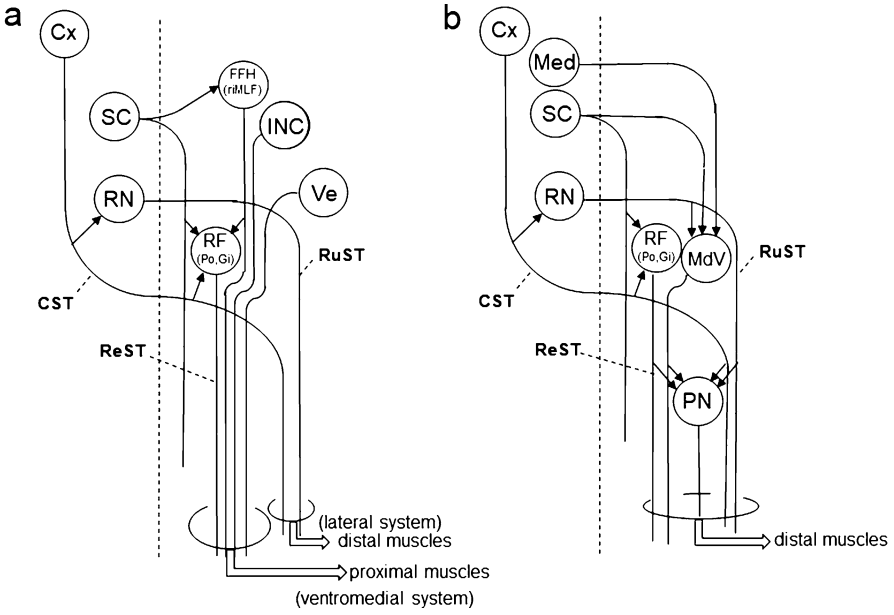

Fig. 1 (**a**) Schematic diagram of the classical lateral/ventromedial systems based on proposal by Kuypers (1962) with some other addition from later findings. (**b**) More recent view on the skilled forelimb control systems. The existence of MdV in primates needs to be investigated. Abbreviations: *Cx* cerebral cortex, *Gi* nucleus reticularis gigantocellularis, *FFH* Forel's field H, *INC* interstitial nucleus of Cajal, *MdV* medullary reticular formation ventral part, *Med* medial cerebellar nucleus, *PN* propriospinal neuron, *Po* pontine reticular formation, *RF* reticular formation, *riMLF* rostral interstitial nucleus of medial longitudinal fasciculus, *RN* red nucleus, *SC* superior colliculus, *Ve* vestibular nuclei

brainstem-spinal pathways are constituted of a wider variety of neuronal subgroups and some of them are involved in the control of distal forelimb muscles. Arber and colleagues have analyzed the premotor neurons of forelimb muscles by using monosynaptic rabies virus in the mouse and clarified a group of neurons in the caudal brainstem, namely the medullary reticular formation ventral part (MdV) receive convergent inputs from the higher motor-related areas such as motor cortex, red nucleus, superior colliculus and medial cerebellar nucleus, and connect to the forelimb motoneurons (Esposito et al. 2014). Blockade of this neuron group impairs the reach and grasp movements in mice. The MdV in primates should be explored in the future. In macaque monkeys, Bufford and colleagues showed the excitatory stimulus-triggered effects from the pontomedullary reticular formation to arm and shoulder muscles in monkeys (Davidson and Bufford 2006). They also showed that many neurons in the medial pontomedullary reticular formation became activated during reaching movements in monkeys (Bufford and Davidson 2004), suggesting that the ReST neurons are involved in reaching movements in monkeys. Similar findings were also made in cats (Schepens and Drew 2006). In addition, Baker and colleagues made intracellular recordings from distal motoneurons and found predominant excitatory effects are induced by electrical stimulation of the medial reticular formation in monkeys. They suggested that the primate ReST neurons may form a parallel pathway to distal muscles, alongside the CST and are therefore in a position to influence upper limb muscle activity after damage to the CST as may occur in stroke or spinal cord injury, and may be a target site for therapeutic interventions (Riddle et al. 2009).

The dexterous digit movements, the ability of independent control of individual digits such as precision grip, are developed uniquely in higher primates and parallel the evolution of the CST (Heffner and Masterton 1975, 1983). Lawrence and Kuypers' studies of the bilateral pyramidotomy (1968a, b) showed that the precision grip did not recover after the pyramidotomy, suggesting that the RuST and ReST cannot fully compensate for the dexterous finger movements. Furthermore, Lemon and colleagues showed that some cortico-motoneurons are uniquely activated for the performance of precision grip (Buys et al. 1986). All these findings suggested that the ability of independent finger control is uniquely achieved by the direct cortico-motoneuronal pathway. However, more recent studies have shown that the signals of the CST are effectively transmitted to digit motoneurons via spinal cord interneurons such as propriospinal neurons (PNs) and segmental interneurons (sINs) (Alstermark et al. 1999; Isa et al. 2006). The recent experimental technique enabled testing the effect of selective blockade of the propriospinal neuron (PN) – motoneuron pathway in macaque monkeys (Kinoshita et al. 2012; Fig. 2). The authors used the viral vector which is specifically retrogradely transmitted from the nerve terminal to the cell body (highly retrograde gene transfer vector; HiRet). They injected HiRet-TRE-eGFP.eTeNT into the ventral horn of the lower cervical spinal cord (C6-T1), where motoneurons of digit muscles are located. Then, the second vector, AAV-CMV-rtTAV16 was injected into the intermediate zone of the C3-C5 segments, the location of the cell bodies of PNs. Then, the PNs are double-infected by the two vectors (Fig. 2a1). rtTAV16 is a novel "Tet-on" sequence that is bound to TRE upon

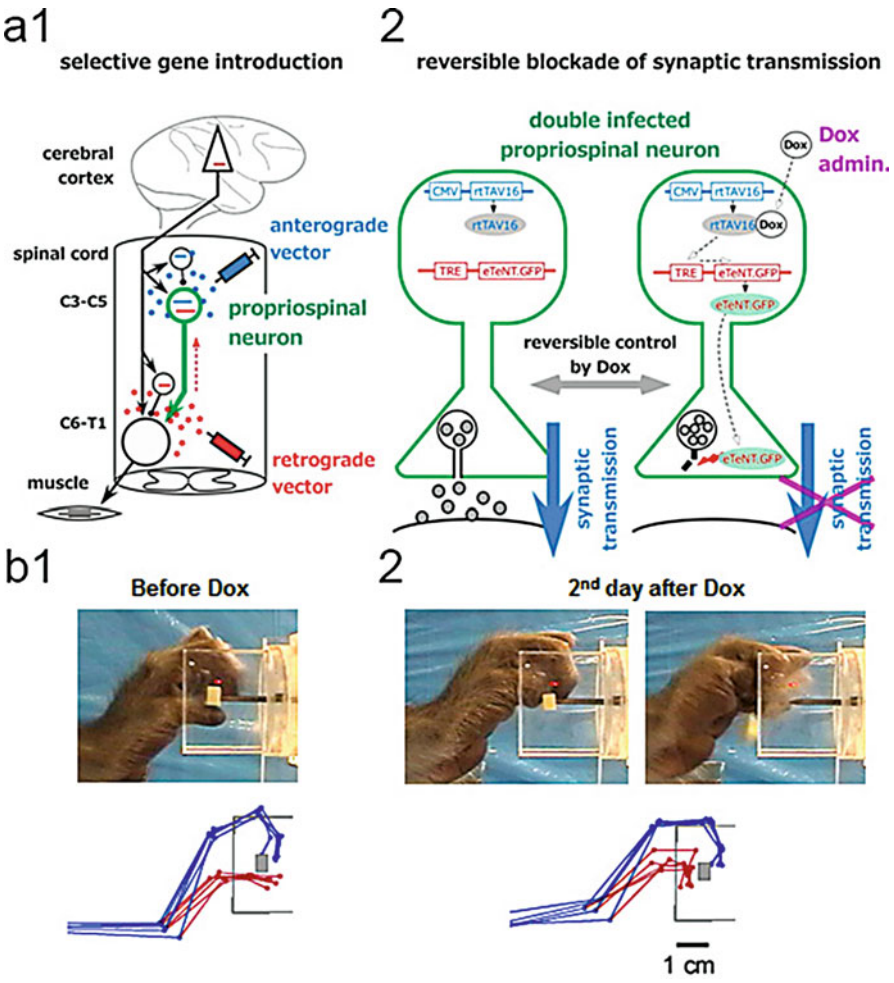

Fig. 2 Pathway-selective and reversible blockade of synaptic transmission using double infection with viral vectors. (**a1**) Experimental arrangements, (**a2**) How the gene sequences carried by the two vectors interact with each other under the presence of Dox and block the synaptic transmission. (**a**) Adapted from Isa et al. (2013). (**b1**) Photo image and superimposition of stick diagrams of precision grip before Dox administration. Blue sticks indicate the index finger and red sticks indicate the thumb at the timing of grasping a small piece of sweet potato. (**b2**) The same arrangement taken on the second day after the start of Dox administration. (**b**) Adapted from Kinoshita et al. (2012)

administration of doxycycline (Dox), which initiates transcription of eTeNT, enhanced tetanus toxin light chain. eTeNT is then carried to the nerve terminal and cleaves VAMP2, a neurotransmitter release machinery, and stops synaptic transmission (Fig. 2a2). The authors applied this technique and tested the effect of blockade of transmission by PNs by Dox administration on the performance of reaching and grasping. Then, it was found that the ability of precision grip was impaired (Fig. 2b).

These results suggested that the PNs are also involved in the control of dexterous digit movements as well as the direct cortico-motoneuronal pathway. As described above, the classical view of the lateral versus medial systems has been updated by recent studies.

2. *Roles of the Brainstem-Spinal Pathways in the Functional Recovery After Lesion of the CST*

2.1 Compensation by the Rubrospinal and Reticulospinal Tracts

Lawrence and Kuypers studied the contribution of the brainstem-spinal cord pathways to the functional recovery after the bilateral pyramidotomy (made at the brainstem pyramid) in rhesus monkeys. The bilateral pyramidotomy, which transected the corticospinal tract, like in the patients of stroke or spinal cord injury, caused severe deficits in movements at distal joints of the extremities (Lawrence and Kuypers 1968a). However, several weeks after lesion, the monkeys exhibited considerable recovery although digit movements remained somewhat clumsy. The authors then found that additional lesion of the lateral brainstem resulted in impairment of digit movements. Based on these findings, they concluded that the RuST was involved in the compensation of independent control of individual muscles, particularly of the hand (Lawrence and Kuypers 1968b). Several lines of studies have followed to clarify the compensatory pathway for recovery after such damage to the CST. Belhaj-Saif and Cheney studied the connectivity of the RuST on the forearm muscles by the stimulus-triggered averaging (StTA) technique in both intact monkeys and in a monkey after recovery from a partial lesion of the CST (Belhaj-Saif and Cheney 2000). They delivered weak single microstimulation pulses to the red nucleus, averaged thousands of the electromyographic responses of hand and arm muscles while the monkeys are performing the reach and prehension task, and investigated the output effects on a variety of hand and arm muscles. In the intact monkeys, the output effects of the RuST were extensor dominant, as previously reported, but in the monkey that recovered from the pyramidal lesion, the normally prominent extensor preference of the excitatory output effects was greatly diminished and suppression effects, which were normally prominent in flexor muscles, became more evenly distributed in flexor and extensor muscles. These results suggested that the RuST could be reorganized so as to contribute to the recovery of motor functions after the lesion of the CST.

In a more recent study on rats, the intracerebral hemorrhage was induced by injection of collagenase into the internal capsule, which caused paralysis of the contralateral forelimb (Ishida et al. 2016). The rats showed considerable recovery of the forelimb functions through forced use of the impaired forelimb (forced limb use; FLU) and the underlying neural mechanism was studied. The authors tested the effect of the pathway-selective blockade of the cortico-rubral pathway by injecting the retrograde gene transfer vector NeuRet-TRE-eGFP.eTeNT into the red nucleus (NeuRet: neuron-specific retrograde gene transfer vector) and AAV-CMV-rtTAV16 into the motor cortex. Administration of Dox after the recovery caused impairment of the forelimb function again, which demonstrated that the cortico-rubral tract contributed to recovery after lesion of the corticofugal fibers in the internal capsule (Fig. 3a).

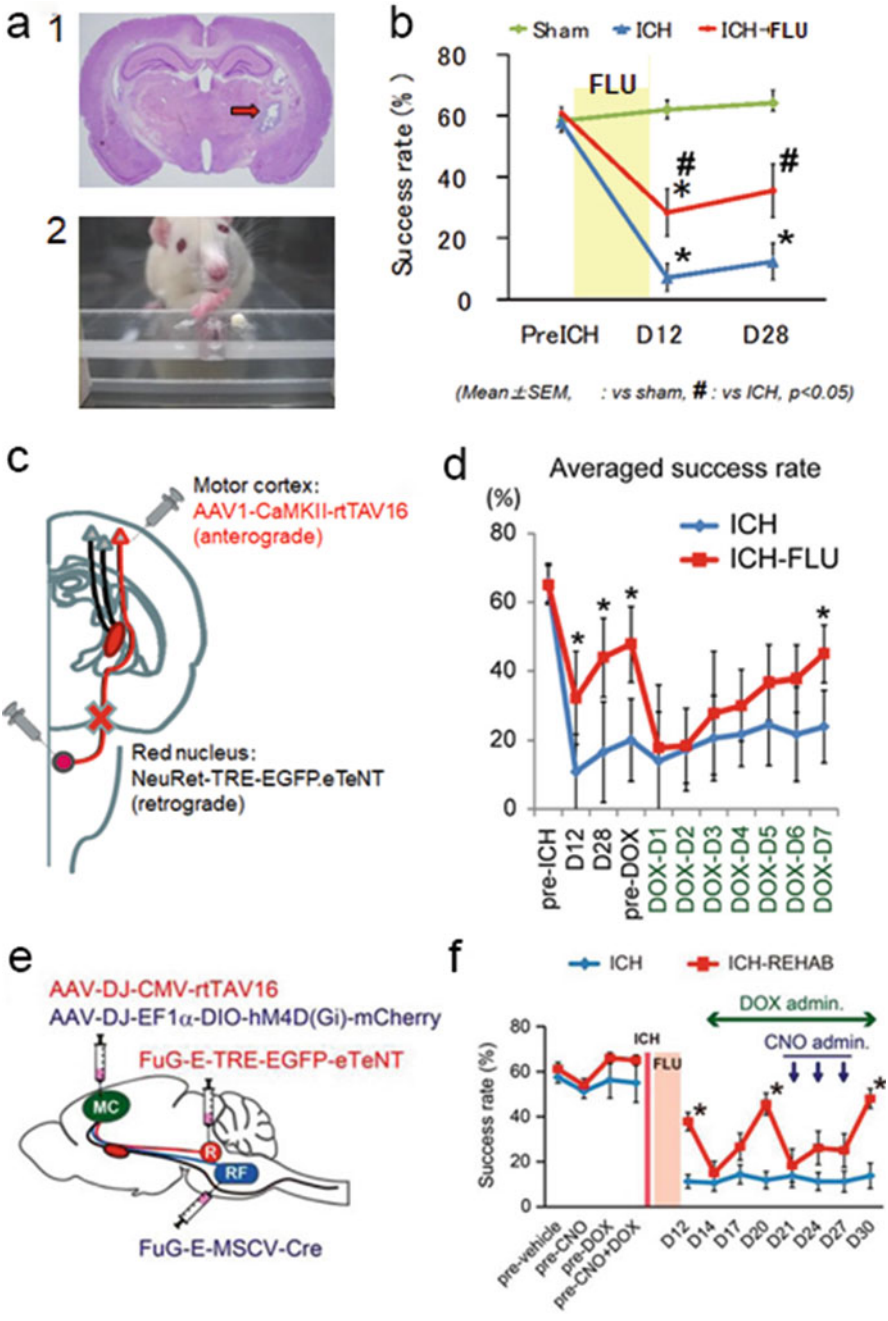

Fig. 3 The effects of blockade of the cortico-rubral and cortico-reticular pathway on the recovery after intracerebral hemorrhage (ICH) with forced limb use (FLU) in rats. (**a1**) Lesion of the internal capsule (red arrow). (**a2**) Forelimb reaching task. (**b**) Success rate of the forelimb reaching task in

Other recent studies highlighted the roles of ReST in the compensatory process after the CST lesion. For instance, Darling and colleagues showed that the cortical projection to the brainstem reticular formation was upregulated during the recovery from the extensive cortical injury (Darling et al. 2018). Furthermore, the synaptic effect of ReST neurons on hand muscles was upregulated after pyramidotomy in macaques (Zaaimi et al. 2012).

In the above intracerebral hemorrhage model in rats, the blockade of the cortico-rubral pathway impaired the forelimb function, but the behavioral performance improved after several days of blockade. The authors additionally blocked the cortico-reticular pathway by combining the double vector technique with chemogenetical technique using Designer Receptors Exclusively Activated by Designer Drugs (DREADD) (Ishida et al. 2019; Fig. 3b). Here, the authors injected FuGE-MSCV-Cre into the reticular formation and injected AAV-EF1a-DIO-hM4Di (Gi)-mCherry into the motor cortex (Fig. 3e). Thus, hM4Di (Gi) was expressed in the cortico-reticular pathway in addition to the expression of TRE-eTeNT in the cortico-rubral pathway in the same animal. They administered CNO (Clozapine N-oxide) to the rats which showed recovery of forelimb functions additionally during the administration of Dox (which blocked the cortico-rubral pathway). Then, the rats showed impairment of the forelimb function again (Fig. 3f). This result indicated that after the damage of the corticofugal fibers in the internal capsule, the cortico-rubrospinal tract compensates for the lost function. If the cortico-rubrospial pathway is additionally blocked, the cortico-reticulospinal pathway takes over the lost functions. Thus, the brainstem-mediated pathways interact with each other to recover the impaired motor functions.

2.2 Compensation by the Propriospinal Tract After the Spinal Cord Injury

A possible contribution of the propriospinal neurons (PNs) to recovery from damage to the direct cortico-motoneuronal pathway was tested by making a lesion of the dorsolateral funiculus (DLF) at the C4/C5 segments in macaque monkeys which aimed at transecting the CST (Sasaki et al. 2004). Surprisingly, these monkeys after the C4/C5 DLF lesion showed markedly good recovery of precision grip in several weeks (Fig. 4a). To demonstrate the contribution of PNs to the recovery from

Fig. 3 (continued) the sham group (green), ICH-only group (blue), and ICH + FLU group. (**c**) The experimental design of the selective blockade of the cortico-rubral pathway. (**d**) Effect of blockade of the cortico-rubral pathway on the recovery process after the ICH and FLU. After the Dox administration, the success rate was declined again. (**a**)–(**d**) Adapted from Ishida et al. (2016). (**e**) Design of the experiments to selectively block the cortico-rubral and cortico-reticular pathways independently in the same animal. (**f**) The effects of the selective blockade of the cortico-rubral pathway and additional blockade of the cortico-reticular pathway by administration of Dox alone and addition of CNO. Abbreviation: *NeuRet* neuron-specific retrograde gene transfer vector. (**e**) and (**f**) Adapted from Ishida et al. (2019)

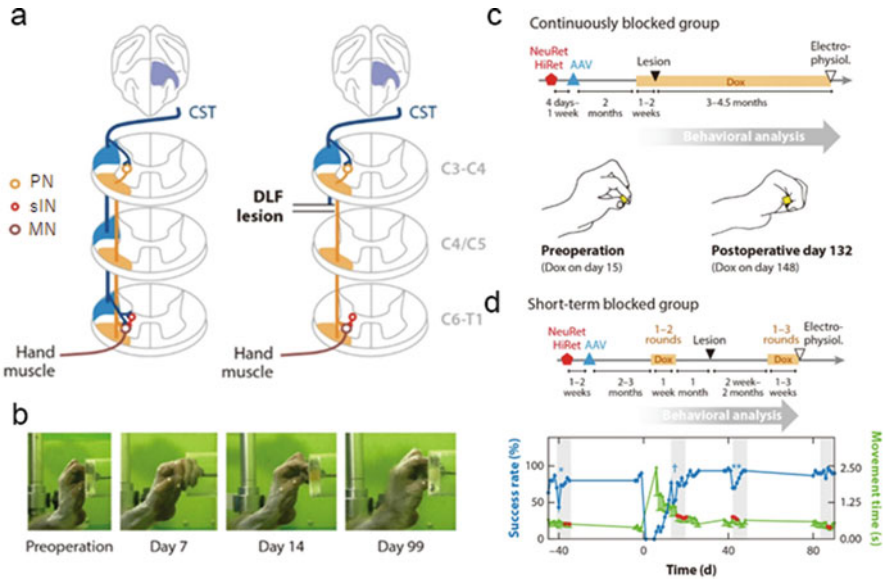

Fig. 4 Contribution of PNs to recovery of dexterous digit movements after C4/C5 DLF lesion in macaque monkeys. (**a**) Descending motor pathways from the motor cortex to motoneurons innervating hand and arm muscles and how the DLF lesion at the C4/C5 segment affects the system. (**b**) Precision grip ability preoperation and on postoperative days 7, 14, and 99. (**a**) and (**b**) Adapted with permission from Isa (2017). (**c**) Effect of the continuous blockade of the PNs on the recovery of precision grip (adapted from Isa 2019). (**d**) Effect of the transient blockade of PNs at different stages before and after lesion [success rate (*blue*) and movement time (*green*)]. (**c**) and (**d**) Adapted from Tohyama et al. (2017) and Isa (2019). Abbreviations: *AAV* adeno-associated viral vector, *CST* corticospinal tract, *DLF* dorsolateral funiculus, *Dox* doxycycline, *eTeNT* enhanced tetanus neurotoxin light chain, *HiRet* highly efficient retrograde gene transfer vector, *MN* motoneuron, *NeuRet* neuron-specific retrograde gene transfer vector, *PN* propriospinal neuron, *sIN* segmental interneuron, *TRE* tetracycline responsive element

the CST lesion at the C4/C5 segment, the blockade of the PN transmission was combined with the spinal cord injury (Tohyama et al. 2017). As shown in Fig. 4b, if the CST lesion was made while the PN transmission was continuously blocked by the double viral vector technique shown in Fig. 2, the recovery of precision grip stopped at the premature stage and not fully recovered (Fig. 4c), which suggested that PN transmission is necessary for recovery. However, if the PN transmission was blocked after the recovery from the spinal cord injury was achieved, the results were different. During the early recovery stage, the PN blockade impaired the precision grip again, while the effects were not observed if the PN transmission was blocked after the full recovery was achieved (Fig. 4d). These results suggested that the PN transmission is required for the early-stage recovery, but once the recovery is achieved, other unknown descending pathways might have participated in recovery and the PNs would no longer be the sole system that compensates for the impaired function of the CST.

2.3 Re-extension of CST

Recent studies have shown extensive extension of the CST axons during recovery from the spinal cord injury. In sub-hemisection model macaques, Nakagawa et al. showed that the descending axons from the contralesional M1 extended, bypassing the lesion area of the spinal cord, descending through the gray matter, and reached the ventral horn of the lower cervical spinal cord (Nakagawa et al. 2015). They seem to have re-established the cortico-motoneuronal connection. Another recent report that after BDA injection into the M1 of macaques with cervical hemisection showed remarkable sprouting of axon collaterals and terminals from the re-crossing corticospinal neurons, suggesting the contribution of re-crossing corticospinal axons from the contralesional M1 to the functional recovery (Rosenzweig et al. 2010). Thus, the extensive plasticity of CST axons themselves could also be a neural substrate of recovery.

2.4 Compensation by the Uncrossed Corticospinal Tract

Many clinical studies showed that after the stroke or the spinal cord injury which impaired the motor cortex of one hemisphere or the corticospinal tract arising from it, the activity of the intact motor cortex in the other hemisphere, ipsilateral to the affected hand is increased (Ward et al. 2003; Marshall et al. 2000). A huge amount of arguments have been made on the function of the ipsilateral cortex in the compensatory process after the lesion of the corticospinal tract (for review, see Hallet 2001). It has been proposed that the activity of the ipsilateral motor cortices is higher in patients who show slow recovery. Similarly, the effect of the transcranial magnetic stimulation has been reported to evoke responses in ipsilateral muscles after stroke, but these were not always observed and were more often seen in patients with poor than good recovery. On the other hand, recently, it has been shown that the bilateral motor cortex is activated during the early stage of recovery (1 month) by brain imaging in a monkey model of the spinal cord injury (dorsolateral funiculus lesion at the C4/C5 level) and pharmacological inactivation of the ipsilateral motor cortex resulted in impairment of recovered hand movements also during the early recovery phase after lesion. Thus, the activation of the ipsilateral motor cortex contributes to the movements of the affected hand during recovery (Nishimura et al. 2007). Then, the question is how? Most of the previous clinical and basic researches on the corticospinal tract have been focused on the control of contralateral limb movements. However, many articles have also reported that some of the corticospinal fibers are also terminated at the ipsilateral gray matter of the spinal cord via various routes (Kuypers and Brinkman 1970; Dum and Strick 1996; Lacroix et al. 2004; Yoshino-Saito et al. 2010). Recent series of studies by Jankowska and colleagues showed that the ipsilateral cortical effects are mainly relayed by the brainstem reticulospinal neurons (for review, see Jankowska and Edgley 2006). There, three pathways were shown to be involved; (1) one group of ReST neurons are located in the ipsilateral pontomedullary reticular formation and mediate excitation from the ipsilateral cortex to the ipsilateral motoneurons, and (2) the other group of ReST neurons located in the contralateral pontomedullary reticular formation are excited by the ipsilateral CST inputs, or

(3) ReST neurons in the ipsilateral side and descend in the contralateral side after crossing the midline at the brainstem level and regulate the ipsilateral motoneurons via the commissural spinal cord interneurons. In general, the bilateral pyramidal lesion results in a severer deficit than the unilateral lesion. Lawrence and Kuypers also reported that spinal hemisection made following the recovery from the bilateral pyramidal lesion resulted in less severe effects than bilateral lesion of the medial or lateral descending system (Lawrence and Kuypers 1968b). These results suggested that the ReST neurons on the contralateral side, which are activated by the ipsilateral CST, are connected to the commissural spinal interneurons and contribute to the excitation of the ipsilateral corticospinal tract to motoneurons.

3. *Plasticity During Early Developmental Period*

It has been shown that infants who underwent the surgery of hemidecortication to cure the intractable epileptic seizure exhibit relatively minor motor deficits. This is considered to be because the infant brain is much more plastic than the adult brain and could show large-scaled reorganization. To explore the large-scale reorganization of the motor system during the early developmental stage, many researchers have studied the early hemidecortication model in rats. If one side of the cortical hemisphere is removed during the first postnatal period in rats, the animals grow normally and exhibit a relatively minor deficit in the control of movements of contralesional forelimbs (Barth and Stanfield 1990; Takahashi et al. 2009). However, if an additional (second) lesion was made at the adult stage to the sensorimotor cortex of the intact side, the control of bilateral forelimbs was impaired, suggesting that the sensorimotor cortex on the intact side was involved in the control of the ipsilateral forelimb after the first lesion. When the descending pathways from the sensorimotor cortex on the intact side were investigated by anterograde neural tracer after the first lesion, the corticofugal fibers were found to terminate in the target regions contralateral to normal targets at various levels in the brainstem and spinal cord. In immature cats and rats, ipsilateral corticospinal projections are still widespread and individual fibers often terminate bilaterally at the spinal level. The disappearance of the axonal projections to the targets contralateral to the normal targets at maturation depends on the competition for synaptic targets (Martin 2005). In rats, the ipsilateral corticospinal projection is very sparse, compared with primates. Therefore, the removal of one hemisphere would have led to a lack of such competitive mechanism, which resulted in the maintenance of bilateral projections at the adult stages. The pathways from the remaining sensorimotor cortex to ipsilateral forelimb motoneurons were investigated electrophysiologically in anesthetized rats with early hemidecortication at their adult stage. Electrical stimulation of the remaining brainstem pyramid induced oligosynaptic large excitatory synaptic potentials (EPSPs) in ipsilateral forelimb motoneurons. Such effects remained to large extent after the transaction of the corticospinal tract at the C2 cervical level, which suggested that a considerable amount of the cortical excitation is mediated via the brainstem, presumably by ReST neurons to the ipsilateral forelimb motoneurons (Umeda et al. 2010; Fig. 5). Thus, the

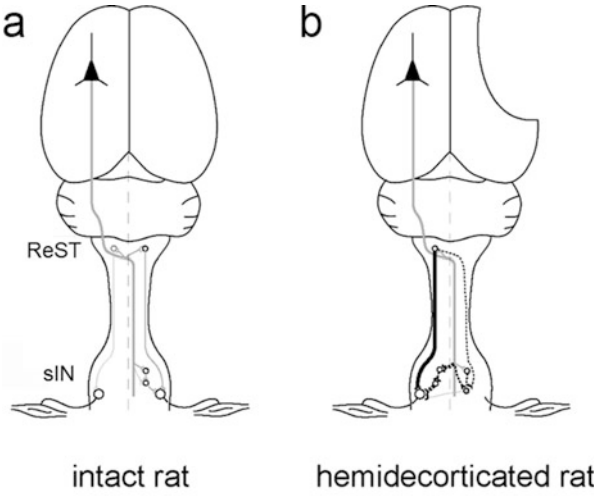

Fig. 5 Schematic diagram of the large-scale reorganization of the corticospinal and related pathways before (a, intact rat) and after neonatal hemidecortication (b). Ipsilateral corticospinal projection is not obvious in intact rats; however, in the hemidecorticated rats, ipsilateral projections via the reticulospinal neurons and segmental interneurons remain

brainstem-spinal projection plays a major role in the compensatory process for motor functions after early brain injury.

Outlook

Previously, it has been considered that the room for functional recovery is very limited after the lesion of the corticospinal tract. Recently, it has been found that the capacity of spontaneous recovery considerably varies depending on the location and extent (complete or incomplete) of the damage. Furthermore, the extent of possible recovery that could be expected through rehabilitative training is now regarded to be much larger than before. For functional recovery of the hand and arm movements after brain/spinal cord injury, the rubrospinal, reticulospinal, and propriospinal neurons, together with the corticospinal neurons on the intact side, could be the target of therapeutic therapies.

Glossary

EPSP: excitatory synaptic potential

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