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Review

The Brain Is Needed to Cure Spinal Cord Injury

Tadashi Isa[1,*]

Damage to corticospinal fibers in the cervical spinal cord is known to impair dexterous hand movements. However, accumulating evidence has shown that precision grip can recover considerably through rehabilitative training. Recent multidisciplinary studies have revealed that, at the spinal level, this recovery is possible due to an indirect neural pathway through propriospinal neurons (PNs), which relay cortical commands to hand motoneurons. Although this indirect spinal pathway is heavily involved in recovery, its role is dwarfed by a simultaneous large-scale network reorganization spanning motor-related cortices and mesolimbic structures. This large-scale network reorganization is key to the regulation of recovery and future therapeutic strategies will need to take into account the involvement of these supraspinal centers in addition to the known role of the spinal cord.

Trends

Many studies have focused on molecular biological approaches to cure spinal cord injury, such as stem cell and pharmacological therapies. These approaches are generally nonselective treatments of impaired neural functions.

In recent years neural mechanisms of functional recovery after spinal cord injury have become better understood. These discoveries now allow the development of novel therapeutic strategies targeting particular neural circuits to promote recovery.

Experimental studies on nonhuman primate models are particularly important in this context, because the structure and function of their motor circuits and body plans are similar to those of humans.

Multidisciplinary approaches, most importantly those selectively targeting regions via pharmacological agents or viral vectors, have started to identify the neuronal mechanism of recovery. Reorganization during recovery appears to occur in multiple areas of the CNS.

Neural Pathways Controlling Hand Dexterity and Its Recovery Following Spinal Cord Injury

Dexterous hand movements (see Glossary) are exquisitely developed in higher primates [1–4]. Dexterous hand movements have given humans the ability to manipulate small and fine objects, a skill enabling complex behaviors such as writing and drawing. One of the most serious problems for patients with spinal cord injury is deficiency in hand functions [5]. Evolution of the corticospinal tract (CST), and especially the formation of direct contact with spinal motoneurons in higher primates [the **direct corticomotoneuronal (CM) connection**], parallels the development of dexterous hand movements both phylogenetically [1,2,6] and ontogenetically [7,8]. Less dexterous animals such as rodents [9], cats [10], and even marmosets (a type of primate) [11] do not possess the direct connection between CST axons and spinal motoneurons. Therefore, it is commonly believed that the direct CM connection is the neural basis for dexterous hand movements. However, from the anatomical point of view the direct CM connection originates from a very limited region of the primary motor cortex (the 'new M1′, along the bank of the central sulcus of *Cebus* monkeys [12]). Furthermore, the majority of corticofugal fibers terminate at the brainstem, or outside the ventral horn of the spinal cord in macaque monkeys [13–15]. Therefore, even in higher primates the direct CM pathway is not the sole pathway from M1 to the spinal motoneurons: a major portion of descending commands from M1 reaches the motoneurons via indirect pathways outside the CM pathway. These indirect pathways are well positioned to play significant roles in the control of hand movements, despite the conventionally accepted view that the indirect pathway's contribution to hand movements is minimal [16].

This review is broadly divided into two parts. In the first part, I describe recent studies on the role of indirect pathways in the control of the dexterous hand movements in primates. I specifically focus on those indirect pathways mediated by **PNs** in the mid-cervical segments. Then, the second part focuses on the role of PNs in the recovery of dexterous hand movements after spinal cord injury. It is important to use a nonhuman primate model (rather than a rodent or

[1]Department of Neuroscience, Graduate School of Medicine, Kyoto University, Kyoto 606-8501, Japan

*Correspondence: isa.tadashi.7u@kyoto-u.ac.jp (T. Isa).

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carnivore model) to study the mechanism for motor recovery because, as described above, the motor system for the control of dexterous hand movements differs considerably between primates and rodents or carnivores [3,4,17–20]. A series of studies on this subject have revealed that the recovery mechanism is not limited to the spinal cord but spans a large-scale network of supraspinal regions. Thus, this can be taken as an example of how a local change in the CNS leads to the reorganization of large-scale networks.

Neural Circuits for the Control of Dexterous Hand Movements: Importance of the Direct CM Pathway

A large body of literature describes the effects of damage to the pyramidal tract in macaque monkeys [21–24]. For example, it was shown that bilateral lesions of the brainstem pyramid caused permanent loss of precision grip in rhesus monkeys. Considerable recovery of gross hand movements following brainstem pyramid lesions could be observed; however, this recovery was impaired by additional lesions of the lateral brainstem, presumably the rubrospinal tract [24]. By contrast, in these cases additional lesions of the medial brainstem, which would affect the reticulospinal tract, mainly impaired the animals' postural control [24]. Based on these findings, it was proposed that the CST is the anatomical basis of dexterous hand movements, while other descending pathways, such as the rubrospinal and reticulospinal tracts, mainly control gross hand movements or postural adjustment during hand movements, respectively. Later studies in rhesus monkeys (e.g. [25]) found that CM cells showed activity closely linked to precision grip but not to power grip, although a similar level of activity was observed in target muscles. These studies indicate the importance of the direct CM pathway in the control of dexterous hand movements. However, as noted in [23]: 'The initial impairment of independent movements of the distal parts of the limb might be related to preferential distribution of the interrupted cortical fibers to the interneurons and motoneurons related to distal limb muscles. Recovery of these movements would then presumably be due to the readjustment of these interneurons so that they become increasingly responsive to the control exerted by brain-stem pathways'. Thus, even studies focused on the direct CM pathway acknowledge that spinal interneurons may have been involved in the control of precision grip and its recovery.

Neural Circuits for the Control of Dexterous Hand Movements: Roles of Indirect Pathways

In cats, which do not possess a direct CM connection, it has been shown that PNs located in the intermediate zone of the C3–C4 segments mediate the cortical command to forelimb motoneurons [26] and control reaching movements. By contrast, reticulospinal neurons (RSNs) have been shown to control more proximal parts of the body such as the neck and trunk [27,28], with only weak connections to limb motoneurons [29]. The roles of these descending pathways have recently been revisited in nonhuman primates, as described below.

First, it was shown that the PNs that mediate commands from M1 to motoneurons exist in nonhuman primates as well as in cats (Figure 1A, left). It is important to note that in monkeys the PN-mediated disynaptic excitation of motoneurons could be unmasked only when glycinergic inhibition was reduced by systemic injection of strychnine in anesthetized preparations (Box 1). Thus, in contrast to cats, the PN-mediated pathway in primates appears to be under stronger inhibition, presumably by feedforward inhibitory interneurons, than in cats [30]. In addition to PNs, it has been shown that electrical stimulation of the medial pontomedullary reticular formation can induce oligosynaptic excitation in distal motoneurons [31–34]. Moreover: (i) many RSNs in the medial pontomedullary reticular formation respond to electrical stimulation of M1; and (ii) the activity of these RSNs was modulated during the performance of forearm movements [35]. Based on these observations, it was proposed that the RSNs in macaque monkeys are more involved in the control of hand movements than was previously considered.

Glossary

Dexterous hand movements: there are a variety of 'dexterous' hand movements. In this review I mainly refer to 'fractionated (or relatively independent) digit movements' as represented by precision grip movements.

Direct corticomotoneuronal (CM) connection: in higher primates the shortest pathway from M1 to motoneurons is monosynaptic. This direct connection has been termed the CM connection. In this review I stress the indirect pathway from the motor cortex to motoneurons. Therefore, I have differentiated the 'direct CM pathway (or connection)' and the 'indirect CM pathway'.

Propriospinal neurons (PNs): a class of interneurons in the spinal cord that connect different spinal segments via axons in the white matter. In addition, PNs form segmental circuits via local axon collaterals and they can also project to the brainstem through ascending collaterals.

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