Control of Hand/Arm Movements

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Direct and Indirect Cortico-Motoneuronal Pathways and Control of Hand/Arm Movements

Recent studies from our group have demonstrated the existence of a disynaptic excitatory cortico-motoneuronal (CM) pathway in macaque monkeys via propriospinal neurons in the midcervical segments. Results from behavioral studies with lesion of the direct pathway suggest that the indirect CM pathway can mediate the command for dexterous finger movements.

The corticospinal tract (CST) is a major descending pathway for the control of voluntary movements. It is a phylogenetically new system that appears first in mammals and develops predominantly in primates (38, 56, 58, 61). It is generally believed that, during evolution, the ability of dexterous hand movements develops in parallel to the establishment of monosynaptic CM connections (15, 28). The direct CM connection predominately develops in higher primates such as Old World monkeys, apes, and humans (28, 29, 38, 51).

In a classical study in monkeys by Lawrence and Kuypers (40), lesion of the pyramidal tract at the level of the brain stem resulted in permanent loss of precision grip, despite recovery of power grip. Generally, this result has been taken to indicate that the direct CM connection is essential for the control of dexterous finger movements. Thus the importance of the direct CM connection has been much highlighted in the history of motor control research (41, 58). On the other hand, the role of indirect pathways from the cerebral cortex to motoneurons (MNs) via subcortical or spinal interneuronal systems has received much less attention, despite the fact that such pathways contribute to the majority of inputs to MNs (25). In cats, which have no direct CM connection, the shortest pathway from the cerebral cortex to forelimb motoneurons is disynaptic (31). A large number of studies have been devoted to clarify the organization of the interneuronal systems that mediates descending excitation from the cerebral cortex to forelimb motoneurons (1, 2, 6). These studies showed that the descending excitation from the cerebral cortex is transmitted to forelimb MNs (C6-Th1) via two different routes: interneuronal systems in the same segments as the forelimb MNs [these interneurons are henceforth denoted "segmental interneurons (sINs)] and propriospinal neurons (PNs); i.e., interneurons located outside the forelimb segments] in the C3-C4 segments (11, 32–34, 37).

The functions of these interneuronal systems have been studied by Alstermark et al (7), in a behavioral task by analyzing effects of partial lesions selective for cortico- and rubrospinal pathways, taking advantage of the differential axonal location of the C3–C4 PNs (in the ventrolateral funiculus) from that of the cortico- and rubrospinal fibers (in the dorsolateral funiculus). The results showed that the C3–C4 PNs are primarily involved in mediating the descending command for forelimb “target reaching” and that the sINs are involved in mediating the descending command for “food taking” (i.e., grasping a morsel of food with the digits and bringing it to the mouth).

An obvious question was whether similar interneuronal systems exist in primates in addition to the monosynaptic CM connections. Many neuroanatomical studies in primates have shown that the majority of terminations of corticospinal fibers are not distributed in the lamina IX but in the intermediate zone of the spinal gray matter (18, 38, 59), where interneurons of various types are located. In several previous studies, the synaptic effects from the CST have been investigated in anesthetized monkeys using intracellular recording from hand and hindlimb MNs and electrical stimulation of the motor cortex or the pyramidal tract. Monosynaptic EPSPs and disynaptic IPSPs have been shown (24, 36, 39, 44, 61), but the existence of disynaptic EPSPs was not reported except in the study by Maier et al. (44). But the authors found disynaptic EPSPs only in 3% of recorded MNs in intact spinal cord preparation in Macaque monkeys and in 14% of MNs after transection of the dorsolateral funiculus (corticospinal axons) at C5, a manipulation made to isolate the non-monosynaptic effects mediated via more rostrally located interneuronal systems by eliminating the monosynaptic EPSPs.

Since the initial proposal by Bernhard, Bohm, and Petersén (15), in most of the literature, the “CM system” has been taken to indicate the monosynaptic connection. In this article, we use the terminology “direct” and “indirect” CM systems, to indicate the fact that both types of pathways exist in the primate and that the significance of the “indirect” pathway should not be underestimated.
Existence of Indirect CM Pathway in Primates

To explain much less frequent and weaker disynaptic action of corticospinal neurons in primates than in cats, despite massive termination of the corticospinal fibers in the intermediate zone of the cervical segments (18, 38, 59), where in cats interneurons mediating disynaptic pyramidal excitation are located (4, 33, 37), we considered the following. In cats, it has been shown that C3–C4 PNs are under feed-forward inhibition from the corticospinal input (FIGURE 1A) (8, 9).

We presumed that, if the feed-forward inhibition is stronger in primates than in cats, it should be difficult for the pyramidal stimulation to activate the C3–C4 PNs because the monosynaptic pyramidal EPSPs would be sharply curtailed by disynaptic IPSPs in the C3–C4 PNs.

To examine our hypothesis, we tried intracellular recordings from MNs in macaque monkeys and investigated the effects of electrical stimulation of the contralateral medullary pyramid (Pyr) under two different conditions (3). In a similar preparation as in the study of Maier et al. (44), we likewise found monosynaptic EPSPs and disynaptic IPSPs but no clear disynaptic EPSPs. However, when we injected strychnine intravenously to reduce the glycinergic inhibition, the disynaptic IPSPs first disappeared and then large oligosynaptic EPSPs appeared in all of the 41 MNs examined (FIGURE 1B). After a lesion of corticospinal tract fibers in the lateral funiculus at C5, the latencies of these EPSPs were in a disynaptic range in 39 of the 41 MNs. However, disynaptic EPSPs remained only in 2 of 25 MNs after a corresponding lesion at C2 (FIGURE 1, C AND D). These results suggested that PNs located in the C3–C4 segments could mediate the disynaptic excitation to MNs. In two MNs, disynaptic EPSPs remained after C2 DLF lesion, which suggested involvement of more rostrally located neurons system, e.g., reticulospinal neurons.

We then tried to record directly from the C3–C4 PNs in monkeys (35). As shown in FIGURE 2, we found a group of neurons in the intermediate zone of the C3–C4 segments that were antidromically activated from the motor nuclei in the C6/C7 segments, which we consider as homologs of “C3–C4 PNs” in the cat. These neurons were only rarely activated by electrical stimulation of the contralateral Pyr (FIGURE 2B). However, after intravenous injection of strychnine, the probability of their activation at monosynaptic latencies gradually increased (FIGURE 2, C–E).

Intracellular recording from a C3–C4 PN revealed that the Pyr stimulation induced disynaptic IPSPs in addition to monosynaptic EPSPs, which were eliminated by intravenous strychnine injection. Taken together, these results show that disynaptic feedforward glycinergic inhibition may prevent firing of the C3–C4 PNs from responding to pyramidal stimulation in monkeys. The trajectory of axons of these PNs was investigated by antidromic threshold mapping technique showing that these neurons descend in the dorsolateral funiculus and project to the lamina IX in the forelimb segments (35).

Thus we demonstrated a group of PNs that can mediate corticospinal excitation to forelimb MNs.

FIGURE 1. Disynaptic corticospinal excitation of motoneurons revealed after intravenous injection of strychnine

Intracellular recordings from forelimb MNs in the C6–C8 segments. A: diagram of the circuits and experimental arrangement. Interneurons mediating the feed-forward inhibition to the C3–C4 PNs are indicated as a black circle. B: records in the intact spinal cord. Electrical stimulation was applied to the contralateral Pyr with a train of 4 pulses. In all figures except B4, the top traces are intracellular recordings (superimposed single records) and the bottom traces are surface recordings from the cord dorsum. B1: Pyr stimulation before intravenous injection of strychnine (str). B2: 40 s after str injection (0.1 mg/kg). B3: 120 s after str injection. B4: top: superimposed averaged intracellular records from B2 and B3. Bottom: the result of subtraction of averaged records B2 from B3 (top arrow indicates onset of the disynaptic EPSP; bottom arrows indicate the Pyr stimuli). C: records from another MN after CST lesion at C5. Disynaptic EPSPs evoked after injection of strychnine. D: records from another MN, after CST lesion at C2. Figure was modified from Alstermark et al. (3).
However, we noticed some differences between these neurons and the C3–C4 PNs in cats.

First, they appear to receive stronger feedforward inhibition than in cats. Second, in cats, a majority (84%) of the C3–C4 PNs have ascending collaterals to the lateral reticular nucleus in the medulla, which may convey the efference copy signal to the cerebellum as mossy fiber inputs. However, in monkeys, only about 30% (26/86) of the PNs were found to project to the lateral reticular nucleus. Third, stimulation of the lateral reticular nucleus induced sizable monosynaptic EPSPs in MNs in cats (5) but much smaller EPSPs in monkeys, only about 30% (26/86) of the PNs were found to project to the lateral reticular nucleus. Another reason might be that a much smaller proportion of monkey than of cat C3–C4 PNs have bifurcating projection to the forelimb MNs and to the lateral reticular nucleus. Another reason might be that stimulation of the lateral reticular nucleus in monkey induced concomitant IPSPs over-riding the monosynaptic EPSPs, which might be caused by the connection between C3–C4 PNs and inhibitory interneurons (35).

Role of Indirect CM Pathway in the Control of Hand/Arm Movements

To study the function of the indirect pathways via C3–C4 PNs, we made lesions of the CST at the border between C4 and C5 segments, that is, caudal to the location of C3–C4 PNs and rostral to forelimb MNs, and investigated the effect on the hand/arm movements of the monkeys. These lesions interrupted the direct CM connections, while a major portion of the descending axons of the C3–C4 PNs remained intact. The monkeys were trained, sitting in a primate chair, to reach and grasp a small piece of food (sweet potato or carrot, 8-mm cube) presented in a tube protruding from a vertical wall in front of the animal and bring it to the mouth.

Three monkeys were used in the initial series of the study (60). As shown in FIGURE 3, one monkey (monkey Y) could reach and grasp the food piece between the tips of the index finger and thumb (“precision grip”) already the first day after the lesion. However, at this stage, the remaining three fingers moved simultaneously with the index finger and thumb. Thus the independency of the fingers was affected. During daily training, the performance improved, and on the day 7 independent finger movements had recovered to some degree. However, preshaping of the thumb and index finger prior to contact with the morsel, the force of the fingers, and the speed of the movements remained affected during the total postoperative recording period of 4 mo.

Independent finger movements were present regularly on postoperative day 9 in monkey Y (smallest
suggests that C3–C4 PNs may play a significant role in the control of precision grip after recovery from the CST lesion at the C4/C5 level.

At the end of the observation period in the animals with C4/C5 or C1/C2 CST lesions, the monkeys were anesthetized and immobilized, and the effects of Pyr stimulation were tested by intracellular recordings from forelimb MNs.

Such recording was made from a total of 59 forelimb MNs in C6–C8 in the three animals with C4/C5 lesion, on the intact \( (n = 22) \) and lesioned \( (n = 37) \) sides (FIGURE 4). Stimulation of the contralateral Pyr evoked EPSPs in all MNs on the intact side (IPSPs were recorded in 4 cells) and in 18 MNs on the lesioned side (IPSPs were seen in 9 cells). Measurements of the latencies with respect to the descending Pyr volley showed a monosynaptic range of latencies (from 0.4 to 1.0 ms) on the intact side (FIGURE 4H; white area), but a disynaptic range (from 1.0 to 1.8 ms) in 15 cells on the lesioned side and possibly a trisynaptic range (from 1.8 to 2.0 ms) in 3 cells. FIGURE 4, A–C, shows that on the intact side, a single Pyr stimulus

FIGURE 3. Prehension movements in monkey Y

Prehension movements in monkey Y before the lesion of the CST at C5 (A) and at postoperative days 1 (B) and 7 (C and D). A–C: the view of the fingers from above. D: view of the fingers from below. The time intervals (ms) relative to the leftmost image are indicated in the top right corner of the digitized video images. From Sasaki et al. (60).
(Figure 4A) evoked a monosynaptic EPSP, which was curtailed by a disynaptic IPSP (see arrow in Figure 4G). On the lesioned side (Figure 4, D–F), recordings from another deep radial MN show that Pyr stimulation failed to evoke a monosynaptic EPSP but disynaptic EPSPs were evoked even by single Pyr stimuli. After the second and third Pyr volleys, the EPSPs were slightly facilitated. Based on these electrophysiological results, we concluded that the CST lesions were complete, but that disynaptic Pyr excitation could still be evoked in forelimb MNs on the lesioned side. Since the disynaptic Pyr EPSPs are not usually evoked in intact monkeys (3, 44), these results suggested that some plastic change had occurred to facilitate the disynaptic excitatory transmission from Pyr to MNs during the course of functional recovery, enhancing the excitatory synaptic transmission or reducing the feedforward inhibition on the C3–C4 PNs. This pathway could thus be used in the control of dexterous hand movements like precision grip after lesion of the direct CM connection.

The question of the role of this pathway in the intact animals has been taken up in recent studies using single unit recordings from C3 to C4 neurons in macaque monkeys, some of which are identified as premotoneurons by antidromic activation from forelimb motor nuclei or by spike triggered averaging technique. The results obtained so far have shown that the activity of these neurons is modulated during hand and arm movements (49) and suggest that the C3–C4 PNs in macaque monkeys are involved in the control of hand/arm movements also in the intact state.

Remaining questions

So far, little is known about the organization of the PNs in monkeys compared with cats. A remarkable feature of the C3–C4 PNs in cats is that they receive convergent inputs from various descending tracts other than CST, such as the rubro-, reticulo-, and tectospinal tracts. Based on such descending convergence, Lundberg and colleagues proposed that various subcortical motor centers can directly update the ongoing motor command from the motor cortex at the level of the PNs (33). This hypothesis has been investigated in the cat using a behavioral test involving trajectory updating in response to a sudden change of the location of the target during ongoing reaching (53, 55). To test the “updating hypothesis” in primates is an interesting

**FIGURE 4.** Effects of stimulation of pyramids on forelimb MNs

A–C: 4–6 superimposed single intracellular records from a deep radial MN recorded (top traces) on the intact side. Bottom traces: records from the cord dorsum in the same segment as the MN, showing the direct CST volleys followed by synaptic volleys. D–F: records from another deep radial MN on the side of transaction of the CST at C5. The cord dorsum recordings show the absence of the direct CST volleys but the presence of the synaptic volleys. The onset of disynaptic EPSPs is indicated by arrow; in D the arrow is missing. Arrow in F shows the onset of a presumed trisynaptic IPSP, which starts at the peak of the disynaptic EPSP. The arrow is missing in G. Averages of records shown in A and D. The stimulus artifacts have been removed. The dashed line indicates the onset of the disynaptic IPSP in A and the disynaptic EPSP in D. The arrows show the latency difference between the monosynaptic and disynaptic EPSP recorded from the intact and lesioned sides, respectively. H: histogram of latencies of Pyr EPSPs (from the 3d volley) in forelimb MNs recorded in the C6–C8 segments. Latency measurements are made with respect to the incoming direct CST volleys on the intact side. From Sasaki et al. (35).
issue and as the first step for this purpose, it is necessary to investigate whether the C3–C4 PNs in monkeys receive similar convergent inputs from subcortical motor centers or not. Second, C3–C4 PNs in cats receive weak excitation from group Ia afferents of forelimb muscles, but the major effect from primary afferents is inhibitory. Thus it was suggested that the C3–C4 PNs function as mediators of descending commands from cortical and subcortical motor centers to MNs rather than mediators of spinal reflexes and that the inhibition from primary afferents may serve, e.g., to assist in terminating reaching. It would be of interest to investigate whether the transmission in the C3–C4 PN system in the monkey is controlled by inhibitory pathways from primary afferents in a similar manner as in the cat. Third, it has been shown that, in addition to the primary motor cortex, many other frontal motor related areas of the macaque monkey project to the spinal cord (20, 26, 27). They include the supplementary motor cortex, dorsal and ventral premotor areas and cingulate motor area. Interestingly, anterograde tracing studies showed that descending axons from these areas terminate in the lateral portion of the intermediate zone of the C3–C4 segments, where the C3–C4 PNs are located (18, 21). If these areas are really connected to the C3–C4 PNs, the function of such direct connections of these hierarchically higher order areas to the C3–C4 PNs would indeed be of interest to investigate.

Comparison with Other Animal Species

In cats, it has been shown that the minimal synaptic linkage from the CST to forelimb MNs is disynaptic and transmitted by both C3–C4 PNs and sINs in the C6–Th1 segments (11, 32, 33, 34, 37). An earlier selective lesion study suggested that the C3–C4 PNs mediate commands for forelimb “target reaching” and that sINs mediate commands for “food taking” movements (7). In more recent studies, some digit movements were observed also in cats, even after combined lesions of the cortico- and rubrospinal tracts in C5 and the reticulospinal tract in C2, which suggests that the C3–C4 PNs can mediate the command for digit movements, albeit with less dexterity than in primates (17, 54).

In man, the existence of a disynaptic excitatory CM pathway via the PNs has been proposed first by the demonstration of non-monosynaptic Ia excitation of wrist flexor motoneurons by facilitation of H reflexes, suggesting that the facilitation was mediated by PNs located rostral to the MNs (45). Baldissera and Pierrot-Deseilligny (13) showed that the facilitation was enhanced at the onset of voluntary movements, and Pauvert et al. (52) showed, using TMS, that apparent disynaptic pyramidal excitation was mediated by PNs. Moreover, a patient case report showed that a lesion of the VLF in C6/C7 segments resulted in interruption of transmission of cortical excitation via rostrally located PNs (46).

It is well known that in rodents a majority of CST axons descend in the dorsal funiculus and mainly terminate in the dorsal horn of the spinal cord, which are major anatomical differences from the CST in cats and monkeys (19, 38). Some of the previous electrophysiological (12, 14, 22) and anatomical (42) studies suggested the existence of a monosynaptic CM connection in rats. However, this has not been confirmed in a more recent electron microscopic neuroanatomical study (62). Alstermark et al. (10) investigated this issue by testing the effects of electrical stimulation of the medullary pyramid (Pyr) on forelimb MNs using intracellular recording in anesthetized rats. No monosynaptic EPSPs were found to be evoked by Pyr stimulation in any of the 104 forelimb MNs examined. Stimulation of Pyr induced fast EPSPs at latencies that were in a disynaptic range and slow EPSPs at longer latencies. The disynaptic EPSPs remained after transection of the CST at the C1/C2 level, which suggested that they were mediated via reticulospinal neurons. On the other hand, when the axons of the reticulospinal neurons (RSNs) or PNs were transected by lesioning the lateral and ventral funiculi at the C1/C2 or C5 level, the fast disynaptic EPSPs disappeared, whereas the slow EPSPs remained. The segmental latencies of the slow EPSPs were sometimes in a disynaptic range and slow EPSPs at longer latencies. The disynaptic EPSPs remained after transection of the CST at the C1/C2 level, which suggested that they were mediated via reticulospinal neurons. On the other hand, when the axons of the reticulospinal neurons (RSNs) or PNs were transected by lesioning the lateral and ventral funiculi at the C1/C2 or C5 level, the fast disynaptic EPSPs disappeared, whereas the slow EPSPs remained. The segmental latencies of the slow EPSPs were sometimes in a disynaptic range and slow EPSPs at longer latencies.
naptic range, but usually they were in a tri- or polysynaptic range. To test the possibility of a PN relay, the effects of Pyr stimulation were tested after combined lesion of the CST (within the dorsal column) in C4/C5 and the ventral and lateral funiculi at C1/C2 level. In this case, even after intravenous injection of strychnine, no synaptic effects were observed in any of the 14 MNs. All these results suggested that the earliest effects of the indirect CM pathway are mediated via RSNs and that slow excitation (most frequently at a more than tri-synaptic linkage) is mediated via sINs. The major effects from the CST on spinal MNs are mediated via tri- or polysynaptic pathways, whereas the fastest excitation is mediated via a cortico-reticulospinal pathway. It has been shown that rats use skilled digit movements when taking and handling food (30, 47), suggesting that such movements are controlled by indirect CM pathways.

FIGURE 5 summarizes in a simplified manner the direct and indirect CM pathways in the rat, cat, and macaque monkey as described above. Polysynaptic indirect pathways via the brain stem and spinal cord are not indicated, although they may also be important. As shown in the figure, there is a gradual change in the organization of direct and indirect CM pathways. In the rat, indirect CM pathways are mediated via RSNs and sINs. In the cat appears, in addition, an indirect CM pathway via C3–C4 PNs (red). And finally in the macaque monkey, the direct CM pathway has been added (red).

It is interesting to note that the indirect CM pathways, albeit with different properties, have remained in these species despite the appearance of new pathways, including the direct CM pathway. On the other hand, Lemon and colleagues failed to detect disynaptic excitation of MNs in monkeys by motor unit recording and either pyramidal stimulation via chronically implanted electrodes in the medulla or transcranial magnetic stimulation of the motor cortex (50). The same authors found disynaptic EPSPs more frequently in squirrel monkeys that have less developed hand dexterity than in macaque monkeys but less frequently than in cats (44, 48). Based on these findings, the authors hypothesized “in primates with more advanced hand function the CM system may have replaced PN-mediated control” and “the C3–C4 PN system, as described in the cat, is unlikely to be responsible for significant transmission of cortical command to upper limb motoneurons” (48). Our current schema does not support their interpretation of the experimental data. The comparison among different animal species suggests that each of them experienced its own evolutionary process especially for the phylogenetically new system, such as the CST, and that older indirect CM pathways have also remained functional. It seems reasonable to assume that these changes in the neuronal organization reflect an increased need of digit and arm control during phylogeny.

Clinical Implication

The above results show that, even though the direct CM connection is impaired in monkeys, the ability of dexterous finger movements, i.e., precision grip and to some extent independent control of different digits, can be restored by the function of indirect CM pathways, presumably via PNs in the midcervical segments. Such findings provide further insights into the mechanisms of neuro-rehabilitation in humans by utilizing the potential of interneuronal pathways after partial injury of the spinal cord. Accordingly, the prognosis of possible functional recovery would depend not only on the extent of lesion of the CST and other descending tracts but also on the extent of damage to spinal interneuronal systems. If the extent of lesion can be precisely estimated by combining modern MRI techniques and electrophysiological estimates of operation of different neuronal systems might be more correct, the information provided might be of use in rehabilitational training. With respect to the potential to control dexterous finger movements by indirect CM pathways, at least one case of recovery of finger dexterity following a lesion of the CST at the level of the brain stem has been reported (16, 43).}

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