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Corticospinal projections to lower limb motoneurons in man

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Summary. The projections of cortical neurons activated by transcranial magnetic stimulation to single lower limb spinal motoneurons were examined in 34 normal subjects. Peristimulus time histograms of the discharge times of single, voluntarily activated motor units were used to derive information about postsynaptic potentials in single spinal motoneurons produced by magnetic stimuli applied over the contralateral scalp. All tibialis anterior motor units and the majority of motoneurons innervating the small muscles of the foot showed strong short latency facilitation. About half of the motoneurons of proximal lower limb muscles showed this facilitation. Short latency facilitation of the motoneurons of soleus and medial gastrocnemius was only rarely observed and when present was weak. The short latency facilitation is attributed to the projections of the fast corticospinal pathway with monosynaptic projections to motoneurons. The relative strength of the facilitation in different motoneuron pools is considered to reflect the density of corticospinal projections to that motoneuron pool. The observed pattern of projections in man shows some differences from the pattern of projections in subhuman primates that might reflect the different use of the limb.

Key words: Magnetic stimulation – Spinal motoneurons – Motor cortex – Corticospinal – Motor unit – Human

Introduction

In nonhuman primates, corticospinal axons have monosynaptic projections to the motoneurons of lower limb muscles (Bernhard et al. 1953; Bernhard and Bohm 1954; Preston et al. 1967), and in particular to the motoneurons of distal muscles (Jankowska et al. 1975). The relative strength of these projections to the motoneurons of various muscles may reflect the ability of the cortex to control those muscles independently to produce a variety of complex movements. In humans the lower limbs are used quite differently from subhuman primates. Are the corticospinal projections also different?

Strong, anodal stimulation of the scalp overlying the human motor cortex in awake subjects results in the activation of contralateral limb muscles (Merton and Morton 1980; Rossini et al.1985; Benecke et al. 1988). The latency of these evoked responses is short and the contraction is believed to result from the activation of the axons of fast conducting corticospinal neurons which make monosynaptic connections to spinal motoneurons (Day et al. 1989; Zarola et al. 1989). A similar activation of contralateral muscles can be produced by inducing current in the brain using an electromagnet (Barker et al. 1985; Brouwer and Ashby 1990). In this case it is the cortical neurons rather than their axons that are activated (Edgley et al. 1990).

The contractions elicited in lower limb muscles are of smaller amplitude than those evoked in the upper limb muscles and/or require stronger stimuli suggesting that corticospinal projections to the motoneurons of lower limb muscles may be generally weaker (Brouwer and Ashby 1990). There is some evidence that the corticospinal projections to human lower limb motoneuron pools are nonuniform. Tibialis anterior (TA), for example, is strongly facilitated by surface anodal stimulation of the cortex (Cowan et al. 1986; Benecke et al. 1988) and transcranial magnetic stimulation (Brouwer and Ashby 1990) whereas soleus is not (Cowan et al. 1986; Brouwer and Ashby 1990, 1991).

The amplitude of the muscle contraction produced by a cortical stimulus depends not only on the strength of the corticospinal projection, but also on the background excitability of the motoneuron pool under examination. Furthermore multiple volleys in the corticospinal tract (Patton and Amassian 1954; Day et al. 1989) and polysynaptic connections to motoneurons can make an unknown contribution to the compound muscle action

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potential. Thus studies employing surface recorded compound muscle action potentials cannot be used to define the strength of the corticospinal projections to various motor nuclei. The amplitude of the composite monosynaptic excitatory postsynaptic potentials (EPSPs) produced in motoneurons by cortical stimulation however would reflect the strength of the corticospinal projections more closely.

In this study the short latency projections from the cortical neurons activated by magnetic stimulation (at a standardized intensity) to the motoneurons of lower limb muscles were examined. The postsynaptic potentials generated in single spinal motoneurons were estimated from peristimulus time histograms (PSTHs) of voluntarily activated motor units.

Methods

Studies were carried out on healthy volunteers who gave informed consent. All subjects were screened to ensure they had no intracranial metal implants, no cardiac pacemakers and no history of epilepsy. The experimental protocol was approved by the local ethical review board.

Stimulation

Stimuli were delivered over the scalp with a Cadwell MES-10 electromagnetic stimulator. The maximum magnetic field strength of this stimulator is 2 Tesla according to the manufacturer's specifications. A 9 cm (outside diameter) coil was positioned with its center aligned midway between the vertex and either C3 or C4 (International 10–20 System, Jasper 1958), contralateral to the subject's preferred hand. The current discharged through the coil was set according to a linear scale ranging from 0% to 100%. The intensity of stimulation was set 5% below that which resulted in a muscle contraction in the voluntarily contracted TA muscle. The site and intensity were held constant for all recordings in a session.

Single motor unit recordings

Recordings were made from single motor units of the TA muscle in all subjects and, at the same session, recordings were also made from single motor units of one or two other muscles including vastus medialis (VM), biceps femoris (BF), medial gastrocnemius (MG), soleus (SOL), extensor digitorum brevis (EDB) and flexor digitorum brevis (FDB). To record from muscles of the foot and from the anterior leg, subjects were semi reclined with a pillow placed under the knee. Recordings from other muscles were obtained while subjects lay prone, head resting on their arms and the lower leg propped on a pillow. All recordings were obtained using a concentric needle electrode with a recording surface area of 0.07 mm^2 (Dantec 13L49) which was positioned near a motor unit that was activated by gentle voluntary contraction (isometric). The motor unit action potentials were amplified (bandpass 10 Hz to 10 kHz), and a single unit identifiable by its characteristic shape was extracted with a window discriminator and displayed on a storage oscilloscope via a delay line. The pulse from the discriminator was led to a loudspeaker and tachometer. Subjects were provided with visual and auditory feedback of the unit's discharges and instantaneous firing rate and were instructed to keep the unit discharging steadily between 5 and 10 Hz. Successful recordings were those in which there was no contamination by other motor units while approximately 100 magnetic stimuli were delivered at 3 s intervals to the contralateral cortex. PSTHs with 1 ms bins were generated using a laboratory computer. (Due to the limited number of applied stimuli smaller bins were not deemed appropriate as the number of counts per bin would likely be insufficient to determine with any certainty the presence of a response).

Analysis of PSTHs

Information about composite EPSPs and inhibitory postsynaptic potentials (IPSPs) in individual motoneurons was derived from the changes in firing probability of PSTHs of single motor unit's discharge times (see Mao et al. 1984 for details of the method). The mean and variance of the background firing probability of a given unit was calculated from the 100 ms prestimulus portion of each PSTH after frequency histograms had shown that the variation in bin contents of this portion was roughly Gaussian. The profile of a poststimulus change in firing probability (relative to the mean background level) corresponds to the approximate first derivative of the underlying PSP shape. An EPSP is represented by a period of increased firing probability (defined here as a minimum of 2 consecutive bins (bin width 1 ms) with contents greater than the background mean plus two standard deviations) followed by a period of decreased firing probability. The area of the peak of increased firing probability above the mean provided an estimate of the amplitude of the underlying EPSP and the duration of the PSTH peak provided an estimate of the EPSP rise time (Ashby and Zilm 1982a, b; Fetz and Gustafsson 1983; Cope et al. 1987; Midroni and Ashby 1989).

An IPSP is represented in the PSTH by a period of decreased firing probability followed by a period of increased firing probability. If the data collection period is short and/or the composite IPSP is large there may be a period of zero firing probability. In such a case, the profile of the change in firing probability no longer represents the first derivative of the PSP shape (Gustafsson and McCrea 1984). In this study periods of decreased firing probability were identified when 5 consecutive bins had a mean content significantly less than the background mean as determined using the student's t test.

The relative strength of the corticospinal projections to a given motoneuron species was determined in the following way. The magnitude, in extra (or less) counts per 1000 stimuli, of the short latency facilitation (or inhibition) of a motor unit (corrected for the rise time of the motor unit action potential) in a given muscle was expressed as a percentage of the magnitude of the short latency facilitation of TA in that subject. (For each subject, all recordings were made during a single session with the same stimulus intensity). These percentages were then pooled for all subjects and a mean value calculated for each muscle tested (an absence of a response was represented as 0%). This mean value related the strength of the short latency effect of magnetic stimulation to that of the facilitatory response in TA.

Results

Successful recordings were obtained from 93 motor units in 34 normal subjects (mean age ± 1 SD $= 25.1 \pm 6.9$ years). All of the motor units tested were amongst the earliest recruited (within the vicinity of the needle) with gentle isometric voluntary contraction.

All of the TA motor units studied ($n = 34$) showed strong, short latency (24–31 ms), brief facilitations and the majority of the EDB and FDB motor units ($n = 6$) were facilitated. This was not the case in the other lower limb muscles. Only 10% of the MG motor units examined ($n = 10$) and $< 30\%$ of the SOL units ($n = 16$) showed any short latency facilitation, the remainder showed no re-

sponse. In VM ($n=18$) and BF ($n=9$) the responses were much more variable. Approximately 50% of these motor units were facilitated with the remainder showing no response or, in the case of VM, short-latency inhibition. Examples of each type of response are shown in Fig. 1. Figure 2 indicates the percentages of the tested motor units of each muscle showing short latency facilitation, no response or short latency inhibition.

The magnitudes of the short latency facilitations (and the range of response latencies) are shown in Table 1. If the maximum excursion of the membrane potential from threshold of a repetitively discharging motoneuron is assumed to be 10 mV as in cat motoneurons (Calvin 1975) then a PSTH peak of 250 counts per 1000 stimuli represents a composite EPSP of 2.5 mV. The estimated EPSPs generated in TA are on average 10 times larger than those generated in SOL. The mean duration of all the PSTH peaks was 4.48 ms $\pm$1.67 ms (1 SD). The PSTH peak durations were longest for TA (5.12 ms $\pm$1.8 ms) and shortest for SOL (1.17 ms $\pm$1.65 ms).

Figure 3 illustrates the strength of the actions of magnetic stimulation on various motor nuclei normalized to the strength of the effect in TA motoneurons. The effects on TA were significantly stronger than to all other motor nuclei except FDB (TA-VM, $t_{(df=34)}=7.01$, $p<0.001$; TA-BF, $t_{(df=16)}=11.08$, $p<0.001$; TA-SOL, $t_{(df=30)}=11.33$, $p<0.001$; TA-MG, $t_{(df=18)}=29.21$, $p<0.001$; TA-EDB, $t_{(df=4)}=3.89$, $p<0.02$). The differences in the actions of magnetic stimulation upon muscles other than TA were not significant at the $p<0.05$ level.

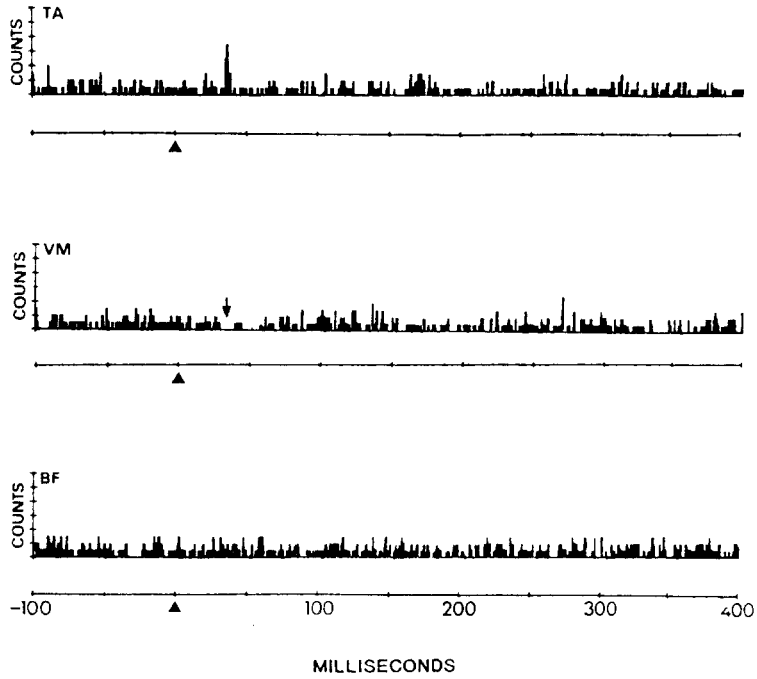

Fig. 1. Peristimulus time histograms of single motor units from TA (top), VM (middle) and BF (bottom) in response to 100 cortical magnetic stimuli applied to the contralateral scalp at time zero (arrowhead). These traces show the different types of responses observed: a brief short latency facilitation in TA, a small inhibition in VM (arrow) and no response in BF. All traces were recorded from the same subject at the same session with the stimulus applied over the contralateral scalp at an intensity of 75%. The mean firing frequencies of these units ranged from approximately 5–7 Hz

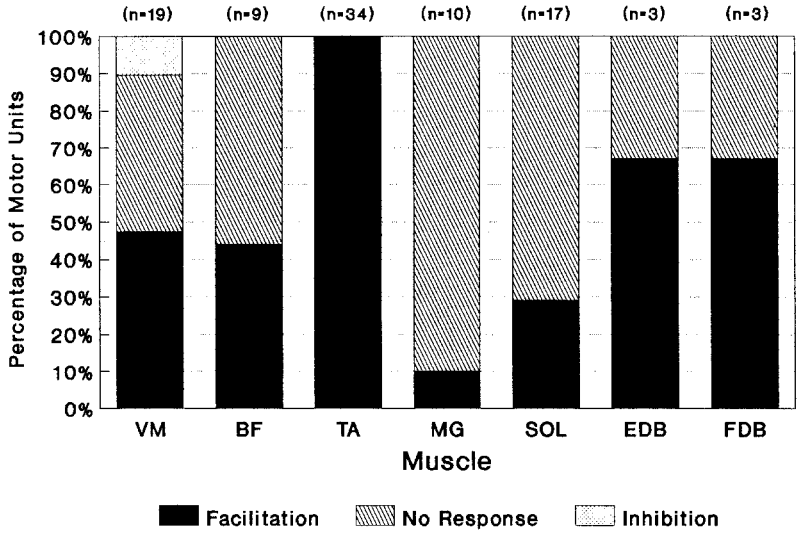

Fig. 2. The frequency (in percent) of facilitation, no response and inhibition produced by magnetic stimulation over the cortex in motor units of various muscles. The number of motor units studied for a given muscle is indicated at the top of each column

Table 1. Magnitudes of the short latency facilitations observed in different groups of motoneurons

	VM	BF	TA	MG	SOL	EDB	FDB
Number of units facilitated	9	4	34	1	6	2	2
Response Latency (range in ms)	20–25	22–32	24–31	30	29–33	38–42	40–45
Response amplitude[a]							
Min.	58	86	99	–	46	84	127
Max.	285	319	733	51	102	96	257
Mean	60	71	252	–	25	90	192

[a] Expressed in extra counts/1000 stimuli

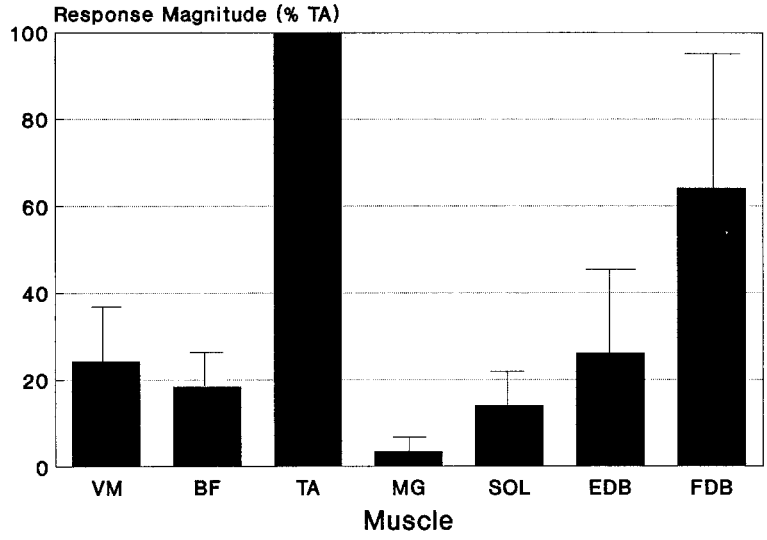

Fig. 3. Net short latency action of magnetic stimulation on the motor units of various muscles. The effect of magnetic stimulation in extra (or less) counts per 1000 stimuli is expressed as a percentage of the magnitude of the TA response in that subject obtained at the same recording session. The mean of these percentages (+1 SE) are shown

Discussion

The short latency facilitation produced in spinal motoneurons by magnetic stimulation over the human motor cortex is brief suggesting that the neurons activated by magnetic stimulation and the spinal motoneurons are tightly coupled and that the range of axonal conduction velocities is small. It is likely that these connections represent monosynaptic activation of motoneurons from a fast conducting corticospinal pathway. The widths of the peaks, which represent the rise time of the underlying EPSP, are wider than usually accepted for monosynaptic effects; however, it is possible that these periods of increased firing probability may have been composed of two or more peaks representing multiple discharges in the corticospinal pathways (Day et al. 1989; Brouwer 1990) which were incompletely resolved with the 1 ms bin width.

The facilitation is much greater for the motoneurons of some muscles, for example TA, than for others, for example SOL or MG. Since the studies were all conducted on repetitively discharging single motor units these differences cannot be attributed to differences in the mean level of depolarization of specific motoneuron pools. There are a number of possible explanations for this finding.

The population of cortical neurons projecting to TA motoneurons and the distal muscles in the foot might be more readily excited by magnetic stimulation than those projecting to the motoneurons of SOL, MG or the more proximal muscles. It is unlikely that the cortical neurons were differentially activated because of their positions or orientation relative to the current induced by the changing magnetic field. The general pattern of activation of various motoneuron pools is not altered by moving the stimulating coil to various sites (Brouwer and Ashby 1990, 1991). In the monkey there is considerable overlap between the populations of cortical cells projecting to the muscles of the shank and foot (Asanuma et al. 1979) and even between proximal and distal muscles implying that they are extensively intermingled (Jankowska et al. 1975). Nor is there any reason to expect that one group of cortical cells would be tonically more depolarized than another and thus easier to excite. Anodal stimulation of the human motor cortex which likely activates corticospinal axons directly (Edgley et al. 1990) results in a similar differential facilitation of TA without SOL (Cowan et al. 1986) and of the distal muscles of the foot without the proximal thigh muscles (Benecke et al. 1988).

It could be that the trajectory of the membrane potential of repetitively discharging motoneurons has a smaller excursion from threshold for TA than for, say, SOL motoneurons. If so, a given EPSP would produce a greater change in firing probability in TA motoneurons (Ashby

and Zilm 1982b). If this were the explanation one might expect a similar difference in the changes in firing probability produced by other inputs. This is not the case. Group I volleys produce a larger change in firing probability of SOL than of TA motoneurons (Mao et al. 1984). The same differential facilitation of TA and SOL is observed when cortical stimulation is used to condition the H reflex (Cowan et al. 1986) where the motoneurons are quiescent. It is concluded that the observed differences in the facilitation of various motoneuron pools reflect the number of corticospinal projections to, and/or the number and spatial distribution of synaptic boutons on the various motoneuron species.

Uemura and Preston (1965) examined the effect of single pulse cortical stimulation on lower limb motoneuron pools of monkeys and baboons in whom the brainstem was destroyed by cauterization sparing only the pyramidal tract. In these "pyramidal" preparations cortical stimulation produced a short latency facilitation in the motoneurons of the flexor muscles of all three lower limb joints whereas in motoneurons projecting to lower limb extensor muscles (except for MG) a weak short latency facilitation was curtailed by prolonged inhibition. Preston and Whitlock (1963) suggested that the cortical outputs were organized to curtail the activity of postural muscles. In the case of the ankle extensor musculature, facilitating MG while inhibiting SOL would overcome the tonic postural mechanisms permitting volitional motor behaviour.

The most detailed study of corticospinal projections to lower limb motoneurons in the monkey was carried out by Jankowska et al. (1975). They stimulated the surface of the motor cortex to activate pyramidal tract cells and recorded intracellularly from motoneurons to detect the resultant PSPs. Monosynaptic EPSPs were recorded from some motoneurons in every motor nucleus examined, but they noted more extensive cortical projections to the motor nuclei of distal than of proximal muscles.

Jankowska et al. (1975) found the mean EPSP amplitude of the gastrocnemius-soleus motoneurons to be 350 μV, about half of that for deep peroneal motoneurons (including TA and EDB). In the present study, the mean response amplitude for TA was five to ten times larger than that of MG and SOL (see Table 1). In Jankowska et al.'s study the small muscles of the foot, innervated by the tibial nerve had slightly larger EPSPs than the deep peroneal motoneurons (but similar range) whereas in man, the mean response amplitude for FDB is smaller than TA. In both studies the number of these motoneurons or motor units examined in small. We conclude that in man, as in monkeys, the density of corticospinal projections is generally greater to motor nuclei innervating distal muscles than proximal muscles. In man the strongest projections are to the TA muscle and not the small muscles of the foot, perhaps reflecting a loss of dexterity of the toes in man.

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