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RESEARCH NOTE

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A propriospinal-like contribution to electromyographic responses evoked in wrist extensor muscles by transcranial stimulation of the motor cortex in man

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Abstract We tested the hypothesis that some of the electromyographic (EMG) responses elicited in preactivated forearm muscles by transcranial stimulation of the human motor cortex are produced by activity in a disynaptic corticospinal linkage involving propriospinal-like interneurones with cell bodies in the spinal C3-4 segments. The experimental design incorporated a previous observation that stimulation of afferents in the superficial radial nerve inhibits propriospinal-like neurones projecting to the extensor carpi radialis (ECR) muscle. Surface EMG responses were recorded from the active ECR muscle after transcranial electrical or magnetic stimulation over the motor cortex. In random trials, single conditioning stimuli at twice perceptual threshold were given to the superficial radial nerve at the wrist at different times before a cortical shock. When the cortex was stimulated electrically, the conditioning stimulus suppressed the EMG responses when the interval between the shocks was 11 ms or more. This was about 3.5 ms longer than the minimum time calculated for a possible direct cutaneous effect on spinal motoneurones. The time course of suppression began earlier and was more complex during magnetic stimulation of the cortex. It is argued that this difference is due to the repetitive I waves generated by the magnetic shock. Whether electrical or magnetic stimulation was used, the first 1–3 ms of the EMG response was relatively unaffected by superficial radial nerve stimulation at any interstimulus interval, whereas clear suppression was seen in the later portion of the response. In contrast, if the EMG response in ECR was suppressed by a conditioning stimulus to the median nerve at the elbow, then all portions of the EMG response were inhibited including the first 1–3 ms. The median nerve effect is thought to be due to direct reciprocal inhibition of the extensor motoneurones. Thus sparing of the initial part of the cortically evoked response with superficial radial stimulation suggests that the latter type of inhibition occurs at a premotoneuronal level. The timing of the effect is compatible with the explanation that corticospinal excitation is produced in ECR motoneurones through both monosynaptic and disynaptic (including propriospinal premotoneuronal) pathways, with superficial radial nerve inhibition being exerted at the propriospinal level.

Key words Propriospinal premotoneurone · Transcranial stimulation · Human

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Introduction

Transcranial stimulation of the human motor cortex produces short-latency electromyographic (EMG) responses that are particularly prominent in distal muscles of the hand and forearm. In view of the prominent corticomotoneuronal projection to distal muscles seen in higher primates, it is usually assumed that the onset of these responses is due to activity in a monosynaptic pathway. As yet, however, it is unknown to what extent activity in other di- or oligosynaptic pathways may contribute to these responses. For example, it is known that the disynaptic Ia inhibitory interneurone of the spinal cord is activated by descending volleys set up by transcranial stimulation of the cortex. The inhibition it produces may cut short the initial excitation of spinal motor neurones caused by monosynaptic corticospinal input (Cowan et al. 1986). More recently a second type of disynaptic input to spinal motor neurones has been investigated: the system of cervical propriospinal premotoneurones. This has been extensively studied in the cat (for references see Alstermark and Lundberg 1992) and consists of interneurones that have cell bodies in the high cervical cord (C3-4) and project monosynaptically to motoneurones in lower segments. They have an important role in transmitting

commands for reaching movements of the forelimb. There is good evidence that a similarly organised system exists in man. The relevant neurones are located rostral to the upper limb motoneurones and they receive excitation and inhibition from peripheral afferents (for references see Pierrot-Deseilligny and Mazevet 1993). They can also be activated monosynaptically by transcranial stimulation of the motor cortex (Gracies et al. 1994). It is possible, however, that this premotoneuronal system is only analagous to that described in the cat and that it may not play exactly the same functional role. Thus this system is referred to as "propriospinal-like" below.

Given this arrangement, Burke et al. (1994) suggested that a portion of the EMG response evoked by transcranial magnetic stimulation of the motor cortex might be produced by activity in this pathway. They showed that stimulation of the superficial radial nerve could suppress cortically evoked responses in extensor carpi radialis (ECR) whilst having little effect on the size of the monosynaptic H-reflex; and they argued that the suppression was caused by cutaneous inhibition of transmission in the system of cervical propriospinal premotoneurones. The short central latency of the effect was compatible with this interpretation, but the estimate of its latency has to take into account the possibility that transcranial magnetic stimulation may give rise to multiple volleys (I waves) that can last for several milliseconds, depending on the intensity of the stimulus (Day et al. 1989). Timing arguments about the locus of suppression are therefore subject to some uncertainty, according to whether reduction in the size of the EMG response occurs because of inhibition of the first or the last of these volleys.

In this report we sought further evidence to support the hypothesis of Burke et al. (1994). First, we used transcranial electrical as well as magnetic stimulation of the motor cortex. This was because, at the low intensities used in normal subjects during background contraction of the target muscle, transcranial electrical stimulation is more likely than magnetic stimulation to evoke a single descending corticospinal volley (D wave; see Day et al. 1989). Thus timing arguments are simplified. Second, we reasoned that if EMG responses are produced by parallel activity in both a monosynaptic (cortico-motoneuronal) and disynaptic pathway (via cervical propriospinal premotoneurones), then premotoneuronal suppression should be able to affect only the later part of the response, with no effect on monosynaptic cortical input. Some of these results have been published previously in abstract form (Mazevet et al. 1994).

Materials and methods

Eight normal subjects (aged 28–58 years) participated in the experiments with informed consent and the approval of the local ethical committees. Surface EMG activity was recorded using 0.9 cm silver electrodes placed 2 cm apart over the belly of the muscle. The EMG was filtered (bandpass 80–1000 Hz) and sampled by computer at a rate of 1–5 kHz. Transcranial stimulation was applied over motor cortex using either a high-powered Magstim 200 (Magstim, Whitland, Dyfed, UK) with a 9 cm mean-diameter circular coil, held at vertex, or with a high-voltage electrical stimulator (D180 Digitimer, Welwyn Garden City, UK), with the cathode placed over the vertex and the anode 6 cm lateral on the inter-aural line. Electric stimuli at 2–3 times perceptual threshold were given to the superficial radial nerve at the wrist. In some subjects stimuli were also given to the median nerve in the cubital fossa at motor threshold intensity. Different frequencies of stimulation or scalp positions were not explored.

Subjects were instructed to maintain a weak tonic contraction of the ECR muscle (5% maximum) whilst transcranial stimuli were given to the contralateral cortex every 4–5 s. In half the trials chosen at random by computer, the cortical stimulus was preceded by a conditioning stimulus to the superficial radial nerve. Means of 20–30 control and conditioned responses were recorded and averaged. A time course of the effect of the conditioning shock was constructed by repeating the process with different interstimulus intervals (ISIs).

Results

In all subjects, stimulation of the superficial radial nerve at the wrist, at an appropriate ISI, could suppress responses in the ECR muscle evoked by transcranial stimulation of the motor cortex. An example from one subject using magnetic stimulation of cortex is shown in Fig. 1A. Suppression began when the superficial radial nerve stimulus preceded the cortical stimulus by 6 ms, and the effect lasted for a further 5–6 ms. In nine experiments on six subjects, suppression began at a mean ISI of 6.5 ms (range 4–8 ms) and lasted 5.6 ms (range 4–6 ms). The mean level of inhibition ranged from 17 to 58% (mean 34%) of the size of the control response.

Transcranial electrical stimulation of the brain was used to elicit responses in three subjects. The data from one of these is shown in Fig. 1B. Suppression began later (ISI of 11 ms) than when magnetic stimulation was used and lasted only 3 ms. The results were similar in the two other subjects, although, in one of them, a non-significant suppression was seen at 6 ms, similar to but much smaller than that observed with magnetic stimulation.

Whether electrical or magnetic stimulation of the cortex was used, conditioning stimuli to the superficial radial nerve never seemed to affect the initial portion of the EMG response recorded from the ECR muscle. Figure 2A illustrates this phenomenon on an extended timescale. Mean control and conditioned responses following magnetic stimulation of the cortex are superimposed at two different ISIs. Note that the time at which the control and conditioned EMG traces separate depends upon the ISI: when short, the traces separate 2.4 ms after EMG onset, whereas, when the ISI is longer, the traces separate earlier (1.2 ms). In nine experiments on six subjects, the EMG traces separated by a mean of 2.7 ms (range 1.6–4 ms) after the onset of EMG activity at the shortest ISI that produced inhibition. When the ISI was 4 ms longer (i.e. about 10 ms), the duration of the initial sparing was significantly ($P<0.01$) shorter (mean 1.4 ms, range 0.8–2 ms).

Such sparing of the initial portion of the EMG response during the period of inhibition was not observed when responses were suppressed by activating the spinal reciprocal inhibitory pathway. An example of this is shown in Fig. 2B. The lower part of the panel shows mean responses to magnetic stimulation of the brain sup-

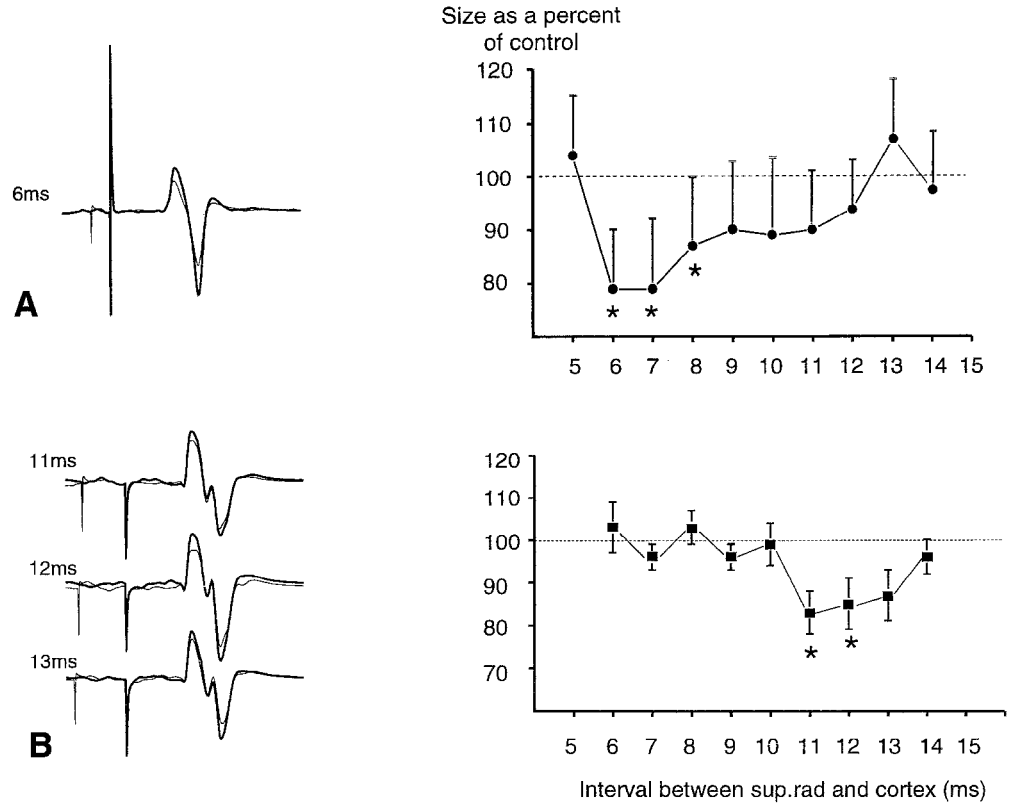

Fig. 1 Time course of superficial radial (*sup. rad*) nerve suppression of EMG responses evoked by transcranial magnetic (**A**), or electrical (**B**) stimulation in two different subjects. The superimposed raw EMG traces on the *left* show control responses to cortical stimulation (*thick lines*) and responses conditioned (at the interval indicated at the *left of the sweep*) by radial nerve stimulation (*thin lines*). Traces are the mean of 20 trials each. The time course to the *right* shows the percentage suppression of the EMG response at different interstimulus intervals. The *asterisks* indicate significant ($P<0.05$) suppression of the response. *Bars* are SEM

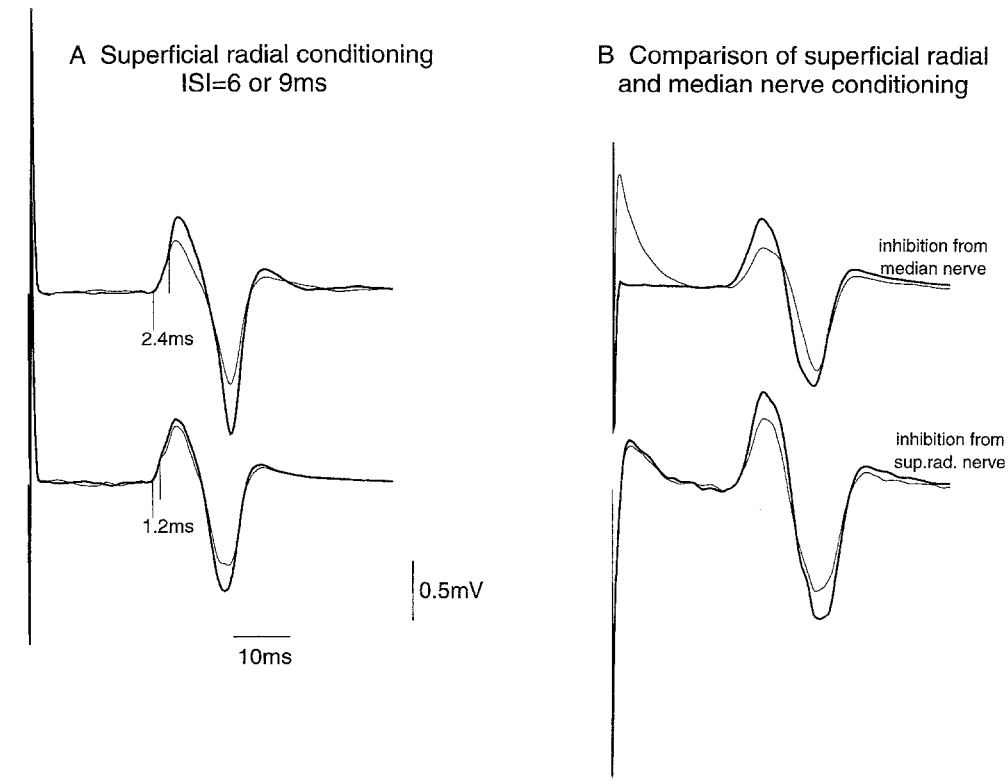

Fig. 2A, B Comparison of inhibition produced by stimulation of the superficial radial nerve at the wrist and stimulation of the median nerve at the elbow. Each trace shows mean (of 30 trials) superimposed EMG records to magnetic cortical stimulation given alone (*thick traces*) and when conditioned by peripheral nerve stimulation (*thin lines*). In **A** are examples of suppression produced by stimulation of the radial nerve at two different interstimulus intervals (*ISI*; *top*, 6 ms; *bottom*, 9 ms). Note that the initial portion of the response is unaffected by the conditioning input. The *thin vertical bars* indicate the approximate time at which the control and conditioned responses diverge. The traces in **B** are taken from a different individual and compare median nerve (*top pair of traces*), and superficial radial nerve (*bottom traces*) inhibition of cortically evoked EMG responses. Note the clear suppression of the initial portion of the response when median nerve stimuli are given

pressed by a stimulus to the superficial radial nerve at an ISI of 11 ms. The upper part shows suppression produced by motor threshold stimulation of the median nerve in the cubital fossa given 3 ms before the cortical shock. Although the percentage suppression of the responses is very similar in both cases, inhibition from the median nerve is apparent even at the onset of the EMG response, whereas that following superficial radial nerve stimulation does not become apparent until about 2 ms or so after EMG onset.

Discussion

There is now strong evidence for the existence of a system of propriospinal premotoneurones in man (see Pierrot-Deseillingy and Mazevet 1993) that resembles the C3-4 system in the cat. The relevant neurones are located above the cervical enlargement and receive monosynaptic excitation and inhibition from cutaneous and muscle afferents (Malmgren and Pierrot-Deseilligny 1988a, b). In addition, recent work has shown that these neurones are facilitated during voluntary muscle contraction (Burke et al. 1992) or by transcranial magnetic stimulation to the brain (Gracies et al. 1994).

The present work provides evidence that some of the EMG responses evoked in the ECR muscle by transcranial magnetic or electrical stimulation are produced by activity in this propriospinal-like pathway operating in addition to the more direct monosynaptic cortico-motoneuronal projection. This interpretation rests on the assumption that the inhibition produced by stimulation of the superficial radial nerve takes place at the level of propriospinal premotoneurones. There are several reasons for assuming that this is true:

1. There is strong evidence from previous studies that stimulation of the superficial radial nerve can indeed inhibit propriospinal-like neurones that have projections to the ECR motoneurones (Nielsen and Pierrot-Deseilligny 1991; Burke et al. 1994).

2. The latency of the inhibition is appropriate for a propriospinal-like pathway. For technical reasons, it is easier to calculate latencies at the spinal cord after electrical rather than magnetic stimulation of the brain, since at low intensities the former is more likely to evoke a single descending (D wave) volley. Thus, in Fig. 1B, inhibition begins when the superficial radial nerve stimulus precedes the electrical brain stimulus by 11 ms. The estimated conduction time in this subject from the wrist to cervical cord was 12 ms (latency of the N11 component of the cervical somatosensory evoked potential), whilst that from the cortex to motoneurones was of the order of 4.5 ms (see Cowan et al. 1986). Thus, the minimum ISI at which cutaneous input could interact with a cortical volley at the motoneurones would be approximately: 12–4.5=7.5 ms. The observed value of 11 ms is 3.5 ms longer than this and therefore would be more compatible with inhibition of neurones located 1–2-ms conduction time rostral to the motoneurones. Such a rostral meeting point implies both a longer route for the cutaneous volley and a shorter route for the cortical volley so that the extra ISI (3.5 ms) is about double the 1–2-ms estimated conduction time between interneurones and motoneurones. The minimum ISI at which a conditioning volley can depress a test response corresponds to the moment when the conditioning IPSP suppresses the last part of this test response (Araki et al. 1960). Thus multiple descending volleys (Day et al. 1989) very likely account for the shorter ISI at which the EMG response elicited by magnetic stimulation is inhibited: the cutaneous-induced inhibition starts to manifest itself when the cutaneous volley can interact with the *last* descending volley (probably the I3 wave). The non-significant inhibition at an ISI of 6 ms seen in one subject using electrical stimulation probably is due to the fact that electrical stimulation at low intensities can sometimes evoke a small amount of I-wave activity as well as an initial D wave.

3. An inhibition exerted directly onto the motoneurone should be apparent even at the very onset of the EMG response. This is what was observed in ECR motoneurones when stimulation of the median nerve was used to evoke reciprocal Ia inhibition. Although stimulation of the superficial radial also produced effective inhibition of ECR EMG, it was never observed to suppress the initial part of the potential. Such initial sparing indicates that cutaneous inhibition is not due to a post-synaptic inhibition of the motoneurones themselves. We suggest that motor cortical stimulation produces excitation in ECR motoneurones via two pathways: a direct monosynaptic route and an indirect disynaptic input via the cervical propriospinal-like system. Cutaneous inhibition affects transmission through propriospinal premotoneurones, but has no effect on the initial monosynaptic input. Thus the initial part of the EMG response to cortical stimulation is spared. There will be, of course, some overlap between monosynaptic and disynaptic inputs, since the rise time of a corticospinal excitatory post-synaptic potential (EPSP) is of the order of 1–2 ms or more. However, the argument only depends on (a) the fact that the first part of the compound EPSP evoked in the motoneuronal pool is monosynaptic in origin, and (b) that in contracting muscle this monosynaptic volley will inevitably discharge some motoneurones that are near their firing threshold. It is the discharge of these early-recruited motoneurones that should be unaffected by the propriospinal-like inhibition. Incidentally, at the shortest ISIs for inhibition, the duration of the spared portion is longer than at other intervals. At these timings, the cutaneous volley interacts at the propriospinal relay with the last cortical volley, and hence a larger part of the initial response is spared.

The temporal resolution of surface EMG responses is limited by the different conduction velocities of peripheral motor axons. Because of this it might have been thought that better timing data could be obtained by studies of single motor unit behaviour. In a small series of experiments on three subjects, we performed post-stimulus time histogram (PSTH) studies of single-unit behaviour during voluntary wrist extension. The ISI between cutaneous and magnetic stimulation was set at 10 ms. In all three individuals, the cutaneous stimulus suppressed the increase in unit activity evoked by the magnetic stimulus. Although there was a pronounced effect on the later part of the response (0.6–1.0 ms after the onset of excitation), we also found that there was mild suppression of the initial part of the response (up to 0.6 ms after onset of excitation), which prevented us from obtaining the temporal resolution that we had expected. The weak suppression of the initial part can be explained as follows: magnetic stimulation is given during voluntary discharge of the unit. This background discharge is produced by activity in all descending path-

ways. If superficial radial stimulation suppresses activity in the propriospinal-like system it will inevitably cause a decrease in this background motor unit firing at a given time later. If a cortical stimulus is applied so that the monosynaptic portion of its input arrives during the suppression of background activity, then the amount of facilitation will appear smaller. This interaction with tonic input to the motoneurone means that all input from a transient magnetic stimulus will be suppressed, not just that part travelling in the propriospinal-like pathway.

This situation does not arise when we consider the whole population of motor units. The size of the response to a cortical input depends on the size of the subliminal fringe of motor units available to discharge. As with a single motor unit, contraction of the whole pool is driven by activity in all descending pathways, and removal of facilitation from the propriospinal system will cause a short-lasting decrease in the total level of EMG activity. However, the number of motoneurones available for discharge in the subliminal fringe may remain similar (see Burke et al. 1994), so that the initial monosynaptic response to a cortical stimulus remains unaffected.

Burke et al. (1994) showed that stimulation of the superficial radial nerve at the wrist could suppress EMG responses evoked in wrist extensor muscles by magnetic stimulation over the motor cortex, even though there was little effect on the size of H-reflexes. The timing at which the effect began led them to conclude that it was due to suppression of transmission through propriospinal neurones, rather than to a direct effect on excitability of spinal motoneurones. The present results have provided further support for this hypothesis in two ways. First, we have provided more accurate timing arguments by using transcranial electrical stimulation to evoke EMG activity in a small number of subjects. Second, we have shown that, as expected from a premotoneuronal effect, cutaneous suppression has no effect on the initial, probably monosynaptic portion of the response, even though the later portion may be substantially suppressed. We conclude that part of the cortically evoked EMG response in wrist extensors is due to activity in a cervical propriospinal-like pathway.

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