Exp Brain Res (2000) 134:274–278
DOI 10.1007/s002210000498

RESEARCH NOTE

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Distribution of non-monosynaptic excitation to early and late recruited units in human forearm muscles

Received: 16 March 2000 / Accepted: 25 May 2000 / Published online: 29 July 2000

Abstract The distribution of monosynaptic and non-monosynaptic excitation was investigated within flexor carpi radialis (FCR) and extensor carpi radialis (ECR) motoneurone (MN) pools. FCR H reflexes of different size were conditioned by various conditioning stimuli eliciting different effects: (1) musculocutaneous-induced non-monosynaptic excitation of FCR MNs at the onset of biceps contraction, (2) heteronymous monosynaptic Ia facilitation, (3) reciprocal Ia inhibition, and (4) presynaptic inhibition of Ia terminals. Musculocutaneous-induced non-monosynaptic excitation increased continuously with the size of the unconditioned reflex. In contrast, heteronymous monosynaptic Ia excitation first increased and then decreased, with increases in the unconditioned reflex size, reciprocal inhibition and presynaptic inhibition showing an approximately similar tendency. This suggests that the non-monosynaptic excitation is distributed more evenly to early and late recruited MNs than monosynaptic Ia excitation, reciprocal inhibition and presynaptic inhibition. A different pattern of homonymous radial-induced monosynaptic and non-monosynaptic excitation was also found for individual ECR MNs investigated with the poststimulus time histogram (PSTH) method. Whereas the monosynaptic Ia excitation tended to be most marked in lower threshold MUs, the non-monosynaptic excitation was evenly distributed to lower and higher threshold MUs. We propose that the even distribution of the non-monosynaptic excitation in the motoneuronal pool may be of significance when it is necessary to activate a wide range of MNs more or less simultaneously.

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Key words Cervical premotoneurones ·
Spinal interneurones ·
Motor control · Human forearm motoneurones

Introduction

The motoneurones (MNs) of human forearm muscles have been shown to receive a substantial disynaptic corticospinal excitation, which is relayed by cervical premotoneurones (PreMNs; Pauvert et al. 1998). It has been suggested that the relevant PreMNs are organised in a way which resembles the C3–C4 propriospinal system in the cat (see review by Pierrot-Deseilligny 1996). The distribution of their synaptic effects within the MN pool is important to know in order to understand the role of such PreMNs in the spinal and corticospinal control of arm movements. MNs are normally recruited in an orderly sequence from slow to fast motor units (MUs) (see Henneman and Mendell 1981). Thus, in man, the first MUs to be recruited tend to be slow MUs in various situations, such as the H reflex (Buchtal and Schmalbruch 1970), the stretch reflex (Calencie and Bawa 1985), slow voluntary contraction (Milner-Brown et al. 1973) and transcranial magnetic stimulation (Bawa and Lemon 1993). However, a skewed distribution favouring fast MUs is possible with some inputs (e.g. see Nielsen and Kagamihara 1993). In the present investigation, which was approved by the local ethics committees, the distribution within forearm MN pools of the non-monosynaptic excitation mediated through cervical PreMNs was explored in healthy subjects.

Investigations using the FCR H reflex

In ten subjects, non-monosynaptic excitation was compared for H reflexes of different sizes, since facilitation of reflexes of small and large size corresponds to recruitment of new (i.e. not involved in the control reflex) units of low and high threshold, respectively (see Crone et al. 1990). It was important in these experiments to have a

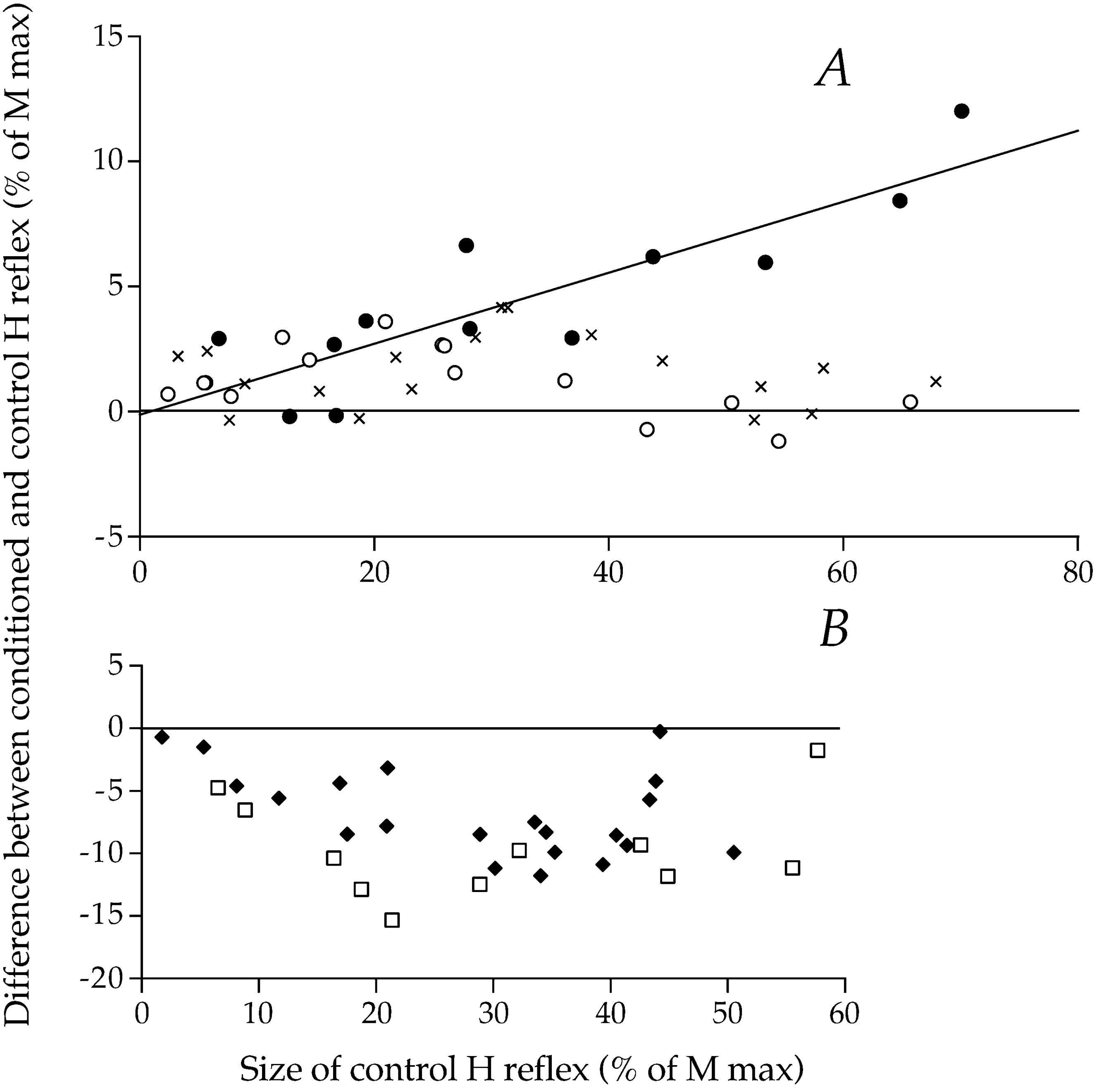

Fig. 1A,B Sensitivity of flexor carpi H reflexes of different size to various conditioning inputs. The amount of facilitation or inhibition of the H reflex (conditioned minus unconditioned reflex, expressed as a percentage of M_{max}) is plotted against the size of the unconditioned reflex (expressed as a percentage of M_{max}) in the same subject. **A** Comparison between the non-monosynaptic excitation elicited by musculocutaneous stimulation (●, 0.75 × MT, 4 ms ISI, onset of biceps contraction) and the heteronymous monosynaptic Ia excitation elicited by stimulation of the ulnar nerve at wrist level (1 × MT, 5.5 ms ISI) at rest (X) or at the onset of biceps contraction (O); *the oblique line* represents the regression line for the non-monosynaptic excitation. **B** Comparison between the amount of radial-induced (1 × MT) reciprocal Ia inhibition (□, 0 ms ISI) and presynaptic inhibition of FCR Ia terminals (◆, data obtained at 8 and 15 ms ISIs) at rest. *Each symbol in* **A,B** represents the mean of 20 measurements

wide range of control reflex sizes: the flexor carpi radialis (FCR) H reflex, obtained by stimulating the median nerve in the cubital fossa, was therefore evoked at a low (0.2 Hz) stimulation rate, and a double shock was often used to elicit the test reflex (a suprathreshold stimulus was preceded 5 ms earlier by a shock just subliminal for the H reflex). The conditioning stimulation was applied to the musculocutaneous nerve, whose stimulation evokes in the poststimulus time histogram (PSTH) of single FCR MUs no monosynaptic Ia excitation (Cavallari et al. 1992) but a peak of non-monosynaptic excitation (Gracies et al. 1991). Musculocutaneous stimulation also evokes, at the onset of an isolated contraction of the biceps muscle, a facilitation of the FCR H reflex, which has all the characteristics of the non-monosynaptic excitation in single MUs: long central delay (3–5 ms), low threshold 0.5–0.6 × motor threshold (MT), brief duration (2–3 ms) and disappearance when the conditioning stimulation is increased above 0.9 × MT (Burke et al. 1992). The absence of effect at rest indicates that summation in the relevant PreMNs of musculocutaneous and contraction-related descending inputs is necessary to discharge them. Musculocutaneous facilitation of the FCR H reflex was therefore investigated at the onset of biceps contraction. Conditioning and test stimuli (randomly alternated in the same sequence) were triggered by the onset of voluntary biceps EMG activity. Conditioning stimuli (0.75 × MT) were applied to the musculocutaneous nerve 4 ms before the test stimulus. Filled circles in Fig. 1A show the amount of reflex facilitation (conditioned reflex minus unconditioned reflex, expressed as a percentage of M_{max}) plotted against the control reflex size. When the control reflex amplitude increased, the amount of musculocutaneous-induced non-monosynaptic facilitation of the reflex increased continuously (linear regression, $r^2=0.76$, $P<0.0001$, Spearman's test). A similar continuous increase in the musculocutaneous-induced facilitation of the FCR H reflex at the onset of biceps contraction with increases in the control H reflex was seen in the six subjects in whom it was possible to obtain H reflexes up to 40–50% of M_{max}, and reached statistical significance (Spearman's test) in four of them.

This contrasts with the other curves of Fig. 1A (same subject) depicting heteronymous monosynaptic Ia excitation of FCR H reflexes from intrinsic hand muscles (Marchand-Pauvert et al. 2000). This excitation was obtained by stimulation (1.0 × MT) of the ulnar or median nerve at wrist level (33 cm more distally) at an interstimulus interval (ISI) of 5.5 ms. As previously described in the lower limb (Crone et al. 1990), the reflex facilitation by the heteronymous monosynaptic Ia input first increased, and then decreased with increasing size of the control H reflex, and very similar curves were obtained at rest (X) or at the onset of biceps contraction (O). At low control reflex amplitudes mono- and non-monosynaptic facilitations increased similarly with the control reflex size (non-parametric Wilcoxon test, $P=0.68$), whereas at higher reflex amplitudes (>25% of M_{max}) the divergence between the continuous increase in the non-monosynaptic facilitation and the progressive decrease in the monosynaptic excitation was significant (Wilcoxon test, $P<0.05$). A similar divergence at high reflex amplitudes between the curves depicting mono- and non-monosynaptic facilitations was obtained in the two other subjects tested in this way. Figure 1B shows that a curve approximately inverse to that depicting monosynaptic excitation (with a tendency for the effect to decrease at reflex amplitudes above 30–40% of M_{max}) was obtained (same subject as in Fig. 1A) when investigating at rest the effects of a radial stimulation (single conditioning shock, 0.95 × MT) eliciting either reciprocal Ia inhibition of FCR MNs (□, 0 ms ISI) or presynaptic inhibition of FCR Ia terminals (◆, 8–15 ms ISIs, Berardelli et al. 1987). The curve depicting the sensitivity of the H reflex to facilitatory and inhibitory inputs as a function of its size is a product of intrinsic mechanisms in the pool (threshold "spacings" between individual MNs) and the distribution of the synaptic inputs to the pool (Crone et al. 1990). Curves such as those depicting the sensitivity of the FCR H reflex to heteronymous Ia facilitation, reciprocal inhibition and presynaptic inhibition are characteristic for those facilitatory and inhibitory inputs which have a more powerful effect on early than on late recruited MNs (Crone et al. 1990). Deviations from this characteristic curve as found for the non-monosynaptic excitation evoked by stimulation of the musculocutaneous nerve indicate a more even distribution of the excitation mediated through PreMNs or even a preferential distribution to high-threshold MNs (Crone et al. 1990).

Investigation in single extensor carpi radialis (ECR) MUs

The distribution of mono- and non-monosynaptic excitation evoked in the PSTH of single voluntarily activated ECR MUs was also investigated in nine subjects (two of whom had also participated in the H reflex experiments and had the characteristic divergence between the curves depicting mono- and non-monosynaptic excitation). Histograms were constructed following stimulation of the radial nerve or in a control situation without stimulation (conditioned and control situations were randomly alternated within a sequence, and differences between the two situations were tested with a χ^2-test). Monosynaptic Ia excitation elicited by stimulation of the radial nerve at 0.95 × MT was initially investigated. Two measures were used to prevent the MU from firing in response to the monosynaptic EPSP when seeking non-monosynaptic excitation: (1) a smaller stimulus intensity (0.6 × MT) was used; (2) the stimulation was triggered with a fixed delay after the previous MU discharge, so that the afterhyperpolarisation following the MN discharge would reduce the firing probability due to the monosynaptic EPSP while having less effect on non-monosynaptic EPSPs occurring later (see Pierrot-Deseilligny 1996).

Data from 84 MUs recorded with needle electrodes are shown in Fig. 2A,B. In 72 MUs a significant ($P<0.05$) peak of monosynaptic Ia excitation was evoked by the radial nerve stimulation at the same latency as the H reflex (after correction for the delay between the onset of the potential and the triggering level of the MU). In the remaining 12 MUs a clear, but non-significant peak was observed. In 39 MUs, weak (0.6 × MT) radial nerve stimulation evoked a significant peak of non-monosynaptic excitation 3–8 ms later than the monosynaptic peak (still often present but non-significant). In the remaining MUs, the largest peak occurring in the 3–8 ms window corresponding to non-monosynaptic excitation was assessed (the resulting possible bias in drawing the curve of Fig. 2B was minimal, since such peaks were then very small). The size of mono- and non-monosynaptic peaks

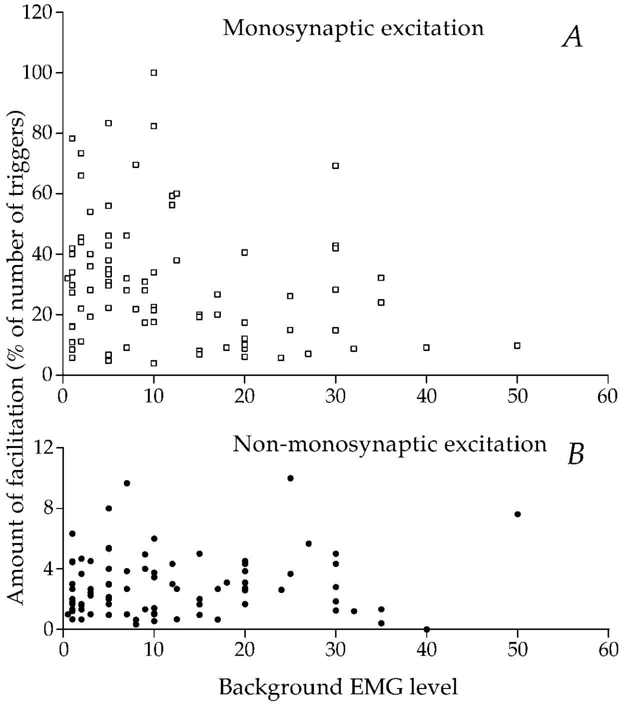

Fig. 2A,B Comparison of the size of the peak of monosynaptic (**A**, □) and non-monosynaptic (**B**, ●) excitations elicited in the same 84 ECR MUs by homonymous stimulation of the radial nerve. *Each point* represents the size of the peak, assessed in the corresponding window of analysis and expressed as a percentage of the number of triggers (see text), which is plotted against the background EMG activity (expressed as a percentage of the EMG recorded during maximal voluntary contraction) at which each MU was recruited. Note that the scale of the ordinate is different in **A** and **B**. Each point was obtained after 100–200 stimuli in **A** and 200–400 stimuli in B

was estimated as the sum of the differences (conditioned minus control counts) in consecutive bins contributing to the peak and expressed as percentage of the number of triggers. This size is plotted in Fig. 2 against the level of EMG activity at which the MU was recruited (recorded with a bipolar surface electrode, and then rectified and smoothed and expressed as a percentage of the EMG recorded during a maximal voluntary contraction of 10 s). The regression between the size of the peak of monosynaptic Ia excitation and the recruitment threshold of the MU (Fig. 2A) was not significantly linear, but the monosynaptic peak tended to be smaller for MUs with higher recruitment threshold than for MUs with lower recruitment threshold ($\rho=-0.23$, $P<0.05$, Spearman's test). This trend is consistent with a distribution of monosynaptic Ia excitation in the ECR motoneuronal pool according to Henneman's size principle, which has been observed in the cat (see Henneman and Mendell 1981) and recently confirmed in the human ECR (Schmied et al. 1997). In contrast, the non-monosynaptic excitation (Fig. 2B) was approximately of equal size in MUs with higher and lower recruitment threshold ($\rho=0.06$, $P=0.60$, Spearman's test). Using ANOVA on repeated measures (to compare the effects of mono- and non-monosynaptic volleys on the same MU), it was shown that the recruitment threshold of the MUs had a significantly ($P<0.01$) different effect on the size of the monosynaptic and non-monosynaptic peaks. This may indicate a difference in the distribution of the synaptic effect of the two inputs in the motoneuronal pool, but other factors must be considered, since high-threshold MUs were recruited when the descending drive and the afferent feedback were stronger. A significant role of these factors could, however, be ruled out, since the amount of mono- and non-monosynaptic excitation remained similar in those early recruited MUs, which could be selectively recorded at two levels of force (below 10% and above 20%). Only results obtained at the level of EMG activity at which the MU was recruited are shown in Fig. 2, and it was checked that the firing rate of the different MUs at their threshold level was not different (ANOVA, $P=0.83$). Neither was there any significant difference between recruitment threshold and the delay at which the stimulus was triggered with respect to the previous discharge of the MU (non-parametric Kruskal-Wallis test, $P=0.50$). Thus, the distributions of mono- and non-monosynaptic excitation elicited by stimulation of the homonymous nerve in single voluntary activated MUs may be considered as different.

The particular pattern of non-monosynaptic excitation described in the present investigation may result from an even distribution of excitatory effects mediated via PreMNs of the presumed propriospinal system onto lower and higher threshold MNs. However, since in our experimental conditions (musculocutaneous-induced effects at the onset of biceps contraction and radial-induced non-monosynaptic excitation during ECR contraction) the PreMNs tested received a descending excitation, another possibility would be that the recruitment of PreMNs by descending inputs favours those projecting to high-threshold MNs. At any rate, the more even activation of the MNs in the pool, which is obtained through the cervical PreMNs, might be of importance when it is necessary to activate a wide range of MNs more or less simultaneously.

Acknowledgements This work was supported by grants from INSERM (CRI 96037), MENRT (EA 2393) and IRME. V M-P was supported by a grant from Institut Lilly.

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