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CORTICAL MODULATION OF TRANSMISSION IN SPINAL REFLEX PATHWAYS OF MAN

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SUMMARY

1. The motor actions in the lower limb of transcranial electrical stimulation of the motor cortex have been studied in sitting human subjects.

2. Cortical stimulation induced a short latency inhibition of H reflexes evoked in soleus motoneurones both at rest and during small voluntary contractions of soleus.

3. Spatial interaction between cortical inhibition of soleus motoneurones and inhibition evoked through identified spinal reflex machinery was investigated.

4. Interactions were found between cortically evoked inhibition and spinal Ia reciprocal inhibition, group I non-reciprocal inhibition and higher threshold components of longer latency reciprocal inhibition (D1 and D2 inhibitions).

5. Interactions were facilitatory when cortical and spinal inhibitory actions were weak and reversed to occlusion when both actions were strong.

6. It is concluded that the corticospinal pathway converges on the interneurones which subserve Ia reciprocal, group I non-reciprocal, D1 and D2 inhibition of soleus motoneurones.

7. No significant interaction was found under the present experimental conditions between cortical stimulation and group Ia–Ia presynaptic inhibition of soleus afferents.

8. The statistical significance of spatial interactions observed with H reflex conditioning was investigated using a control experiment.

INTRODUCTION

It has been known since the work of Sherrington (Sherrington & Hering, 1897), that stimulation of the primate motor cortex, or its outputs through the internal capsule, can lead to contraction of one limb muscle and simultaneous inhibition of the antagonist. In subsequent years the mechanism of the inhibition has become clearer.

Preston and colleagues combined cortical stimulation in the pyramidal monkey with monosynaptic reflex testing of limb motoneurone excitability. They noted a prominent short latency inhibition of some motoneurones, particularly lower limb slow extensors (Preston & Whitlock, 1963). Phillips & Porter (1964) utilized intracellular recording from upper limb motoneurones to demonstrate inhibition

(predominantly disynaptic) from fast-conducting corticospinal fibres. Recent experiments by Cheney and colleagues (see Cheney, Fetz & Sawyer Palmer, 1985), combining chronic recording from pyramidal tract neurones in monkeys with spike-triggered averaging of electromyographic (EMG) activity, indicate that single corticospinal axons may directly excite one group of motoneurones and inhibit the antagonists through spinal interneurones.

The identity of some of the interneurones mediating the antagonist inhibition was first revealed by Lundberg & Voorhoeve (1962) in the cat. They noted spatial facilitation between the inhibition of monosynaptic reflexes produced by pyramidal stimulation and that produced by stimulation of muscle spindle I a afferents from the antagonist muscle. They therefore concluded that some inhibition from the motor cortex was mediated by the interneurones of the pathway of I a reciprocal inhibition. This was later confirmed in primates by Jankowska, Padel & Tanaka (1976), using the intracellular recording technique.

In the last few years evidence has emerged suggesting a similar organization in man. Short latency inhibitory actions on spinal motoneurones following transcranial electrical stimulation of the motor cortex were noted by Cowan, Day, Marsden & Rothwell (1986). In the particular case of soleus motoneurones a pure inhibition was found (this parallels both the methods and results of Preston & Whitlock (1963) in the baboon). Techniques for characterizing spinal reflex machinery in man are now well established (see the preceding paper, Iles & Pisini, 1992 for references). Combination of these techniques with the method of transcranial stimulation of the motor cortex provides an opportunity to study corticospinal control of spinal inhibitory mechanisms in man (paralleling the methods of Lundberg & Voorhoeve, 1962). This approach is described in the present paper. Preliminary reports of some of the work have been published (Iles & Pisini, 1988; Iles & Smith, 1988; Iles, 1989).

METHODS

Experiments were performed on five neurologically normal adult subjects (21–43 years old) of both sexes (three male, two female) with their informed consent and Ethical Committee approval. However, because of the discomfort associated with repeated transcranial electrical stimulation of the motor cortex, most data, and all of such data illustrated in the figures in this paper, have been obtained from the two authors.

The basic experimental procedure was to set up a test monosynaptic reflex (H reflex) in soleus of the right leg of a sitting subject. Transmission in various spinal pathways producing inhibition was assessed by comparison of test (T) and conditioned (C), reflexes and evaluated by dividing conditioned by test reflex amplitude (C/T%). The procedure was then repeated during stimulation of the motor cortex to look for evidence of corticospinal control of transmission in reflex pathways. The amplitude of test reflexes (T_c) and reflexes conditioned by a spinal inhibitory pathway (C_c) both during cortical stimulation were compared to yield a measure of spinal transmission in the presence of corticospinal action (C_c/T_c%). Transmission in the spinal inhibitory pathway in the presence and absence of corticospinal action was then compared by calculating the difference ($C/T - C_c/T_c$%). Positive values, indicating spatial facilitation show that corticospinal actions are mediated via the same interneurones as the spinal inhibitory pathway. This comes about when both of the inputs to the interneurones are subthreshold in isolation, whereas the two together induce firing. Strong activation of either pathway can monopolize the shared interneurones and lead to occlusion (a negative value for the difference).

This experimental approach is analogous to that of Lundberg & Voorhoeve (1962) and is described in more detail in both the preceding paper and the Appendix of the present paper.

Transcranial electrical stimulation of the motor cortex

Single high-voltage electrical stimuli were given from a low output impedance stimulator (D180, Digitimer Ltd using a 50 μs time constant). The electrodes consisted of sheets of stainless steel gauze (area 5 cm^2) wrapped in saline-soaked fabric gauze. The anode was coated with electrode jelly and placed over the foot area of the motor cortex just to the left of the vertex (Rothwell, Thompson, Day, Dick, Kachi, Cowan & Marsden, 1987; Cohen & Hallett, 1988). The cathode was placed on a frontal area in contact with a band of braised stainless steel wrapped in saline-soaked gauze which encircled the crown of the head. Both the anode and encircling cathode were held in place with a soft bicyclist's helmet. This electrode arrangement has elsewhere been referred to as 'belt unifocal' (Rossini, Marciani, Caramia, Roma & Zarola, 1985) or as a 'unifocal montage' (Caramia, Pardal, Zarola & Rossini, 1989). Modelling studies suggest that the cathode does not have to make good electrical contact with the skull at every point along its length (Grandori & Rossini, 1988). Human and animal work has shown that smaller stimuli can be effective with the unifocal method.

Cortical stimuli were applied at an average rate not exceeding 0·125 Hz. These low rates were chosen primarily to avoid discomfort but have the additional advantage of minimizing depression of spinal mechanisms (see Crone & Nielsen, 1989*a*).

Activation of spinal inhibitory pathways

Methods for activation of Ia reciprocal inhibition by electrical stimulation of the common peroneal nerve, group I non-reciprocal inhibition by electrical stimulation of the nerve to medial gastrocnemius, and group Ia–Ia presynaptic inhibition of soleus afferents by pulsed vibration of biceps femoris have been described in the preceding paper. The same methods have been used in the present experiments except that longer latency components of reciprocal inhibition of soleus motoneurones termed D1 and D2 inhibition (Mizuno, Tanaka & Yanagisawa, 1971) have been included. These longer latency actions were evoked by stimulation of the common peroneal nerve with three electrical shocks at 330 Hz.

RESULTS

Action of cortical stimulation on soleus motoneurones

The time course of cortical action on soleus motoneurones was examined using the method of H reflex conditioning in two subjects (Fig. 1, cf. Preston & Whitlock, 1963, for the monkey). In both subjects cortical stimulation induced a short latency inhibition of soleus motoneurones when at rest or performing small (< 1 N m torque at ankle) voluntary contractions of soleus. Excitatory actions were manifest during stronger voluntary contractions. These results are identical to those reported by Cowan *et al.* (1986). Inhibition was produced by weak cortical stimuli that did not produce excitatory responses in the other relaxed muscles of the lower limbs. The major question addressed in the remaining experiments described in this paper is whether this cortical inhibition of soleus motoneurones is mediated via 'private' pathways or through spinal machinery that can be recognized by other criteria, namely activation by a peripheral (reflex) input.

Spatial interactions between cortical and spinal inhibitory actions on soleus H reflexes

Spatial facilitation using the H reflex

The experimental approach consisted of evaluating the strength of a spinal inhibitory action by conditioning soleus H reflexes, expressing the result as conditioned reflex amplitude as a percentage of test reflex amplitude (C/T%). The subjects performed a very weak soleus contraction (0·5 N m). The same inhibitory action was then evaluated with conjoint stimulation of the motor cortex.

The cortical stimulus was applied at near to peak inhibition conditioning intervals (−1 ms for J.V.P.; −0·5 ms for J.F.I.; see Fig. 1) and at a strength that itself induced about 20% inhibition of the test reflex. The short conditioning intervals should have avoided interference by any descending cortical volleys following the

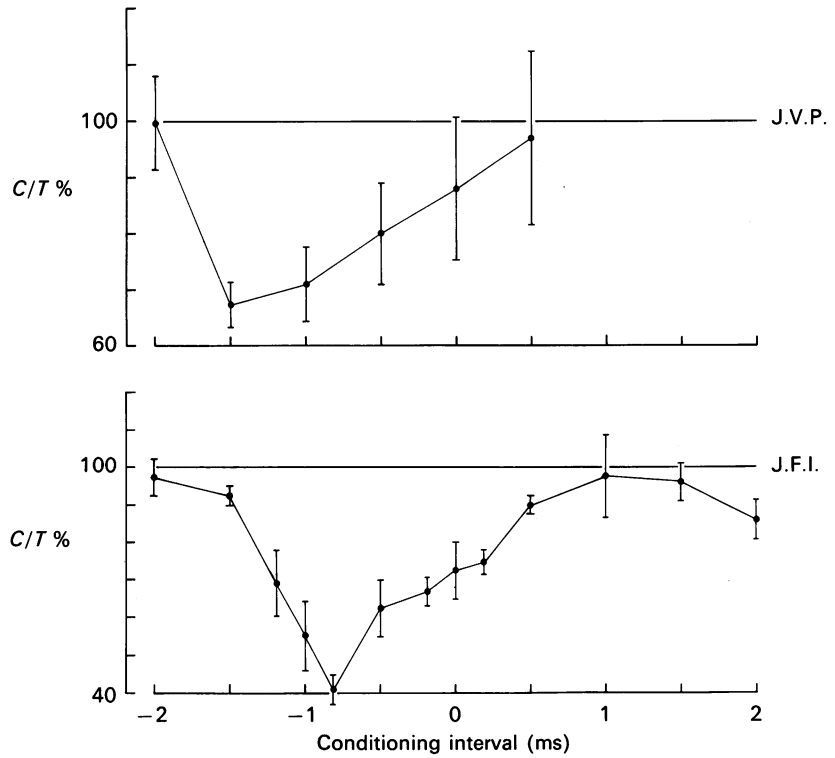

Fig. 1. Time course of cortical action on soleus motoneurones. Cortical action is evaluated by comparison of the amplitude of H reflexes conditioned by prior cortical stimulation (C) with test reflexes (T) and expressed as C/T% (ordinate). The time interval between electrical stimulation of the motor cortex and stimulation of the tibial nerve (to initiate the H reflex) is given on the abscissa (negative intervals refer to the tibial nerve stimulus preceding the cortical stimulus). The strength of the cortical stimulus was in the range 100–200 V. Because there was no independent way of monitoring the effectiveness of the cortical stimulus, more measurements were taken at the peak times of inhibitory action (−1·5 ms for J.V.P., −0·8 ms for J.F.I.) and the cortical stimulus strength was adjusted if changes in inhibitory action were noted. The mean action and its standard error (obtained from several averages each of thirty-two conditioned and thirty-two test reflexes) is plotted at each conditioning interval.

first one (Day, Rothwell, Thompson, Dick, Cowan, Berardelli & Marsden, 1987*b*; Zidar, Trontel & Mihelin, 1987). The inhibition induced by the cortical stimulus alone was compensated by a small increase in the strength of the stimulus applied to the tibial nerve, so that the test reflex in the presence of cortical stimulation (T_c) was on average equal in amplitude to the test reflex alone (T). The spinal inhibitory action in the presence of conjoint cortical stimulation was assessed by measuring the doubly conditioned reflex (C_c; the tibial nerve stimulus was boosted as for T_c). The changes

in spinal inhibitory action associated with conjoint cortical stimulation were evaluated as $C/T - C_c/T_c\,\%$. A positive value for this difference indicates spatial facilitation and suggests that the cortical and spinal inhibitory actions share the same interneurones.

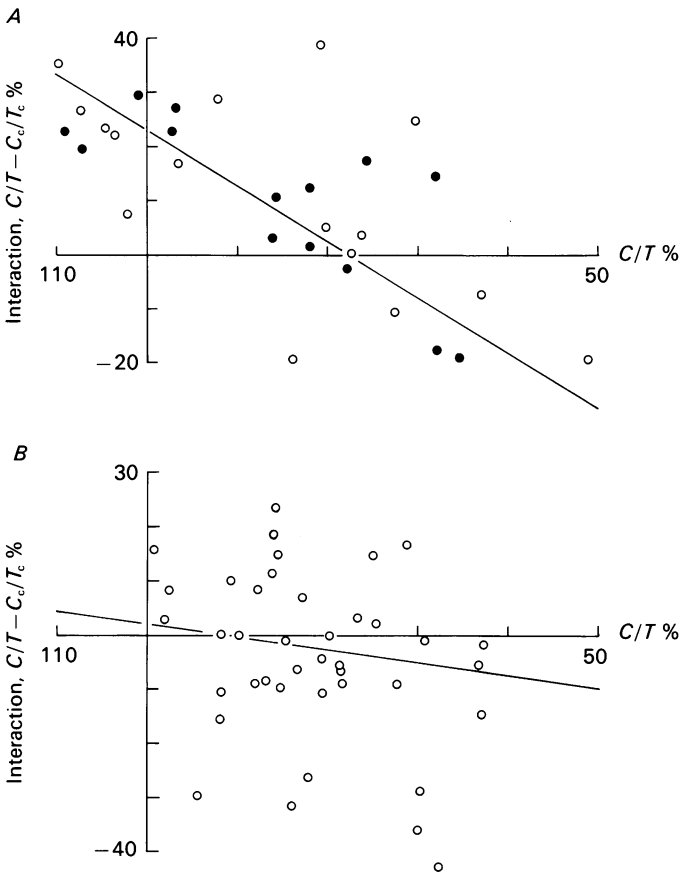

Fig. 2. Spatial interactions between inhibition evoked by cortical stimulation and spinal inhibitory actions. The interaction is plotted (ordinate) as the difference in spinal inhibitory action on the soleus H reflex in the absence and presence of cortical stimulation ($C/T - C_c/T_c\,\%$). Cortical action alone induced around 20% inhibition which was compensated by boosting the test stimulus. The abscissa expresses the strength of the spinal inhibitory action alone. Data from J.V.P. and J.F.I. are combined. Each point is obtained from sixty-four reflexes. Filled circles refer to a regular sequence of stimulus presentation (C, T, C_c, T_c, C...) and open circles to a pseudo-random sequence. Typically, ten data points could be obtained in an experimental session of approximately 1·5 h. Regression lines have been fitted to the data. *A*, interaction with Ia reciprocal inhibition. *B*, interaction with group I non-reciprocal inhibition.

Interaction with Ia reciprocal inhibition

Reciprocal inhibition of a wide range of strengths was induced by electrical stimulation of the common peroneal nerve (2·5 ms before the test) with shocks varied in intensity from 0·6 to $2 \times \alpha$T (α-motor threshold). The data illustrated in Fig. 2*A* show that spatial facilitation occurs between cortical inhibition and Ia reciprocal

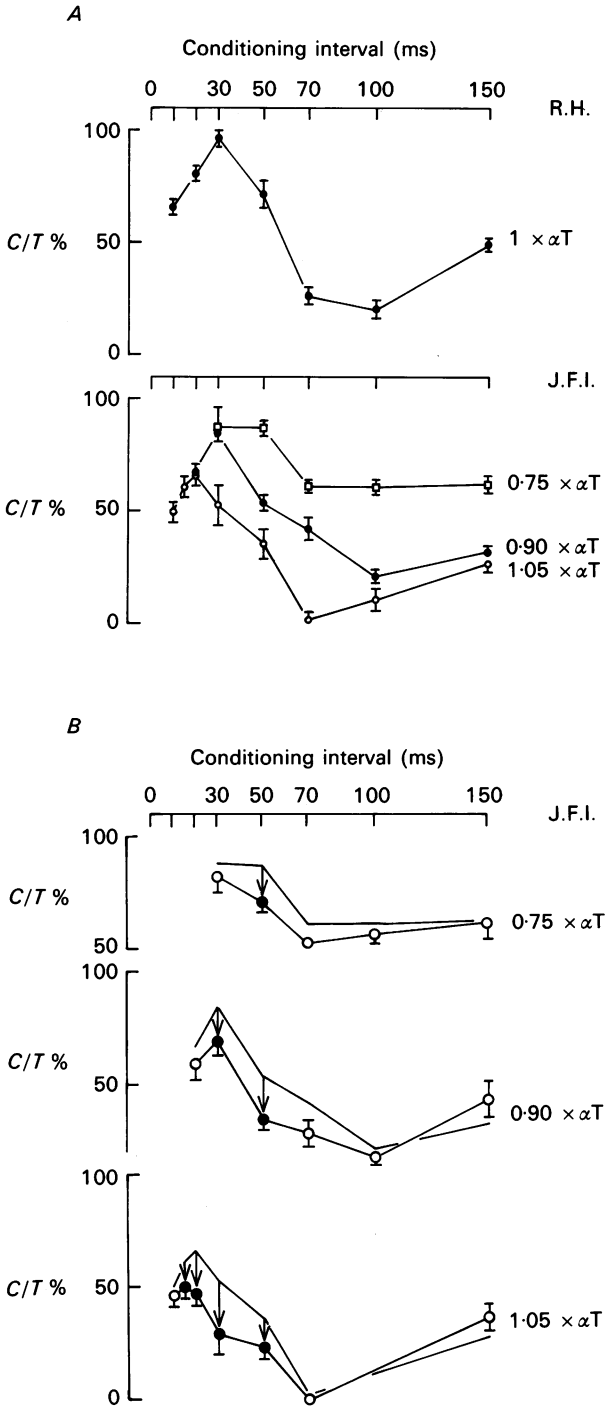

Fig. 3. Time course of long latency reciprocal inhibition of the soleus H reflex. Conditioning action ($C/T\%$) is plotted (ordinate) against the time interval between the last of three electrical shocks applied to the common peroneal nerve and the test stimulus (abscissa). Each point represents the mean and standard error obtained from at least five

inhibition, provided that the latter is weak ($C/T > 75\%$; Wilcoxon two tailed matched pairs test, $P < 0{\cdot}0002$), there is some indication that stronger reciprocal inhibition leads to occlusion.

Interaction with group I non-reciprocal inhibition

Non-reciprocal inhibition was induced by electrical stimulation of the nerve to medial gastrocnemius (2 ms before the test) with shocks varied in intensity from 0·8 to $1{\cdot}2 \times \alpha$T. The data plotted in Fig. 2*B* indicate a slight tendency towards facilitation when non-reciprocal inhibition is weak, and towards occlusion when it is stronger, but the slope of the regression of the interaction on the strength of the peripheral action is not significantly different from zero ($P > 0{\cdot}1$).

Group Ia–Ia presynaptic inhibition

Presynaptic inhibition was induced with activation of Ia afferents from a flexor muscle by pulsed vibration of biceps femoris muscle. Conditioning intervals from 100 to 200 ms (see previous paper) and degrees of inhibition from $C/T = 100$–30% were studied in two subjects. There was no significant tendency towards either facilitation or occlusion from cortical stimulation.

Interaction with long latency reciprocal inhibition

Longer latency reciprocal inhibitory actions were induced by electrical stimulation of the common peroneal nerve with three shocks at 330 Hz. The time course of action is illustrated for two subjects in Fig. 3*A*. Two phases of inhibition can be distinguished. The phases preceding and following a conditioning interval of 30 ms will be referred to as D1 and D2 inhibition respectively in accord with Mizuno *et al.* (1971). However, observation of two phases does not necessarily establish that there are only two underlying spinal mechanisms. For this reason, cortical interaction was not studied in the first instance at a single peripheral input conditioning interval (as for example with Ia reciprocal inhibition) but instead over the whole range of long latency actions. The result is illustrated in Fig. 3*B*. Cortical stimulation facilitates long latency reciprocal actions (conditioning intervals from 15 to 50 ms). Subject J.V.P. was studied at 20 and 50 ms intervals only: facilitation from cortical stimulation was evident.

Conditions leading to facilitation and occlusion

Experiments described in the preceding section reveal some spatial facilitation between inhibition induced from the cortex and Ia reciprocal, group I non-reciprocal

averages each of sixty-four reflexes (thirty-two conditioned, thirty-two test). *A*, data from subject R.H. using a conditioning stimulus at motoneurone threshold; and from subject J.F.I. at three different strengths of conditioning stimulation applied to the common peroneal nerve expressed in relation to the threshold for activation of motor axons to tibialis anterior muscle ($\times \alpha$T). Similar inhibitory time curves were obtained for subject J.V.P. *B*, the data for J.F.I. from part *A* have been reproduced (linking lines only) along with the long latency reciprocal inhibition observed during conjoint cortical stimulation (C_c/T_c, points with standard error bars). Significantly enhanced inhibition with conjoint stimulation is indicated by the arrows and ● ($P < 0{\cdot}06$; Wilcoxon matched pairs signed ranks test for $n > 8$, otherwise randomization test for matched pairs.)

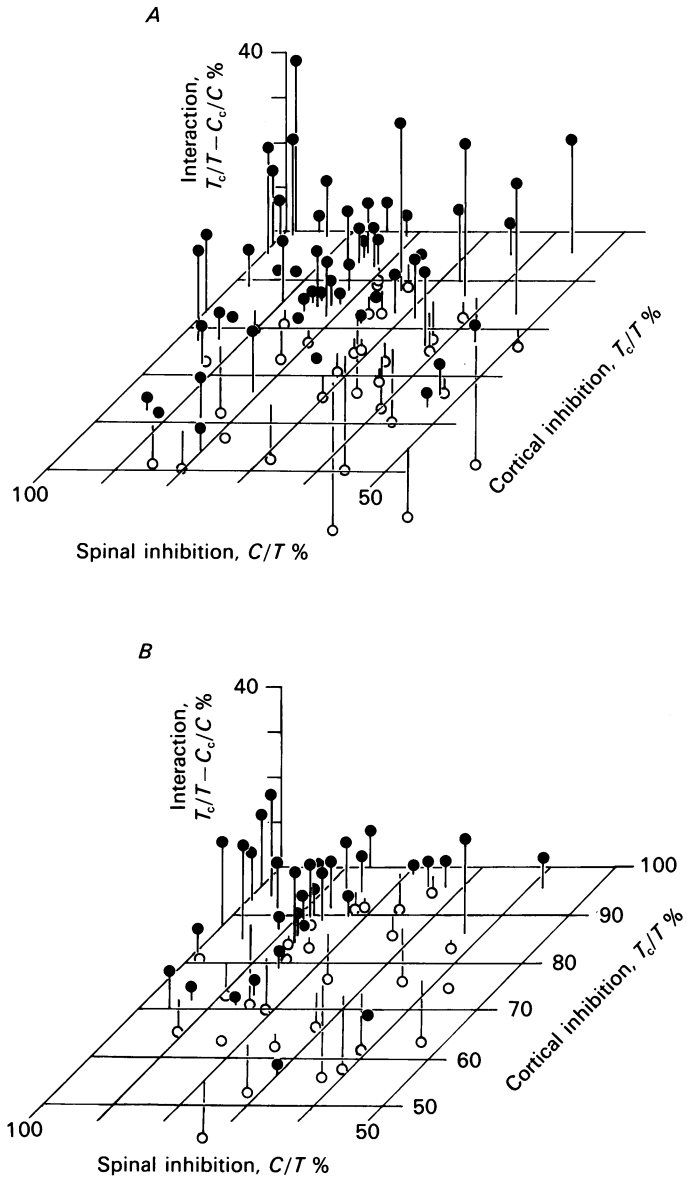

Fig. 4*A*,*B*. For caption see facing page.

(equivocally), D1 and D2 inhibitions. Facilitation is clearest when the peripheral action is weak and tends to reverse to occlusion when the peripheral action is stronger, but the phenomena are obscured by variability in the interaction. One possible source of variability is related to the strength of cortical inhibition itself. This was set at around 20% at the start of each experiment but tended to vary with time, possibly as a result of changing scalp electrode contact resistance. Because cortical inhibition was compensated its strength could not be continuously monitored. Changes in the strength of cortical inhibition could alter the relative

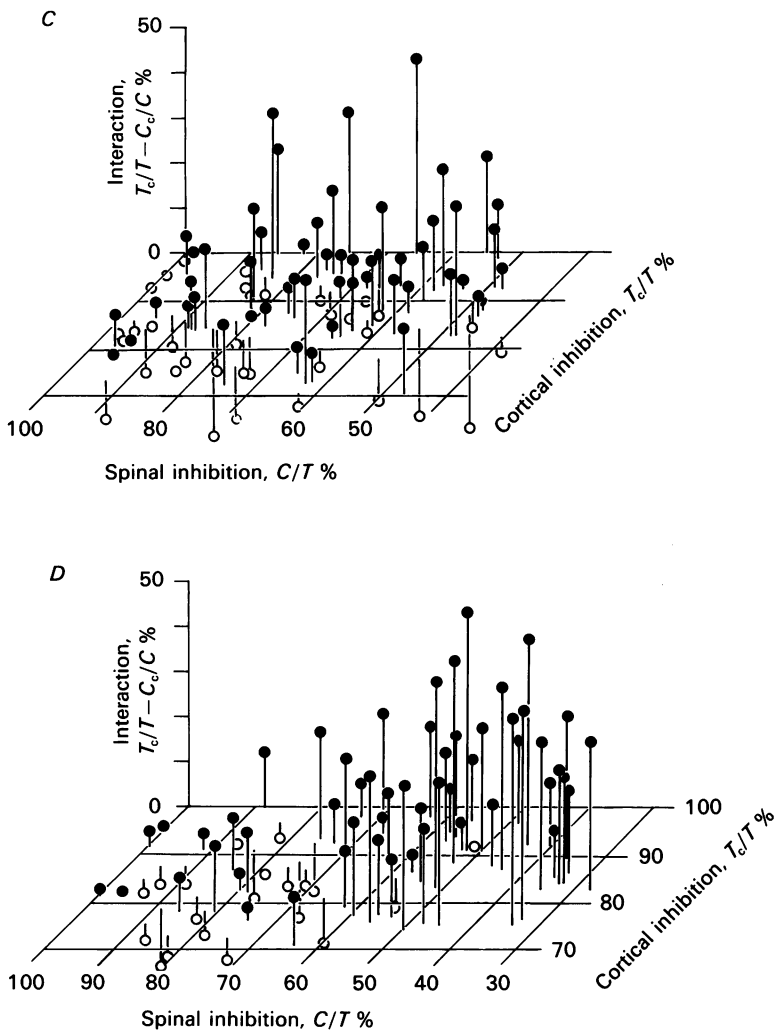

Fig. 4. Three-dimensional plots relating spinal inhibitory action (C/T%, x-axis), cortical inhibitory action (T_c/T%, y-axis) and spatial interaction ($T_c/T - C_c/C$%, z-axis): facilitation is plotted upwards using pins with filled heads, occlusion is plotted downwards using pins with open heads at the same scale. All data are from subject J. F. I. at rest (pilot experiments on J. V. P. were consistent). Cortical stimulation was timed to occur 1 ms after the test stimulus. Each point is obtained from an average of sixty-four reflexes (sixteen each of test, T; conditioned by spinal inhibitory action, C; conditioned by cortical stimulation, T_c; and conjointly conditioned, C_c). *A*, Ia reciprocal inhibition; *B*, group I non-reciprocal inhibition; *C*, D1 inhibition using a conditioning interval of 20 ms; *D*, D2 inhibition using a conditioning interval of 50 ms.

expression of facilitation and occlusion (just as with changes in the strength of peripheral inhibition). For this reason further experiments were performed in which the strength of both cortical and peripheral inhibitions were systematically varied (without compensation).

The experiments were organized in a similar fashion to the preceding ones and

both cortical inhibition and peripheral inhibitions were measured ($T_c/T\%$ and $C/T\%$ respectively). The degree of interaction is plotted against both peripheral and cortical inhibitory strength in three dimensions in Fig. 4. In these experiments the interaction was defined as the difference in strength of cortical inhibitory action in the presence and absence of spinal inhibitory action ($T_c/T - C_c/C\%$) but results are similar using the previous definition ($C/T - C_c/T_c\%$) (see also Appendix). In the cases of Ia reciprocal and group I non-reciprocal inhibition facilitation is evident when either the peripheral inhibition or the cortical inhibition, or both are weak. Occlusion occurs when both inhibitory actions are strong (Fig. 4*A* and *B*).

In the cases of D1, and D2 inhibition facilitation is present when the cortical action is weak and the peripheral action is fairly strong (Fig. 4*C* and *D*). This difference is also evident in Fig. 3*B*: cortical facilitation is most marked when D1, and D2 inhibition are induced with the strongest conditioning stimulus ($1{\cdot}05 \times \alpha T$).

DISCUSSION

Spatial interactions between cortical and spinal inhibitory actions on soleus H reflexes in man

The experiments on spatial interaction illustrated in Figs 2 and 3 indicate that cortical stimulation facilitates the pathways of Ia reciprocal inhibition and longer latency reciprocal inhibitions (D1 and D2). Results with group I non-reciprocal inhibition were equivocal, and those with presynaptic inhibition were negative. Facilitation was strongest when spinal inhibitory actions were weak, and tended to reverse to occlusion as the spinal action was made larger. Theoretically, large spinal or large cortical actions could lead to occlusion if shared interneurones exist. Experiments in which both spinal and cortical inhibitory actions were controlled and monitored (Fig. 4) demonstrated this effect, and removed some of the variability in strength (and sign) of the interaction. Experiments performed with this refinement showed a clearer cortical interaction with group I non-reciprocal inhibition (further discussion of experimental design and statistical treatment is included in the Appendix to this paper).

The interaction of cortical inhibition with Ia reciprocal and group I non-reciprocal inhibition shows both the facilitation and occlusion components expected theoretically. This is readily interpreted in terms of convergence of corticospinal and peripheral paths on the relevant spinal interneurones. Barker, Eyre, Kenyon & Miller (1987) have noted a facilitation of Ia reciprocal inhibition from triceps to biceps brachii. Rothwell, Day, Berardelli & Marsden (1984) reported a cortically evoked reduction of reciprocal inhibition in wrist and finger flexor muscles which parallels the occlusion found in the present experiments.

In the case of Ia–Ia presynaptic inhibition induced by pulsed vibration of biceps femoris no evidence of interaction was found. Furthermore, the longer latency (> 70 ms) component of reciprocal inhibition produced by three weak electrical shocks to the common peroneal nerve may be largely Ia–Ia presynaptic inhibition; and this component shows no significant interaction with cortical stimulation (Fig. 3*B*). However, negative results are not easy to interpret. Since we used short cortical conditioning intervals only corticospinal convergence with last order interneurones on the pathway of presynaptic inhibition is likely to have been revealed and even

then weak interaction could be obscured by variability in reflex amplitude. Nevertheless, Advani & Ashby (1990) have also failed to find any evidence for cortical control of the Ia input to soleus motoneurones.

The longer latency components of reciprocal inhibition of soleus motoneurones induced by electrical stimulation of the common peroneal nerve (D1, D2) facilitated corticospinal action. However, maximal facilitation was achieved when the peripheral action was substantial ($C/T = 60\%$, Fig. 4*C* and *D*), not when it was minimal (in contrast to both reciprocal and non-reciprocal inhibition: Fig. 4*A* and *B*). The simplest explanation for this result is that both D1 and D2 inhibition result from the combined actions of one pathway recruited by weak (group I) stimulation of the common peroneal nerve and not facilitated by the corticospinal system, and other pathways activated by stronger (group I–group II) peripheral stimulation which do interact with the corticospinal system. It is possible that the pathway activated at low threshold and not facilitated from the corticospinal system, which dominates at the longest conditioning intervals is that of Ia–Ia presynaptic inhibition (see above).

A role for cutaneous afferents cannot be excluded in the components of D1 and D2 inhibition that interact with the motor cortex, because cutaneous and muscle group I fibres in the common peroneal nerve have similar conduction velocities and thresholds. However, stimulation of the cutaneous sural nerve at the lateral malleolus did not reproduce the D1 and D2 inhibitions, even with concurrent cortical stimulation, and in some subjects had an excitatory action at a conditioning interval around 30 ms (cf. Berardelli, Day, Marsden & Rothwell, 1987). Long-latency components of D1 and D2 could represent a transcortical action (cf. excitatory actions on tibialis anterior: Iles, 1977), in which case spatial facilitation with the effects of cortical stimulation could be occurring at the cortex itself, rather than in the spinal cord. However, Yanagisawa (1980) has reported that D1 inhibition persists in paraplegia and is therefore a spinal action; the situation with respect to D2 is uncertain.

Crone & Nielsen (1989*b*) have reported that a polysynaptic (possibly propriospinal) reciprocal Ia inhibition of soleus motoneurones, maximal at conditioning intervals of 5 ms is prominent during tonic dorsiflexion of the foot. This action is thus intermediate in latency between classical Ia reciprocal and D1 inhibition and has not been studied in the present experiments.

The conclusion of the present work is that the corticospinal tract can inhibit soleus motoneurones through at least four spinal mechanisms: those responsible for Ia reciprocal, group I non-reciprocal, and higher threshold components of D1 and D2 inhibitions respectively. The lateral corticospinal tract does indeed have extensive anatomical projections to the human lumbar spinal cord (Nathan, Smith & Deacon, 1990).

Spatial interactions between cortical and spinal inhibitory actions in the cat

Corticospinal facilitation of Ia reciprocal and group I non-reciprocal inhibition in the cat lumbar spinal cord was demonstrated by Lundberg & Voorhoeve (1962). Subsequent work has shown that cortical actions are weakest for the non-reciprocal system (Harrison & Jankowska, 1985) as also observed for man in the present work. Comparisons with D1 and D2 inhibition are difficult because no clear homologies

have been established between these reflex actions in man and spinal mechanisms in the cat.

The components of D1 and D2 inhibition which were facilitated from the corticospinal tract in the present experiments originated from higher threshold stimulation of the common peroneal nerve (muscle group I/II, and possibly cutaneous afferents). Lundberg, Norssell & Voorhoeve (1962) described convergence of flexor reflex afferents (FRA), group I afferents in the deep peroneal nerve and the corticospinal tract on to lumbar interneurones. The longer latency reciprocal inhibitory actions in man may reflect the existence of a system of group II inhibition (cf. Lundberg, Malmgren & Schomburg, 1987 for the cat).

There is evidence that stimulation of the pyramidal tract in the cat inhibits the primary afferent depolarization induced in Ia afferents by Ia afferents (Rudomin, Jiminez, Solodkin & Duenas, 1983). This action occurs on interneurones early in the pathway of presynaptic inhibition and might not therefore be revealed in the present experiments which used short cortical conditioning intervals (though the cortical-induced reduction of inhibition at 150 ms conditioning interval visible in Fig. 3*B* might warrant further investigation). Cutaneous inhibition of presynaptic inhibition can be revealed in man (Iles & Roberts, 1987; Day, Marsden, Nakashima & Rothwell, 1987*a*). However, several strong stimuli to cutaneous nerves are generally required and it may not be practicable to produce an equivalently intense corticospinal volley in man.

Although further investigation of the D1 and D2 systems is required there is as yet no conflict between the data on cortico-spinal interaction with spinal inhibitory actions in man and in the cat.

Effects of cortical lesions on spinal inhibitory actions

There is general agreement that cortical or capsular lesions in man leading to hemiparesis are accompanied by reduced transmission in spinal reflex inhibitory pathways: Ia reciprocal inhibition (Nakashima, Rothwell, Day, Thompson, Shannon & Marsden, 1989); group I non-reciprocal inhibition (Delwaide & Oliver, 1988); Ia–Ia presynaptic inhibition (Iles & Roberts, 1986; Ongerboer de Visser, Bow, Koelman & Speelman, 1989); D1 and D2 inhibition (Ashby & Wiens, 1989; Nakashima *et al.* 1989). In all the examples except Ia–Ia presynaptic inhibition this result can be most simply interpreted as a withdrawal of corticospinal facilitation of the relevant interneurones. However, changes in extrapyramidal actions could also contribute as a variety of motor responses to cortical stimulation have been observed in a subject with lesions of the pyramidal tract (Fries, Danek & Witt, 1991).

Nakashima *et al.* (1989) have demonstrated dissociation of effects on Ia reciprocal and longer latency reciprocal inhibition (which includes D1, D2 and presynaptic actions) in cases of dystonia. If the longer latency inhibition studied by these authors includes a significant presynaptic component then the dissociation might reflect the differences in descending control of Ia reciprocal and Ia–Ia presynaptic inhibition indicated by the present work in man and that published for the cat (see above).

Functional considerations

Although soleus motoneurones receive a predominant inhibitory input from the corticospinal system in man, other lower limb functional extensors receive

predominant excitation (gastrocnemius: Zidar, Trontel & Mihelin, 1987; Benecke, Meyer, Göhmann & Conrad, 1987; vastus lateralis: Iles & Smith, 1988; flexor hallucis longus: Iles & Cummings, 1992). Differential actions on soleus and gastrocnemius were noted in the monkey by Preston & Whitlock (1963). This may in part reflect the distribution of motor unit type (Johnson, Polgar, Weightman & Appleton, 1973) if inhibition predominates in type I units. Such a differential distribution could permit the excitation of gastrocnemius and inhibition of soleus motor units observed during voluntary isotonic lengthening of triceps surae in man (Nardone, Romano & Schieppati, 1989). However, it is unlikely that the corticospinal modulation of spinal inhibitory actions on soleus motoneurones is unique to soleus, merely that in other muscles combined inhibitory and excitatory effects exist.

Kasser & Cheney (1985) found that in the monkey 29% of corticomotoneuronal cells distributing excitation to an agonist also inhibited the antagonist during a reciprocal movement task. During a task controlling joint stiffness, cortical systems producing excitation without concomitant reciprocal inhibition are activated (Humphrey & Reed, 1983). Cortical outputs producing predominant or exclusive inhibition of spinal motoneurones probably exist but are not segregated from areas producing excitatory actions (Schmidt & McIntosh, 1990).

All of the spinal inhibitory actions studied in the present experiments are modulated during voluntary movement (Ia reciprocal inhibition and group I non-reciprocal inhibition: see preceding paper and Yanagawa, Shindo & Nakagawa, 1991; long latency reciprocal inhibition: Iles & Roberts, 1987; Berardelli, Day, Marsden & Rothwell, 1987; Crone & Nielsen, 1989*b*; presynaptic inhibition: Iles & Roberts, 1987; Hultborn, Meunier, Pierrot-Deseilligny & Shindo, 1987; Ruegg, 1989). In all instances except the last (presynaptic inhibition) it could be proposed that the cortical controls revealed in the present experiments are operating during voluntary movement. However, those spinal inhibitory actions which were investigated were also modulated during vestibular-evoked postural reactions (see preceding paper) and are presumably controlled by pathways descending from the brainstem. The relative importance of direct cortical control of spinal reflex machinery and indirect control via the brainstem during voluntary movement therefore remains unclear.

Where both corticospinal and brainstem systems control the same machinery there may well be quantitative differences in their actions. Possibly the phylogenetically recent corticospinal pathway provides more selective control for breaking up fundamental synergies (paralleling its directed actions on motoneurone groups). The present experiments do not yet address this issue and spinal Ia–Ia presynaptic inhibition remains the system showing major differences in control by corticospinal and other descending pathways.

APPENDIX

Analysis of cortical modulation of spinal inhibitory actions including statistical treatment

The method of reflex testing and the expression of conditioning action in terms of the relation between conditioned and test reflex amplitude (C/T%) relies upon the

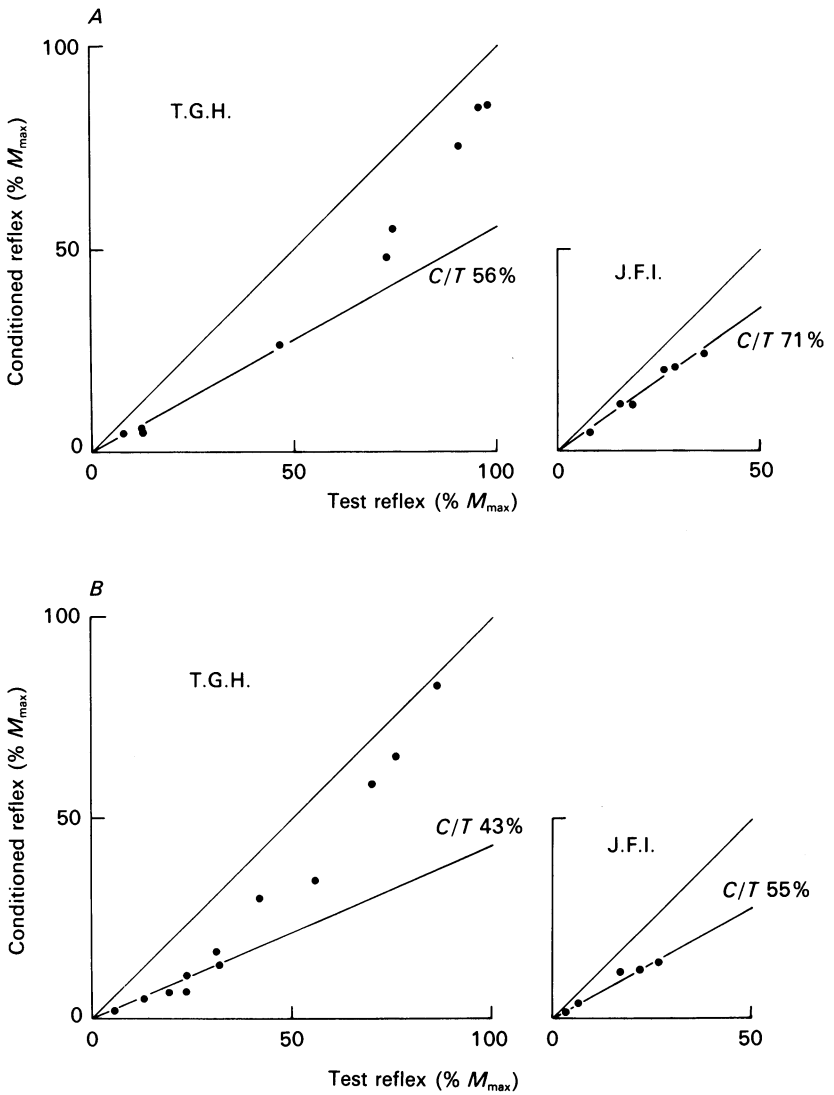

Fig. 5. *A*, estimates of Ia reciprocal inhibition of soleus H reflexes made with different sized test reflexes. Reflex amplitude is expressed as a percentage of the maximal motor response recorded from soleus (%M_{max}). Each point is obtained from the average of thirty-two conditioned and thirty-two test reflexes. Subject T.G.H.: ankle torque −8 N m (dorsiflexion), conditioning stimulus to common peroneal nerve 1·2 × αT, randomized presentation. Note that for test reflexes < 50% maximal motor discharge, C/T = 56%; for larger test reflexes it is closer to 100%. The regression line has been drawn through the origin and fitted to data points up to test reflex = 50% M_{max}. Subject J.F.I.: torque −7 N m, conditioning stimulus 1·02 × αT, randomized presentation. All reflexes are < 40% maximal motor discharge and C/T is constant at 71%. The regression line has been drawn through the origin and fitted to all the data points. *B*, estimates of group I non-reciprocal inhibition of soleus H reflexes made with different sized test reflexes. Subject T.G.H.: resting, conditioning stimulus to medial gastrocnemius nerve 1·05 × αT. Note that for test reflexes < 40% maximal motor discharge C/T = 43%, for larger reflexes it is closer to 100%. The regression line has been drawn through the origin and fitted to data points up to test reflex = 40% M_{max}. Subject J.F.I.: torque

fact that for a given conditioning input this ratio remains constant over a range of amplitudes of the test reflex.

This is illustrated in Fig. 5*A* for conditioning with Ia reciprocal inhibition and in Fig. 5*B* for group I non-reciprocal inhibition. These plots of conditioned reflex amplitude *versus* test reflex amplitude, over the full range of test reflex amplitudes that could be elicited from the subjects, show a constant slope (C/T%) for test reflexes up to about 35% of the maximal motor response. For larger reflexes the slope increases. The same result has been illustrated for Ia–Ia presynaptic inhibition (Iles & Roberts, 1986 their fig. 4). Essentially similar results have been presented by Crone, Hultborn, Mazieres, Morin, Nielsen & Pierrot-Deseilligny (1990: in their figures near linear plots of decrease in conditioned reflex size *versus* test reflex size correspond to the linear regions in Fig. 5 for small test reflexes). In the experiments on cortical modulation of spinal reflexes reported in the present paper, test reflexes of 5–25% of the maximal motor response of soleus (M_{max}) have been used, which are comfortably within the range of close to linear behaviour (constant C/T%).

An alternative strategy has been utilized by Yanagawa *et al.* (1991). This consists of using large test reflexes (30 to 70% M_{max}) where the absolute quantity of inhibition (defined as $(T-C)/M_{max}$% using the conventions of the present paper) is relatively constant. The choice of strategy depends primarily on the range of test reflex amplitudes that are encountered. In the present experiments, involving interactions of inhibitory phenomena, small reflexes inevitably resulted.

Two approaches have been used to investigate cortical modulation of spinal inhibition. Both rely on evaluating spinal inhibitory action in the absence and presence of cortical stimulation (C/T and C_c/T_c respectively). The null hypothesis of no spatial interaction predicts identical spinal inhibitory actions ($C/T-C_c/T_c = 0$). Cortical facilitation of spinal inhibitory action predicts a positive spatial interaction ($C/T-C_c/T_c > 0$).

In the experiments illustrated in Fig. 2 (and analogous experiments in the preceding paper) adjustments were made to the stimulus eliciting the reflexes to ensure that test reflex amplitude remained constant ($T_c = T$). The same procedure was used by Lundberg & Voorhoeve (1962). This has the merit of decreasing reliance on the linearity of reflexes discussed above, but also the deficiency that information on the strength of cortical action is lost. The preliminary data of Fig. 2, and the data described in the preceding paper both indicate that facilitation depends upon the strength of the spinal reflex action, changing to occlusion as this becomes stronger. Since the same should be true as the strength of cortical action increases there is an obvious advantage in retaining information about both spinal reflex and cortical actions. Experiments of this type are illustrated in Fig. 4. In the simplest cases of Ia reciprocal and group I non-reciprocal inhibition, facilitation predominates in the predicted region: where both spinal and cortical inhibitory actions are weak.

Two questions arise when interpreting this result. The first is whether it could emerge from some remaining non-linearity in the relationship between conditioned

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+6 N m (plantar flexion), conditioning stimulus 1·1 × αT. All reflexes are < 30% maximal motor discharge and C/T is constant at 55%. The regression line has been drawn through the origin and fitted to all the data points. It should be noted that subject T.G.H. was most unusual in showing a near maximal H reflex even during voluntary dorsiflexion.

and test reflexes. This is unlikely. If the plot of conditioned *versus* test reflex amplitude is always concave upwards (as it is for large test reflexes: Fig. 5) then facilitation would be expected to increase as either (or both) spinal and cortical inhibitory actions increase (i.e. the reflexes become smaller). In fact, the reverse is

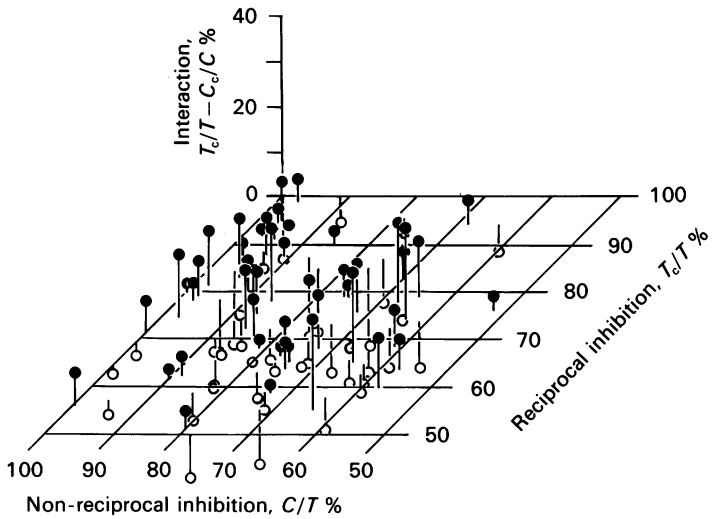

Fig. 6. Three-dimensional plot for the control experiment relating group I non-reciprocal inhibitory action (C/T%, x-axis), Ia reciprocal inhibitory action (T_c/T%, y-axis) and spatial interaction ($T_c/T - C_c/C$%, z-axis). All data from subject J.F.I. at rest. Other conventions as for Fig. 4.

found: facilitation changes to occlusion. The second question concerns statistical reliability: the spatial interaction still shows some variability in Fig. 4. This would arise from variability in reflex amplitude. Unfortunately, although the coefficient of variation of soleus H reflexes has been evaluated under these experimental conditions (Iles & Roberts, 1987, their fig. 1) it is not possible to predict the variation in spatial interaction that would arise from this source alone because the interaction is expressed as a difference ($T_c/T - C_c/C$%).

The questions of whether the observed spatial interactions could arise spuriously from some non-linearity in the relationship between conditioned and test reflexes, or by chance from random variations in reflex amplitude have instead been approached experimentally. The relevant control experiment consisted of studying the spatial interaction of two examples of spinal inhibition: Ia reciprocal and group I non-reciprocal inhibition. These were chosen because extensive animal experimentation has confirmed that there are no interneurones common to these two reflex pathways.

Schieppati, Romano & Gritti (1990) have proposed an interaction between *Ia afferents* in the medial gastrocnemius nerve and Ia reciprocal inhibition of soleus in man. This interaction was observed with shorter medial gastrocnemius conditioning intervals than used here and could not be confirmed on the subject (J.F.I.) used for the control experiment.

Therefore, an experiment analogous to that with Ia reciprocal and cortical actions

(Fig. 4*A*) but using Ia reciprocal and group I non-reciprocal spinal actions would be predicted to show no net facilitation (or occlusion) and to reveal the variability in spatial interactions arising from random variation in reflex amplitude.

The control experiment is illustrated in Fig. 6 where the data are plotted in the same format as Fig. 4 (and use the same subject). Simple inspection indicates that although the individual experimental averages show differences in the value of reciprocal inhibition alone and in the presence of non-reciprocal inhibition, these occur with random sign (facilitation or occlusion) and randomly disposed in relation to the strength of reciprocal and non-reciprocal inhibition. This is confirmed by statistical analysis. The average spatial interaction has the value $1{\cdot}1 \pm 9{\cdot}0\,\%$ (mean $\pm$ S.D.). A multiple regression of the spatial interaction on the values of reciprocal and non-reciprocal inhibition shows that there is no significant relationship between the interaction and the strength of either inhibitory action (only 0·3 % of the squared deviations are accounted for by the regression). By way of contrast a multiple regression performed on the data of Fig. 4*B* shows a significant ($P < 0{\cdot}02$) relation between the interaction and the strengths of both non-reciprocal and cortical inhibitory actions (23 % of the squared deviations are accounted for by the regression). The mean of the squared deviations for the data of Fig. 6 is very close to that not accounted for by the regression for the data of Fig. 4*B*. This result shows firstly that where no interaction between two inhibitory pathways is predicted no consistent interactions (facilitation or occlusion) are found, and secondly that the variation observed in the control experiment is a good estimate of the variation contributed by random fluctuation in reflex amplitude.

The control experiment also provides an opportunity to test the statistical significance of the results illustrated in Fig. 4. To do this, five regions were defined on the basis of the strength of spinal reflex and cortical inhibition (Fig. 7). The population of interactions in a particular region were compared statistically with the population in the corresponding region of Fig. 6. For example, in the case of the interaction between Ia reciprocal inhibition and cortical inhibition (Fig. 4*A*) there are nine data points for the region of weakest inhibitory strength ($C/T > 90\,\%$, $T_c/T > 90\,\%$). Comparison with the seven points in the corresponding region of Fig. 6 shows a difference in mean value of $+13{\cdot}8\,\%$ (Fig. 7*A*). This degree of facilitation is statistically significant ($P = 0{\cdot}024$). This analysis confirms that in the case of interaction between Ia reciprocal inhibition and cortical inhibition, and between group I non-reciprocal inhibition and cortical inhibition there is significant facilitation when the inhibitory actions are weak and significant occlusion when they are strong (Fig. 7*A* and *B*). In the case of interaction between D1 and cortical inhibition, and D2 and cortical inhibition, there is significant facilitation when the spinal inhibition is strong and the cortical inhibition is weak. This statistical approach is conservative and used the same subject for test and control. A case could be made for testing the data of Fig. 4 against the complete data set of Fig. 6 (rather than small regions thereof), or even against the hypothesis that the interaction is zero.

The final issue to be considered is the size of the spatial interactions observed. The data presented in Fig. 2*A* show a maximal facilitation of Ia reciprocal inhibition by corticospinal action of 20 %. The parallel experiment in the cat reported by

Lundberg & Voorhoeve (1962, their fig. 5) shows facilitation of 70% (defined as $C/T - C_c/T_c\%$). Two factors may contribute to this difference. First, in the larger organism, man, dispersion in the peripheral and cortical volleys when they arrive at the spinal cord may lead to optimal timing of inputs for facilitation in a much smaller

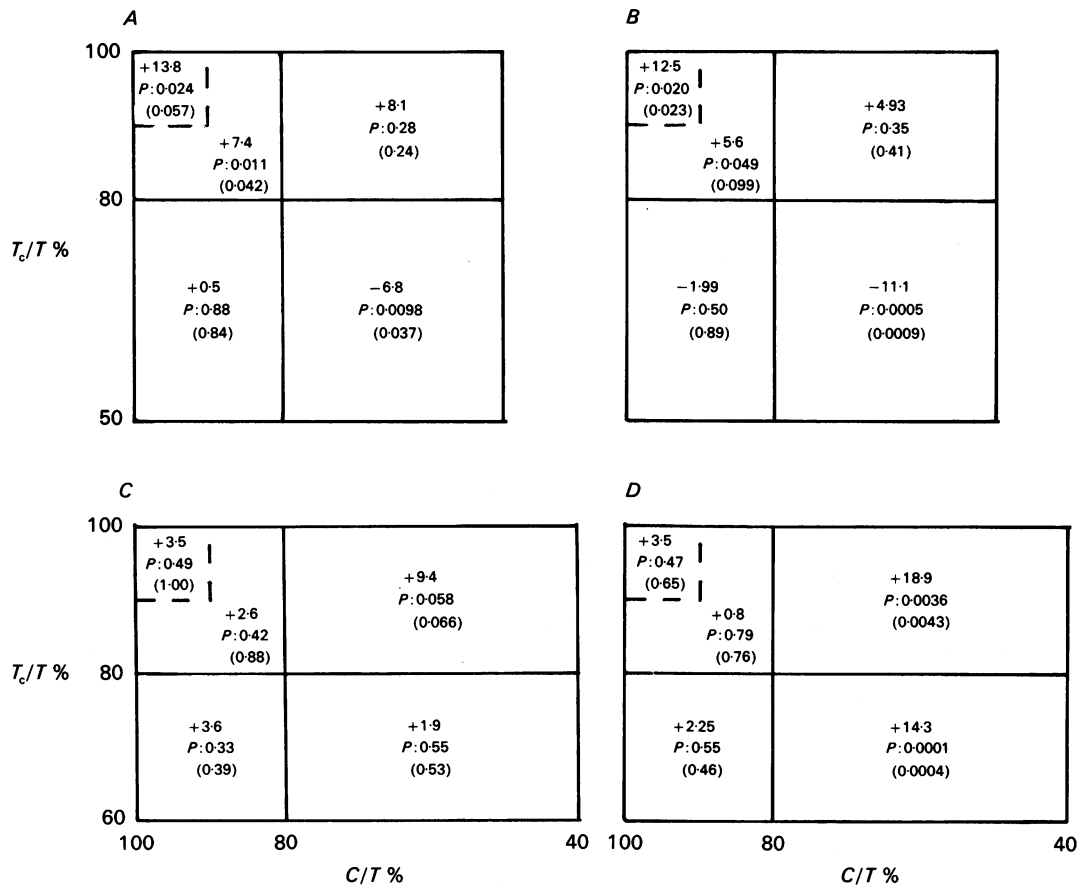

Fig. 7. Summary of statistical comparisons between the spatial interactions observed in Fig. 4 and the control experiment of Fig. 6. In each case the data have been grouped into five regions on the basis of strength of spinal and cortical inhibitory actions (C/T% and T_c/T% respectively). In each region the figures give the difference in the mean value of the interaction between the data sets of Figs 4 and 6 (positive values: facilitation; negative values: occlusion); the statistical significance of the difference: two tailed t test with pooled variance and (in brackets) the significance level reached by the more conservative Mann–Whitney U test. *A*, I a reciprocal inhibition; *B*, group I non-reciprocal inhibition; *C*, D1 inhibition; *D*, D2 inhibition.

proportion of the spinal inhibitory interneurones. Second, in the anaesthetized cat, the membrane potential of the interneurones is likely to be substantially below threshold thus permitting a large degree of spatial summation (see Discussion in the preceding paper).

Theoretically, more information can be obtained from the maximum degree of

occlusion that results from strong activation of either cortical or peripheral pathways. In Fig. 8 the limits of facilitation and occlusion with the two possible definitions of spatial interaction are enclosed by continuous lines.

Complete occlusion of spinal inhibition by strong cortical inhibition (for example an interaction of -90% at $C/T = T_c/T = 10\%$ in Fig. 8*A*) would be evidence that

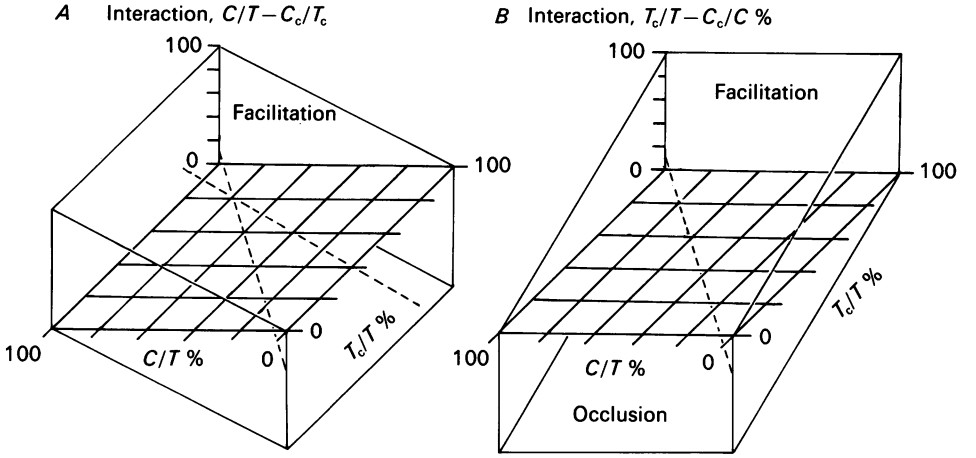

Fig. 8. *A*, spatial interaction defined as the difference in spinal inhibitory action in the presence and absence of cortical stimulation ($C/T-C_c/T_c\%$: z-axis) plotted against strength of spinal inhibitory action ($C/T\%$: x-axis) and cortical inhibitory action ($T_c/T\%$: y-axis). The maximal extent of facilitation and inhibition using this definition are indicated (ignoring effects introduced by random variation in H reflex amplitude). The regression from Fig. 2*A* has been plotted as an interrupted line (at $T_c/T = 80\%$). A multiple regression of the data set illustrated in Fig. 4*A* (but using this definition of spatial interaction) has been plotted as the second interrupted line. *B*, spatial interaction defined as the difference in cortical inhibitory action in the presence and absence of spinal inhibitory action ($T_c/T-C_c/C\%$: z-axis). Other details as for part *A*. A multiple regression of the data of Fig. 4*A* has been plotted as the interrupted line.

all the spinal inhibitory interneurones activated receive cortical input. In practice the multiple regression from the data set of Fig. 4*A* extrapolates to less than maximal occlusion (-27% at that point). However, cortical inhibition that great was not achieved and extrapolation could be invalid. Magnetic stimulation of the cortex may permit direct investigation of occlusion during strong cortical inhibition without gross discomfort to the subject (Iles, 1991).

Complete occlusion of cortical inhibition by strong peripheral stimulation (Fig. 8*B*) would be evidence for all that cortical inhibition being mediated via the set of spinal interneurones activated by the peripheral input. The regression line shows less than maximal occlusion. Although extrapolation is again suspect, incomplete occlusion would be consistent with the conclusion from the present work that cortical inhibition utilizes at least four separate spinal inhibitory mechanisms.

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