Evidence for cutaneous and corticospinal modulation of presynaptic inhibition of Ia afferents from the human lower limb

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1. Presynaptic inhibition of soleus muscle Ia afferent fibres, produced by stimulation of group I afferents in the common peroneal nerve, was assessed from changes in the H reflex at long conditioning intervals, in six normal subjects.

2. Stimulation of the ipsilateral sural nerve at the malleolus, just before stimulation of the common peroneal nerve at the head of the fibula, decreased the presynaptic inhibition. This effect was strongest during voluntary plantar flexion and weaker during dorsiflexion or at rest.

3. Stimulation of other cutaneous nerve branches serving the dorsum of the ipsilateral foot, and also the contralateral sural nerve, decreased presynaptic inhibition. Adequate stimulation of low threshold cutaneous mechanoreceptors by light brushing of both distal dorsal and plantar surfaces of the ipsilateral foot decreased presynaptic inhibition.

4. Stimulation of the ipsilateral plantar nerves increased presynaptic inhibition, but this action is attributed to activation of group I afferents from the intrinsic muscles of the foot.

5. Transcranial magnetic stimulation of the lower limb area of the contralateral motor cortex decreased presynaptic inhibition. This effect was strongest during voluntary plantar flexion and weaker during dorsiflexion or at rest.

6. The actions of cutaneous and corticospinal pathways completely occluded each other. However, when both effects were adjusted to be liminal, a spatial facilitation between them was observed.

7. It is concluded that in man, as in the cat, cutaneous and corticospinal axons converge on interneurones that inhibit the machinery of presynaptic inhibition of group Ia afferents. These actions may be responsible for the modulation of presynaptic inhibition which has been observed to precede and accompany a wide range of human movements.

The control of motoneuronal excitability by muscle spindle Ia afferents is a fundamental feature of organization in the segmental motor system of vertebrates. In the cat, monosynaptic excitatory projections are very precisely focused onto homonymous motoneurones and heteronymous motoneurones where the muscles are close synergists, with other connections being infrequent (see Hultborn & Illert, 1991). Transmission between Ia afferents and motoneurones is under presynaptic inhibitory control (Rudomin, 1990). Presynaptic inhibition is stimulated by activity in group Ia and Ib afferents from many muscles ranging from close synergists to those acting at distant joints. The only discernible pattern in this action is that flexor group I afferents are more potent than those from extensors, and that extensor Ia afferents receive more presynaptic inhibition than flexor Ia afferents. A broadly similar pattern of presynaptic inhibition has been found in the human lower limb afferents (Iles & Roberts, 1987).

The paradox of a precisely organized pattern of monosynaptic Ia projections under diffuse group I-activated presynaptic control is resolved by evidence that presynaptic inhibition is very selectively modulated during voluntary movements. In man, presynaptic inhibition of Ia afferents projecting to the motoneurones of a target muscle is selectively reduced during its voluntary contraction (or co-contraction with the antagonist), whereas presynaptic inhibition of afferents terminating on the motoneurones of other (non-contracting) muscles is enhanced (Iles & Roberts, 1987; Hultborn, Meunier, Pierrot-Deseilligny & Shindo, 1987; Nielsen & Kagamihara, 1993*a*). In man, a rather

more complex set of monosynaptic Ia connections exists compared to the cat and it has been proposed that control of presynaptic inhibition provides a mechanism for selection between members of the set (Meunier, Pierrot-Deseilligny & Simonetta, 1993).

Extensive work in the cat has revealed two sites at which presynaptic inhibition of Ia afferents could be controlled (see Jankowska, 1992; Rudomin, Quevedo & Eguibar, 1993; Quevedo, Eguibar, Jiminez & Rudomin, 1995). The first-order interneurones on the pathway of presynaptic inhibition are excited by group I afferents of wide origin and by activation of the vestibular system, are inhibited by the corticospinal, rubrospinal and raphespinal tracts, and are inhibited by cutaneous afferents. The last-order interneurones are inhibited as a result of activation of the bulbar reticular formation.

Some evidence of vestibular control of presynaptic inhibition of Ia afferents in man has been published (Iles & Pisini, 1992*a*). Evidence from the study of voluntary contraction (above) suggests corticospinal control, but the results of direct cortical stimulation in man are currently inconclusive (Advani & Ashby, 1990; Iles & Pisini, 1992*b*) and only limited information is available on cutaneous control of synaptic actions of the lower limb afferents (Iles & Roberts, 1987). The present work was designed to extend the description of cutaneous control and to provide direct evidence for corticospinal modulation of presynaptic inhibition in the human lower limb system. A brief account has been published (Iles, 1994).

METHODS

Experiments were performed on six neurologically normal adult subjects with informed consent and Ethical Committee approval. The overall experimental arrangements have been described previously (Iles & Pisini, 1992*a*, *b*).

The basic experimental procedure was to set up a test monosynaptic reflex (H reflex) in the soleus muscle of the right leg in a sitting subject. Presynaptic inhibition of the soleus Ia afferent fibres responsible for the reflex was induced by a single conditioning stimulus activating group I afferents of the common peroneal nerve at the head of the fibula, or, in some experiments, by mechanical activation of Ia afferents in tibialis anterior muscle. The strength of electrical stimuli to the common peroneal nerve is expressed relative to the threshold for motor axons (× MT). The degree of presynaptic inhibition was assessed by comparison of test (T) and conditioned (C) reflexes, and evaluated by dividing conditioned by test reflex amplitude (C/T %).

The degree of presynaptic inhibition was then re-evaluated with conjoint stimulation of either cutaneous or corticospinal pathways (c). Both test (T_c) and conditioned (C_c) reflexes were preceded by stimulation of the putative controlling pathway and presynaptic inhibition was defined as before (C_c/T_c %). Modulation of presynaptic inhibition is expressed as the difference $C/T - C_c/T_c$ %. A negative value indicates a decrease in presynaptic inhibition.

Single-shock group I stimulation of the common peroneal nerve (stimuli: 0·7–0·99 × MT with electrodes placed to favour stimulation of the nerve branch to tibialis anterior) produced significant inhibition of the H reflex for intervals between conditioning and test stimuli from 70 to 250 ms (see also Iles & Pisini, 1992*b*, their Fig. 3). An interval of 100 ms was used except where otherwise indicated. The inhibition produced by this weak stimulation at such long conditioning intervals is predominantly presynaptic (see Discussion).

Cutaneous afferents were activated by electrical stimulation through electrodes placed 3–6 cm apart on the skin over selected nerve branches (cathode proximal). In most experiments a tetanus of four shocks at 330 Hz was used. Stimulus strength is expressed in multiples of the perceptual threshold for a single shock (× PT). Times are measured from the last shock of a tetanus. The stimulus combinations and interstimulus time intervals employed in these experiments are indicated in Fig. 1.

In some experiments adequate mechanical stimulation of the skin was used. The head of an artist's paint-brush was attached to the spindle of a light 3 V electric motor and placed on the skin of the foot where the bristles contacted an area of about 4 cm^2. A relay was used to connect a 12 V supply to the motor for 100 ms (the low duty cycle enabled the motor to be overloaded). The brush performed around five rotations per current pulse.

The corticospinal tract was activated by transcranial magnetic stimulation with a Novametrix Magstim 200. A 9 cm circular coil was placed on the mid-sagittal line with the rostral part crossing the vertex. Current flow in the coil was from left to right for optimal activation of the left motor cortex foot area. The latencies of responses in lower limb muscles are identical for this mode of magnetic stimulation and surface anodal electrical stimulation (Iles, 1990; Iles & Cummings, 1992). Results can therefore be directly compared with those obtained using electrical stimuli (Iles & Pisini, 1992*b*).

Reflexes were induced in a regular order (T, C, T_c, C_c, T etc.) and accumulated to give an average of sixteen in each condition. These averages were then repeated to give the means and standard errors of the mean depicted in the figures (details of the number of averages contributing to a mean are provided in the legends). All the phenomena reported were confirmed in experiments with a pseudorandom presentation of test and conditioned reflexes. Data with regular and pseudorandom order of presentation are combined in the figures. Except where indicated data from subjects J.F.I. and A.B., both of height 164 cm and with identical reflex and corticospinal conduction times, have been combined. Data from four taller subjects (D.S., height, 175 cm; H.P., 185 cm; P.F., 183 cm; S.B., 178 cm) have been treated independently. In all cases except Fig. 2, which depicts a single experiment, data from several experimental sessions on J.F.I. and A.B. were combined to improve accuracy. Figure 5*A*, for example, includes ten means, each obtained from seven averages; whereas the number of averages obtained in a single, comfortable experimental session rarely exceeded fifteen. The data presented from the taller subjects were all obtained in single sessions and are representative of the variation found between subjects.

Most experiments were performed at rest but in some the subject made small sustained dorsiflexion or plantar flexion contractions under auxotonic conditions (Maier, Bennett, Hepp-Reymond & Lemon, 1993).

RESULTS

The experimental protocol

The present experiments were designed to investigate the time course and local sign of cutaneous modulation of presynaptic inhibition in man, the presence and time course of modulation of presynaptic inhibition from direct stimulation of the corticospinal tract, and the behaviour of both forms of modulation during simple movements.

Test reflex amplitude

Preliminary experiments were performed to investigate the validity of the H reflex method for assessing presynaptic inhibition and its modulation by cutaneous afferent stimulation.

In Fig. 2, the test stimulus to the tibial nerve was varied in strength to obtain a range of test reflex amplitudes on the ascending limb of the H reflex recruitment curve. The amplitude of the reflex conditioned by stimulation of group I afferents of the common peroneal nerve (C) is plotted against test reflex amplitude (T), both expressed as a percentage of the maximal motor discharge (% M_{max}). For reflexes up to 25 % M_{max} the inhibition produced by stimulation of the common peroneal nerve is constant ($C/T = 47{\cdot}4\%$, ●). Stimulation of cutaneous branches of the deep peroneal nerve reduced the inhibition ($C_c/T_c = 57{\cdot}2\%$, □), giving a modulation of inhibition of −9·8%. Similar results were obtained for subject A.B. using both sural and peroneal cutaneous nerves.

These experiments show that the level of presynaptic inhibition and its modulation by cutaneous input are both independent of test reflex amplitude below a level of about 25% M_{max} (see also Iles & Roberts, 1987, their Fig. 4). In subsequent experiments test reflex amplitude was kept within the range 5–10% M_{max} for subject A.B. and 5–15% M_{max} for J.F.I. and the taller subjects.

Conditioning interval for cutaneous modulation

Most experiments were performed with a common peroneal nerve–test stimuli interval of 100 ms, but modulation from stimulation of cutaneous afferents was also found with intervals from 70 to 250 ms. There was no obvious variation of cutaneous modulation with conditioning–testing interval provided that the cutaneous stimulation always preceded the common peroneal nerve stimulus by the same time interval. The cutaneous stimuli themselves had very small or insignificant actions on the test reflex ($95\% < T_c/T < 103\%$) at the intervals used in the present experiments. However, stimulation of the ipsilateral sural nerve at intervals of less than 95 ms or more than 125 ms before the test reflex produced significant facilitation (cf. Delwaide & Crenna, 1983; Aniss, Diener, Hore, Burke & Gandevia, 1990).

Level of presynaptic inhibition

The modulation of presynaptic inhibition from cutaneous stimulation was related to the level of presynaptic inhibition. A linear regression was performed on a data set (51 averages) of subject J.F.I. which used tetanic sural stimulation at 1·5 × PT, 10 ms before the common peroneal nerve stimulus and had a range of C/T values between 16 and 70%. The regression equation for modulation on level of presynaptic inhibition was:

$$\text{Modulation } (C/T - C_c/T_c) = 25{\cdot}7\,C/T - 20{\cdot}8\%$$

($P = 0{\cdot}04$). This would be anticipated: the weaker the presynaptic inhibition, the less scope for a decrease following cutaneous stimulation.

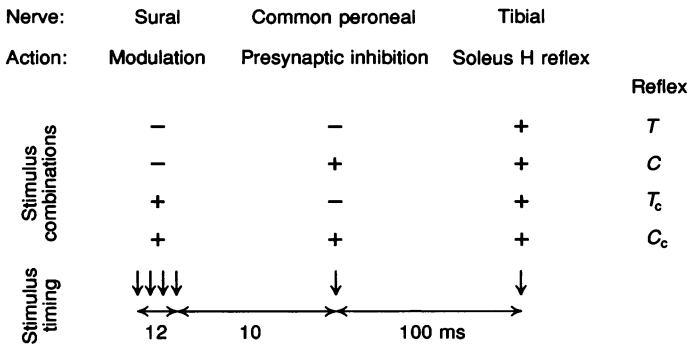

Figure 1. Stimulus combinations and stimulus timing used to demonstrate cutaneous modulation of presynaptic inhibition

The stimulus combinations and standard timings used to produce the test reflex (T), the conditioned reflexes (C, T_c) and the doubly conditioned reflex (C_c) are indicated (+, stimulus present: −, stimulus absent). The standard interval of 10 ms between the last stimulus to the sural nerve and the stimulus to the common peroneal nerve was increased to 12 ms in experiments using the more distal deep peroneal nerve (e.g. experiment of Fig. 2) and was varied systematically between −15 and +25 ms in the experiments illustrated in Fig. 3.

During subsequent experiments small adjustments were made to the stimulus to the common peroneal nerve to keep C/T in the range 40–80%. Where appropriate, data were transformed to remove the dependence on C/T before applying statistical tests (see below).

Afferents responsible for the presynaptic inhibition

Experiments were also performed in which group Ia afferents from tibialis anterior were more selectively activated by a mechanical stimulus to the muscle belly. The stimulus was a single impulse produced by applying a brief voltage pulse to an electromagnetic actuator (Ling Dynamic Systems model 200: see Methods in Iles & Roberts, 1987). This conditioning stimulus produced inhibition at conditioning intervals measured from the onset of the voltage pulse of 50–200 ms, though subsequent experiments used an interval of 80 ms. Because the delays in actuating the probe, activation of the sensory endings and conduction in the sensory nerve terminals are unknown, this conditioning interval cannot be directly equated with those using electrical stimulation. Stimulation of the sural nerve (four shocks at 1·5 × PT) significantly decreased presynaptic inhibition produced by mechanical stimulation (Wilcoxon test, $P = 0{\cdot}014$).

Cutaneous modulation of presynaptic inhibition or interaction of cutaneous pathways?

The common peroneal nerve is a mixed nerve and experiments were designed to test whether stimulation of cutaneous nerves was indeed decreasing presynaptic inhibition originating from group I muscle afferents, or instead was interacting with some action of *cutaneous* afferents in the common peroneal nerve. To do this, peripheral cutaneous branches of the common peroneal nerve (branches of the superficial peroneal nerve on the dorsum of the foot and the deep peroneal nerve at the hallux) were stimulated with single shocks replacing stimulation of the common peroneal nerve. Stimulus strengths were 1·5 and 2 × PT, respectively, which produced a sensation in the foot slightly stronger than that induced by stimulation of the common peroneal nerve over the head of the fibula at just below motor threshold. The interval between stimulation of the peripheral branches and the end of the tetanus of the sural nerve (110 ms before test) was set at 2 ms (i.e. 112 ms before test) to compensate for the distance between the peripheral branches and the normal site of stimulation of the common peroneal nerve. Stimulation of these peripheral cutaneous branches had no significant effect on the test reflex and no modulation was found with concurrent stimulation of the sural nerve. This suggests that there are no significant interactions between cutaneous afferents in the common peroneal nerve and other cutaneous afferents from the foot under the conditions of the present experiments.

Modulation of presynaptic inhibition by cutaneous afferents

Time course of cutaneous modulation

The time course of modulation of presynaptic inhibition by stimulation of the ipsilateral sural nerve is illustrated in Fig. 3*A* and *B*. Maximal reduction in presynaptic inhibition

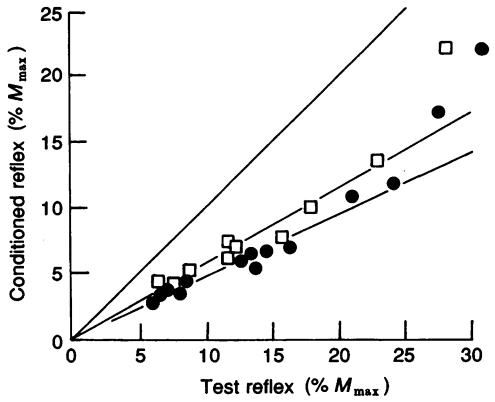

Figure 2. Estimates of presynaptic inhibition of soleus Ia afferents made with different sizes of test reflex

The amplitude of reflexes conditioned by stimulation of the common peroneal nerve (C; ●, stimulus of 0·9 × MT, 100 ms before test) is plotted (ordinate) against the amplitude of the corresponding test reflexes (T, abscissa; both C and T expressed as percentage maximal motor discharge in soleus: % M_{max}). Each point represents an average obtained from 16 test and 16 conditioned reflexes. A regression line is fitted through the origin and data for $T < 25\%\ M_{max}$ (slope $C/T = 47{\cdot}4\%$). □, data for reflexes conditioned by the common peroneal nerve plus stimulation of the deep peroneal nerve (1·5 × PT, tetanus of four shocks ending 112 ms before test). The slope of the regression line for these data is $C_c/T_c = 57{\cdot}2\%$. A line of slope 100% (corresponding to zero inhibition) is plotted for reference. Data were obtained in one experimental session on subject J.F.I.

was produced when the last shock of the tetanus to the sural nerve preceded the common peroneal nerve stimulus by around 15 ms. There was a very small effect at 0 ms when just one of the sural nerve volleys could have entered the spinal cord in advance of the common peroneal nerve volley. There was no modulation when the sural nerve volley was timed to arrive at the spinal cord after the input from the common peroneal nerve. The modulation was smallest in subject S.B. However, in all five subjects considered individually there was a statistically significant ($P \leqslant 0{\cdot}05$, Wilcoxon test) decrease in presynaptic inhibition at an interval of 4 or 5 ms and in the subjects other than S.B. the effect persisted to 20 ms. In the sixth subject, P.F., a *single* shock to the sural nerve at 1·4 × PT, 10 ms before stimulation of the common peroneal nerve, produced a small but statistically significant reduction in presynaptic inhibition (modulation of −2·5%, $P = 0{\cdot}05$).

Threshold for cutaneous modulation

A small reduction of presynaptic inhibition could be observed with electrical stimulation of the sural or deep peroneal nerve at 1·2 × PT and maximal action was found between 1·5 and 2 × PT (tetanus of four shocks, 15 ms interval between end of tetanus and common peroneal nerve stimulus). In most experiments a stimulus of 1·5 × PT was used.

Effects of voluntary muscle contraction

The reduction in presynaptic inhibition produced by submaximal electrical stimulation of cutaneous afferents (sural nerve, 1·3 × PT, three shocks) was present at rest and during a weak dorsiflexion of the foot (2 N m torque about the ankle). It was three times larger during plantar flexion (4 N m torque).

Presynaptic inhibition of soleus Ia afferents is reduced during plantar flexion under the present experimental conditions (Iles & Roberts, 1987; cf. Nielsen & Kagamihara, 1993; though elderly subjects show smaller changes: Roberts, Part, Farquhar & Butchart, 1994), and the cutaneous modulation is proportional to the level of presynaptic inhibition (see above). Therefore, although the stimulus to the common peroneal nerve was adjusted to try to keep the level of presynaptic inhibition within the desired range it was still necessary to transform the data to remove the dependence on the level of inhibition before applying statistical tests for differences under the three conditions of muscle contraction. This was done by calculating $(C/T - C_c/T_c)/(100 - C/T)\%$. The difference (increase) in modulation found during plantar flexion was statistically significant (the mean modulation was 3·3, 3·3 and 9·4% for dorsiflexion, rest and plantar flexion, respectively; Kruskal–Wallis test: $P = 0{\cdot}09$; one-way analysis of variance: $P = 0{\cdot}01$).

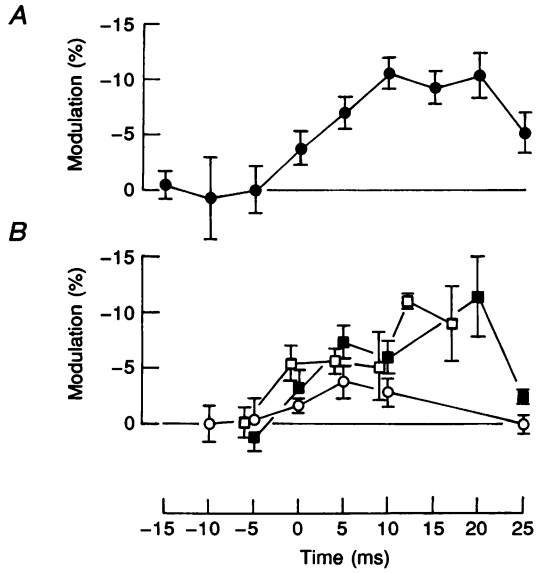

Figure 3. Time course of modulation of presynaptic inhibition by stimulation of the ipsilateral sural nerve (1·5 × PT, tetanus of four shocks at 333 Hz)

Presynaptic inhibition was induced by stimulation of the common peroneal nerve (0·95 × MT, 100 ms before test). The modulation of presynaptic inhibition ($C/T - C_c/T_c\%$) is plotted on the ordinate (decrease in inhibition upwards) against the time interval between the last shock to the sural nerve and the stimulus to the common peroneal nerve (abscissa, negative intervals indicate that the common peroneal nerve stimulus preceded the last sural stimulus). In *A*, data accumulated in several experimental sessions on subjects A.B. and J.F.I. have been combined. From 10 to 51 averages (each of 64 reflexes) were used to calculate the modulation at each time interval. The means and S.E.M. are plotted. In *B*, data from single experimental sessions on three taller subjects are plotted (S.B., ○; H.P., ■; D.S., □). Four or five averages were used to calculate the modulation at each time interval.

Local sign of cutaneous action studied using electrical stimulation of peripheral cutaneous nerve branches

Ipsilateral actions. The effects of stimulating various cutaneous nerve branches in the foot are summarized in Fig. 4*A*. Stimulation of the sural nerve at the lateral malleolus or more distally, the superficial peroneal nerve on the dorsum of the foot and the deep peroneal nerve at the hallux was in all cases effective in reducing presynaptic inhibition of soleus afferents. Stimulation of the cutaneous nerves had no significant effect on the test reflex with the exception of distal branches of the superficial peroneal nerve where stimulation at 2 × PT produced a significant facilitation ($T_c/T = 109 \pm 3\%$; $P < 0{\cdot}02$, Wilcoxon test). Stimulation of the plantar nerves was either without effect (medial branch) or increased presynaptic inhibition (lateral branch).

The plantar nerves are mixed nerves containing afferents from skin on the plantar aspect and from intrinsic muscles of the foot. The increase in inhibition with plantar nerve stimulation was observed at a stimulus intensity close to motor threshold for intrinsic muscles. Furthermore, stimulation of the parent posterior tibial nerve at the medial malleolus and the lateral plantar nerve itself produced inhibition of the test reflex for conditioning intervals extending beyond 250 ms. These observations suggested that muscle afferents were being activated which directly contributed to presynaptic inhibition of soleus afferents.

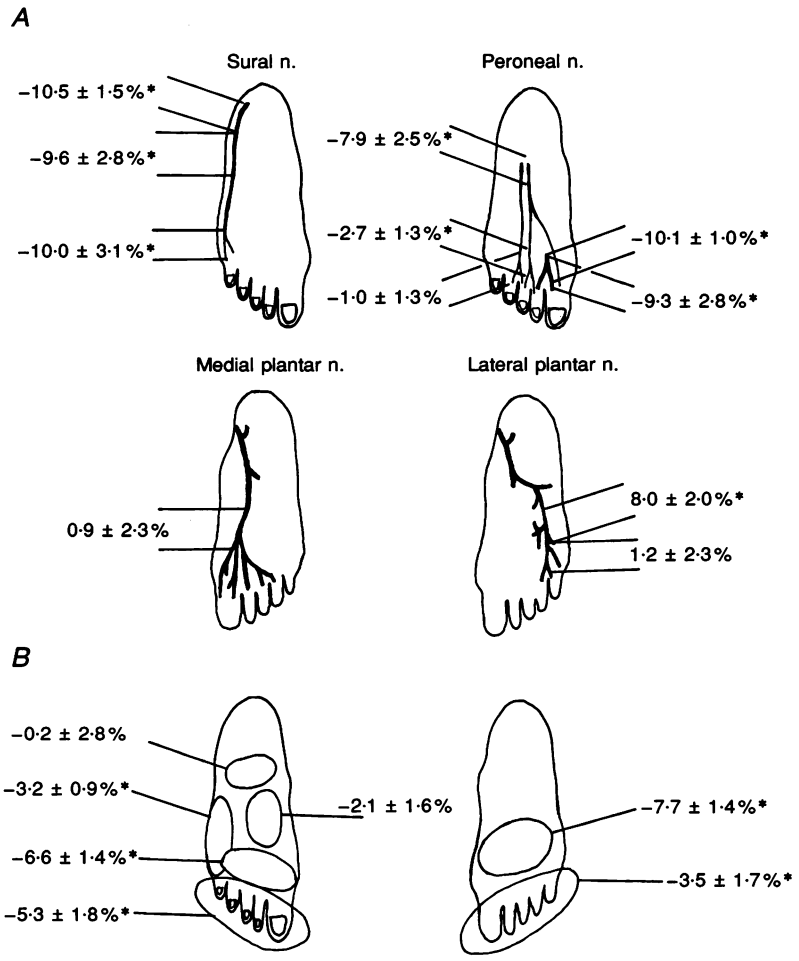

Figure 4. Local sign of cutaneous modulation of presynaptic inhibition

In *A*, electrical stimulation of various nerves in the ipsilateral foot was used (four shocks at 1·5 × PT, 10 ms before common peroneal stimulation for the sural nerve, the timing of stimulation at sites more distal than the lateral malleolus was adjusted assuming a conduction velocity of 40 m s^{-1}). The approximate locations of major nerve branches in the foot are indicated and the positions of stimulating electrodes are marked by parallel lines (cathode proximal). In *B*, modulation of presynaptic inhibition by adequate stimulation of the skin of the foot is indicated. Areas within which the effects of brushing were investigated are indicated by the oval outlines. In both sets of figures the modulation ($C/T - C_c/T_c$%, mean ± S.E.M.) induced is indicated next to the site of stimulation. * Statistically significant modulation (Wilcoxon test, $P < 0{\cdot}058$). Data from subjects J.F.I. and A.B.

This hypothesis was tested on subject J.F.I. using vibration as a more selective stimulus for Ia afferents in the intrinsic muscles. Application of a physiotherapy vibrator (100 Hz, 0·5 mm peak to peak) to the sole of the foot strongly suppressed soleus and quadriceps H reflexes. These effects were abolished by anoxic block of the foot with a cuff applied just above the ankle joint and therefore cannot be attributed to spread of vibration more proximally. Vibration reduced soleus H reflexes to 58 ± 4% of the test value before and to 96 ± 9% after anoxic block (the stimulus to the tibial nerve was adjusted to try to produce similarly sized test reflexes before and after anoxic block: a 9% increase in test reflex amplitude occurred).

It is concluded that electrical stimulation of the plantar nerves activates group I afferents from intrinsic foot muscles which produce presynaptic inhibition of soleus Ia afferents. Previous work has shown that soleus afferents receive presynaptic inhibition from group Ia afferents in many lower limb muscles (Iles & Roberts, 1987).

Contralateral actions. Stimulation of the contralateral sural nerve at 1·5 × PT with a tetanus of four shocks ending 14 ms before the stimulus to the common peroneal nerve significantly decreased presynaptic inhibition (modulation of −9·2 ± 1·2%; Wilcoxon test, $P < 0·0001$; subjects J.F.I. + A.B.; the cutaneous stimulation was advanced 2 ms to compensate for the additional cross-spinal pathway). The reduction in presynaptic inhibition was 3·2 times as strong during ipsilateral plantar flexion compared with ipsilateral dorsiflexion and had an intermediate value at rest (Kruskal–Wallis test, $P = 0·086$; one-way analysis of variance, $P = 0·038$; transformed data).

Local sign of cutaneous action studied using adequate stimulation

Because cutaneous afferents from the plantar surface of the foot could not be selectively activated by electrical stimulation (see above), adequate stimulation by brushing was investigated. Brushing applied to both distal dorsal and plantar surfaces of the foot produced significant reduction of presynaptic inhibition, whereas brushing of the proximal dorsal part of the foot and pretibial area was ineffective (Fig. 4*B*). Although the time of activation of

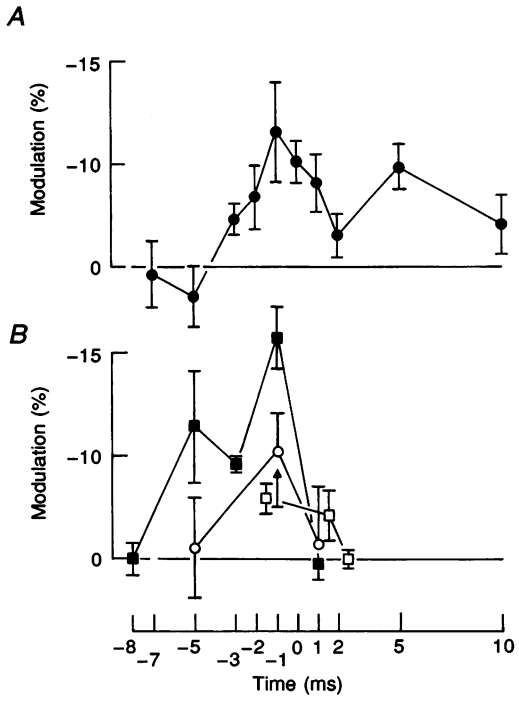

Figure 5. Time course of modulation of presynaptic inhibition by stimulation of the contralateral motor cortex

Modulation is plotted on the ordinate (decrease in inhibition upwards) against the time interval between the single magnetic stimulus to the motor cortex and the stimulus to the common peroneal nerve (abscissa, negative intervals indicate that the common peroneal nerve stimulus preceded the stimulus to the cortex). The interval between the common peroneal nerve stimulus and the test stimulus was kept constant at 100 ms. In *A*, data from several experimental sessions on subjects A.B. and J.F.I. are combined. The cortical stimulus was 55% maximum output. The means and S.E.M. calculated from seven averages (each of 64 reflexes) are plotted at each time interval. The subjects performed a weak dorsiflexion contraction (torque, 2 N m). In *B*, data from single experimental sessions on four taller subjects are illustrated (S.B., ○; H.P., ■; D.S., □; P.F., ▲). Three to six averages were used to calculate each plotted point. The cortical stimulus was 45% maximum output and the subjects were studied at rest.

cutaneous afferents was uncertain, brushing had to precede the stimulus to the common peroneal nerve in order to observe the modulation of presynaptic inhibition. Brushing had no significant effect on the amplitude of the test reflex except when applied over the dorsum of the proximal part of the foot and over the flexor retinaculum ($T_c/T = 105 \pm 2\%$; Wilcoxon test, $P < 0{\cdot}02$).

Modulation of presynaptic inhibition by the corticospinal tract

Time course of corticospinal modulation

The corticospinal tract was activated by magnetic stimulation of the foot area of the contralateral motor cortex. Presynaptic inhibition of soleus Ia afferents was significantly reduced. The time course of the modulation is illustrated in Fig. 5*A* and *B*. Maximal reduction occurred when the (single) cortical stimulus was applied 1 ms after the stimulus to the common peroneal nerve. A statistically significant reduction in inhibition (Wilcoxon test, $P < 0{\cdot}05$) was found in all six subjects considered individually at this interval. The effective cortical stimuli were substantially below the threshold for producing responses in relaxed lower limb muscles. The cortical stimuli used in the experiments illustrated in Fig. 5*A* (55% maximum output of the cortical stimulator) produced a significant inhibition of the test reflex ($T_c/T = 80 \pm 5\%$; Wilcoxon test, $P < 0{\cdot}01$). The smaller stimuli (45% maximum) used in the experiments of Fig. 5*B* and those described in the next section had very small and insignificant effects on the test reflex (T_c/T around 97%).

Previous work has shown that cutaneous and corticospinal inputs which produce spatial *facilitation* of group Ia reciprocal inhibition can produce occlusion if the inhibition is strong ($C/T < 75\%$: Rossi & Mazzocchio, 1988; Iles & Pisini, 1992*b*). For this reason other experiments were performed looking specifically at cutaneous and corticospinal modulation of very weak presynaptic inhibition. No significant facilitation was found leading to the conclusion that the modulation of stronger presynaptic inhibition was a genuine inhibition of that pathway rather than occlusion.

Effects of voluntary muscle contraction

The modulation of presynaptic inhibition from the corticospinal tract was present at rest and during plantar and dorsiflexion of the foot. It was 3·4 times larger during plantar flexion than during dorsiflexion (the mean modulation was 3·0, 4·0 and 10·1% for dorsiflexion, rest and plantar flexion, respectively; Kruskal–Wallis test, $P = 0{\cdot}005$; one-way analysis of variance, $P = 0{\cdot}03$; data from J.F.I. transformed to remove dependence of modulation on C/T before statistical test).

Interaction of cutaneous and corticospinal modulation of presynaptic inhibition

This was investigated by stimulating both the motor cortex and a cutaneous nerve (ipsilateral sural or deep peroneal) using the parameters providing the largest individual actions. The modulation of presynaptic inhibition by cutaneous and corticospinal routes showed complete occlusion when combined. However, when the cutaneous stimulation was reduced until a liminal action resulted (1·25 × PT, three shocks) and the cortical stimulus was reduced (to 35% maximal output of the stimulator), combined stimulation then resulted in a reduction in presynaptic inhibition that exceeded the sum of the individual actions (subjects J.F.I. and A.B.). This is interpreted as spatial facilitation between the cutaneous and corticospinal pathways.

DISCUSSION

Modulation of presynaptic inhibition

Modulation from cutaneous afferents

The present work shows that activation of low threshold cutaneous afferents from both the plantar and dorsal surfaces of the foot reduces the presynaptic inhibition of soleus Ia afferents produced by stimulation of flexor group I afferents. This extends the preliminary observations of Iles & Roberts (1987).

The effectiveness of cutaneous afferents with low electrical threshold is consistent with work in the cat (>1·5 × threshold: Brink, Jankowska & Skoog, 1984), with work on the human upper limb (1·5–2 × PT: Nakashima, Rothwell, Day, Thompson & Marsden, 1990) and with the low mechanical threshold observed with adequate stimulation.

The requirement for cutaneous stimuli to arrive at the spinal cord in advance of the flexor group I input is consistent with observations in the upper limb and indicates an action on interneurones early in the pathway of presynaptic inhibition. In the cat, cutaneous inhibition is directed at the first-order interneurones on the pathway of presynaptic inhibition.

Modulation from the corticospinal tract

Stimulation of the foot area of the contralateral motor cortex reduced the presynaptic inhibition of soleus Ia afferents from stimulation of flexor group I afferents. The optimal time interval for this action was with the cortical stimulus following the group I stimulus (to the common peroneal nerve) by 1 ms (Fig. 5), but some action was detectable at −3 ms in subject J.F.I. In this subject corticospinal facilitation of Ia reciprocal inhibition of soleus (a pathway with just one interneurone) has been demonstrated with cortical stimulation 3 ms after stimulation of the common peroneal nerve (Iles & Pisini, 1992*b*). This suggests that in the present experiments the cortical action occurs on interneurones early in the pathway of presynaptic inhibition. In the cat, corticospinal inhibition is directed at the first-order interneurones. Iles & Pisini (1992*b*) failed to detect any corticospinal action on presynaptic inhibition, but in those experiments the

cortical stimulus was applied *ca* 100 ms *after* the common peroneal nerve stimulus, and could not have influenced interneurones early in the pathway.

Valls-Sole, Alvarez & Tolosa (1994), using an entirely different experimental approach, have also concluded that stimulation of the motor cortex can inhibit presynaptic inhibition.

Technical considerations

There are three major technical objections that can be raised concerning the methodology used in the present experiments.

The nature of the inhibition from the antagonist nerve

It has been assumed in the present work (and in some other published studies on the upper limb: Berardelli, Day, Marsden & Rothwell, 1987; Burke, Gracies, Meunier & Pierrot-Deseilligny, 1992) that the inhibition elicited by group I stimulation of the antagonist nerve is predominantly presynaptic for conditioning intervals beyond the period 1–10 ms where classical Ia reciprocal inhibition is found.

However, inhibition for intervals between approximately 10 and 30 ms (originally named D1 by Mizuno, Tanaka & Yanagisawa, 1971) increases strongly with stimulus strength above motor threshold and may therefore depend upon input from muscle group I and II afferents (El-Tohamy & Sedgwick, 1983). Higher threshold afferents contribute to presynaptic inhibition of Ia afferents in the cat only after treatment with L-β-3,4-dihydroxyphenylalanine (L-DOPA). In man they contribute only in paraplegia and at very long latency (Roby-Brami & Bussel, 1990). Furthermore, Iles & Pisini (1992*b*) reported that stimulation of the corticospinal tract facilitated D1 inhibition for conditioning intervals up to 50 ms (the corticospinal volley was timed to converge with last-order interneurones). These observations suggest that actions at conditioning intervals of 50 ms or less may involve pathways in addition to presynaptic inhibition of Ia afferents, particularly if the conditioning stimulus exceeds motor threshold. In order to avoid these uncertainties longer conditioning intervals and stimuli below motor threshold were used in the present investigation.

Cutaneous action on motoneurone recruitment gain

Nielsen & Kagamihara (1993*b*) have shown that stimulation of the sural nerve inhibits early recruited motor units in tibialis anterior but excites later recruited ones. The resulting change in recruitment gain can give a spurious impression of reduced presynaptic inhibition of tibialis anterior H reflexes. However, such a mechanism can be rejected as an explanation for the results reported in the present paper.

A weak argument against the explanation is that there is no evidence that cutaneous inputs are directed differentially to components of the soleus motoneurone pool. Also, excitatory corticospinal and Ia inputs are reported to have a similar distribution (Nielsen, 1994). A much stronger argument is that in the present experiments the timing of the cutaneous (or cortical) stimulus relative to the group I volley inducing presynaptic inhibition was critical for modulation, whereas timing relative to the reflex was not. For example, with stimulation of the sural nerve at 110 ms and the common peroneal nerve at 100 ms before the test stimulus there was significant reduction in presynaptic inhibition; but with the same sural stimulus timing and the common peroneal nerve stimulated at 120 ms before test there was no modulation. Sural action on the motoneurone pool must be identical in the two situations, but only in the former could the sural volley inhibit the first-order interneurones of presynaptic inhibition.

Convergence between excitatory cutaneous pathways

Since the common peroneal nerve is a mixed nerve, there is a possibility that cutaneous afferents activated by the stimulus used to elicit presynaptic inhibition might spatially facilitate excitatory actions from other cutaneous afferents activated by electrical stimulation of the pure cutaneous nerves or by adequate stimulation of the skin on the foot. This would give a facilitation of the test reflex and a misleading impression of reduced presynaptic inhibition. It is not possible to completely reject this explanation but a number of observations militate against it.

The timing of cutaneous stimulation used in most of the experiments (100–120 ms before the test stimulus) was one where there is little excitatory action on the reflex, and no excitatory action appeared in the control experiments where more distal cutaneous branches of the common peroneal nerve were co-stimulated. Furthermore, the hypothesis does not explain the reduction in presynaptic inhibition produced by stimulation of the corticospinal pathway, the occlusion and spatial facilitation between cutaneous and corticospinal modulation, or the modulation seen in experiments where presynaptic inhibition was induced by mechanical stimulation of receptors in the tibialis anterior muscle.

On balance, the evidence favours an interpretation in terms of modulation of presynaptic inhibition at an interneurone early in the pathway, which is in complete accordance with extensive observations in the cat (see Introduction).

Functional considerations

Local sign of cutaneous actions

In the present experiments activation of low threshold receptors in the skin of both surfaces of the distal foot (but not more proximal areas) reduced presynaptic inhibition of soleus Ia afferents. This is homologous with the pattern described for the upper limb (Nakashima *et al.* 1990). Since contraction of the soleus is likely to activate cutaneous receptors this will reinforce the movement by increasing the gain of the monosynaptic Ia pathway. The conclusion is

supported by the observation that both cutaneous and corticospinal inhibitory actions on presynaptic inhibition are largest during plantar flexion. Since an identical action is produced by stimulation of the contralateral sural nerve the machinery could be strongly activated in circumstances where the two limbs operate in concert, such as during a postural response to sway when standing.

Although only limited information is available, a preliminary comparison can be made with cutaneous actions on two other muscle group I pathways. In the case of Ia reciprocal inhibition cutaneous afferents from both surfaces of the distal foot *increase* the inhibition (Rossi & Mazzocchio, 1988), the action is largest during *dorsiflexion* (author's unpublished observations) and the *opposite* effect is obtained from the contralateral foot (Rossi & Mazzocchio, 1988; though this may not apply in the upper limb: Sabatino, Ferraro, Caravaglios, Sardo, Delwaide & La Grutta, 1992). The function here may be to limit soleus contraction and permit dorsiflexion movement. In the case of non-reciprocal group I pathways cutaneous afferents from the two surfaces of the foot or hand have *opposite* actions, the actions are modulated or *reversed* during movement, and *opposite* actions are elicited from the contralateral limb (Bergego, Pierrot-Deseilligny & Mazieres, 1981; Pierrot-Deseilligny, Bergego & Katz, 1982; Cavallari, Fournier, Katz, Malmgren, Pierrot-Deseilligny & Shindo, 1985). The cutaneous facilitation of non-reciprocal inhibition may serve to terminate movement when a limb makes contact with an object.

Modulation of presynaptic inhibition during movement

The reduction in group I presynaptic inhibition of soleus Ia afferents produced by activation of the corticospinal tract in the present experiments was greatest during plantar flexion. If it can be assumed that the action also extends to other Ia inputs to soleus motoneurones then this pathway is probably responsible for the reduction in soleus presynaptic inhibition that occurs just prior to a plantar flexion movement (Hultborn *et al.* 1987), and contributes to the reduction found during soleus contraction (Iles & Roberts, 1987). However, in the latter case activation of cutaneous afferents may also play a part. The increased presynaptic inhibition of Ia afferents on other motoneurones just prior to soleus contraction (Hultborn *et al.* 1987) may result from activation of a facilitatory descending pathway.

Many authors have reported changes in the level of presynaptic inhibition during changes in posture (e.g. Hayashi, Tako, Tokuda & Yanagisawa, 1992; Koceja, Trimble & Earles, 1993), and during locomotion (e.g. Llewellyn, Yang & Prochazka, 1990; Yang & Whelan, 1993). These changes could be mediated by the descending and cutaneous pathways enumerated above. A further contribution may be provided by muscle group I afferents activated during muscle contraction (Devanandan, Eccles & Stenhouse, 1966). An unexpected observation during the present experiments was the powerful presynaptic inhibition of soleus Ia afferents evoked by stimulation of afferents from the intrinsic foot muscles. If these afferents are activated during rapid locomotion then they may be responsible for some of the differences in level of presynaptic inhibition between walking and running (Edamura, Yang & Stein, 1991).

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