Differential effects of a flexor nerve input on the human soleus H-reflex during standing versus walking

C. Capaday, B.A. Lavoie, and F. Comeau

Abstract: A conditioning (C) stimulus at group I strength was delivered during standing to the common peroneal (CP) nerve before a test (T) stimulus at several C−T intervals ranging from 0 to 150 ms. At sufficiently long C−T intervals (100−120 ms) the soleus H-reflex was strongly inhibited despite little, or no change, in the background level of EMG activity. This finding indicates that a significant portion of the inhibition occurs at a premotoneuronal level, likely via presynaptic inhibition of the Ia-afferent terminals. During standing, at C−T intervals of 100−120 ms (optimal C−T interval) a conditioning stimulus to the CP nerve of 1.5 times motor threshold (MT) intensity reduced the soleus H-reflex by an average of 45.8% (n = 14 subjects). The conditioning stimulus always produced a clear inhibition of the H-reflex during standing at these C−T intervals. The effects of this conditioning stimulus on the soleus H-reflex were then determined in the early part of the stance phase of walking. In contrast to standing, the conditioning stimulus produced little or no inhibition during the early part of the stance phase of walking (average inhibition 45.8 vs. 11.6%, n = 14 subjects). The soleus background EMG, and the soleus and tibialis anterior M-waves were essentially the same during standing and walking. Furthermore, there was no shift of the optimal C−T interval during walking. The difference in the effects of the conditioning stimulus was not due to differences in the size of the test H-reflex in each task. It appears to be due to a genuine task-dependent change in the input−output properties of the underlying spinal cord circuits. There are at least two, mutually compatible, explanations of these results. Firstly, during walking the intraspinal terminals of the afferent fibres (group Ia and Ib) conducting the conditioning volley may be presynaptically inhibited, or their input gated at the interneuronal level. Secondly, on the assumption that the conditioning stimulus is acting via the presynaptic inhibitory network in the spinal cord, it is possible that during walking this network is saturated as a result of increased central or peripheral synaptic inputs. Finally, it seems unlikely that differences in the refractoriness of the CP nerve between the tasks may be involved; the reasons for this are presented in the discussion.

Key words: Ia afferents, motoneurons, presynaptic inhibition, EMG, posture, locomotion, spinal cord.

Résumé : On a appliqué un stimulus de conditionnement (C) au nerf poplité externe (PE) en position debout, avant d'appliquer un stimulus témoin (T) à divers intervalles C−T, compris entre 0 et 150 ms. À des intervalles C−T (100−200 ms) assez longs, le réflexe H du muscle soléaire a été fortement inhibé, malgré une faible variation, ou aucune variation, du taux d'activité de fond de l'EMG. Ceci indique que l'inhibition s'effectue en grande partie à un niveau pré-motoneuronal, probablement via l'inhibition présynaptique des terminaisons des fibres afférentes Ia. En position debout, à des intervalles C−T de 100−120 ms (intervalle C−T optimal), un stimulus de conditionnement au nerf PE, équivalent à 1,5 fois l'intensité du seuil moteur (SM), a réduit le réflexe H du muscle soléaire de 45,8% en moyenne (n = 14 sujets); à ces intervalles C−T, le stimulus de conditionnement a toujours provoqué une nette inhibition du réflexe H. On a ensuite déterminé les effets du stimulus de conditonnement sur le réflexe H du muscle soléaire au début la phase d'appui de la marche. Contrairement à la position debout, le stimulus de conditionnement a causé peu ou pas d'inhibition au début de la phase d'appui de la marche (inhibition moyenne de 45,8 vs. 11,6%, n = 14 sujets). L'activité de fond de l'EMG du soléaire et la réponse directe M des muscles JA et soléaire ont été essentiellement les mêmes durant la position debout et la marche. De plus, il n'y a pas eu de variation de l'intervalle C−T optimal durant la marche. La différence dans les effets du stimulus de conditionnement n'était pas liée aux différences

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dans l'amplitude du réflexe H témoin, et ce dans aucune des tâches. Elle serait due à une variation des propriétés entrée-sortie des circuits sous-jacents de la moelle épinière. On peut expliquer ces résultats d'au moins deux façons. Premièrement, durant la marche, il se pourrait que les terminaisons intraspinales des fibres afférentes (groupes Ia et Ib) qui conduisent la volée des stimuli de conditionnement soient inhibées au niveau présynaptique, ou bien que leur entrée soit contrôlée au niveau interneuronal. Deuxièmement, en supposant que le stimulus de conditionnement agit par l'intermédiaire du réseau inhibiteur présynaptique dans la moelle épinière, il se peut que, durant la marche, ce réseau soit saturé en raison d'une augmentation des influx synaptiques périphériques et centraux. Enfin, il semble peu probable que des différences dans la période réfractaire inter-tâches du nerf PE aient un rôle à jouer ici; on en discute les raisons.

Mots clés : fibres afférentes Ia, motoneurones, inhibition présynaptique, EMG, posture, locomotion, moelle épinière.
[Traduit par la Rédaction]

Introduction

We have previously investigated the modulation of the H-reflex during natural motor tasks such as standing, walking, and running (Capaday and Stein 1986, 1987*a*; Stein and Capaday 1988; Stein et al. 1991). Our motivation was to determine whether the CNS could adaptively modify the stretch reflex output during natural motor activities and, if so, by what mechanism(s). It was found that the amplitude of the soleus H-reflex (an electrically induced analog of the stretch reflex) is strongly modulated during the human step cycle (Capaday and Stein 1986; Crenna and Frigo 1987). It increases progressively during stance and decreases abruptly during the swing phase (Capaday and Stein 1986; Crenna and Frigo 1987; for studies on other leg muscles see Dietz et al. 1990; Brooke et al. 1991). The observations during walking are interesting in themselves and of functional importance for the biomechanical requirements of this task. What is even more interesting is to compare how this reflex is modulated in different natural motor activities (Morin et al. 1982; Capaday and Stein 1986, 1987*a*; Llewellyn et al. 1990; Edamura et al. 1991). The reflex is much smaller during walking than during standing (up to a factor of 5), at the same level of motor output and stimulus strength (Morin et al. 1982; Capaday and Stein 1986). It further decreases in going from walking to running (Capaday and Stein 1987*a*; Edamura et al. 1991). The functional consequences of these patterns of modulation have been described in detail in two review articles (Stein and Capaday 1988; Stein et al. 1991; see also Yang et al. 1991).

On the basis of computer simulation studies and experiments on decerebrate cats we suggested that changes of presynaptic inhibition of the soleus Ia-afferent terminals underlie, at least in part, the adaptive modulation of the H-reflex observed in these tasks (Capaday and Stein 1987*b*, 1989; Stein and Capaday 1988; Morin et al. 1982). We thus hypothesized that presynaptic inhibition of the soleus Ia-afferent terminals increases in going from standing to walking, and increases further during running. However, since that hypothesis was formulated, other mechanisms for controlling the input–output properties of a motoneuron pool have been suggested (Kernell and Hultborn 1990; Brownstone et al. 1992). It thus seemed timely to attempt to test this hypothesis as directly as possible in humans. The experiments described in this paper were initially designed to measure how presynaptic inhibition of the soleus Ia-afferent terminals changes in going from standing to walking in normal human subjects. We approached this problem by trying to access the presynaptic inhibitory network in the spinal cord (Eccles et al. 1962; Jankowska et al. 1981; Rudomin et al. 1987) via a peripheral nerve input. It is well known from experiments in the cat that stimulation of flexor nerves at group I strength (i.e., Ia and Ib afferents) can presynaptically inhibit the intraspinal terminals of group Ia afferents from extensors (reviewed by Schmidt 1971; Rudomin 1990). The idea behind using this method to measure a change in the level of presynaptic inhibition in humans is the following. An increase of presynaptic inhibition should result in a greater reduction of the soleus test H-reflex by the conditioning stimulus because the interneurons involved in producing the presynaptic inhibition should be more excitable, and vice versa (Ashby et al. 1980, 1987; Morin et al. 1984; Hultborn et al. 1987*a*; Iles and Roberts 1987). This assumes that different pathways (e.g., descending tracts and flexor group I fibres) converge onto common interneurons involved in presynaptic inhibition of group Ia afferents. Furthermore, we reasoned that by comparing different tasks at the same mean rectified EMG level, a measure of the recruitment level of the motoneuron pool (Capaday and Stein 1987*b*; Duenas et al. 1990), a difference of the inhibition of the H-reflex between tasks produced by the same conditioning stimulus would be most likely due to a change of presynaptic inhibition (excluding remote dendritic inhibition and changes in neuromodulator levels). This is because, as we have previously shown (Capaday and Stein 1989), postsynaptic inhibitory currents added to active motoneurons cannot change the amplitude of a monosynaptic reflex independently of the level of recruitment of the motoneuron pool (see additional details in Heckman 1994). In the event, we found that the conditioning stimulus is modulated by the motor task and, therefore, cannot be considered to be a constant input, despite the fact that the afferent volley may itself be constant. The implications of this finding are presented in the discussion. An abstract summarizing the present work was recently published (Lavoie et al. 1993).

Methods

The experiments reported in this paper were done on a total of 24 normal human subjects, ranging in age between 21 and 47 years. The actual number of subjects used in each particular type of experiment is given in the appropriate place in the text. All subjects gave their consent after being informed on

the nature and procedures of the experiments. The study was conducted in accordance with the Helsinki Declaration and approved by the local ethics committee. The reader is referred to previous publications for additional details on the methods for obtaining and analyzing reflex responses in freely moving subjects (Capaday and Stein 1986, 1987*a*; Capaday et al. 1990; Edamura et al. 1991).

Electrical stimulation of peripheral nerves

Electrical stimulation of the tibial and common peroneal (CP) nerves was done by placing the cathode (Ag−AgCl electrode of 0.7 cm diameter) on the skin overlying the nerve and the anode, a large metal plate (3 × 7 cm) covered in gauze and moistened with saline, was placed on the opposite side of the leg above the patella. The cathode is covered by an elastic rubber strap wrapped around the leg and tightened so as to maintain pressure upon the cathode. The stimuli, square pulses of 0.5-ms duration, were delivered through constant voltage stimulus isolation units. Whenever possible, the deep branch of the CP nerve (deep peroneal nerve) was stimulated because its only cutaneous innervation is a small patch of skin between the big toe and the first toe. Otherwise the whole CP nerve was stimulated just behind the head of the fibula. There were no obvious differences resulting from stimulation of these two different sites. It should be noted that if the conditioning stimulus electrode was placed on the skin close to the nerves, but not over them, none of the effects on the H-reflex presently reported were observed.

EMG recordings

The EMG activity of the soleus and tibialis anterior (TA) muscles was recorded with bipolar surface Ag−AgCl electrodes. The recording surface of the electrodes had a diameter of 0.7 cm. The electrodes were positioned 2−3 cm apart on the respective muscle bellies. The ground electrode, a large metal plate (3 × 9 cm) covered in gauze and moistened with saline, connecting the subject to the common input of the preamplifiers, was placed over the muscle bellies of the gastrocnemii between the stimulating and the recording electrodes. The EMG signals were recorded with optically isolated preamplifiers. The M-wave and H-reflex responses of the soleus and the M-wave of the TA were amplified, high pass filtered at 20 Hz, and low pass filtered at 1 kHz, with single time constant RC-filters. The level of soleus α-motoneuron pool activity was estimated from the mean value of the surface EMG signal, high pass filtered at 20 Hz, rectified, and low pass filtered at 100 Hz.

Experimental procedures

Before beginning an experiment the M-wave and H-reflex recruitment curves, as functions of the stimulus intensity to the tibial nerve, were determined for each subject during quiet standing. This allowed us to determine the range over which the H-reflex is relatively constant (plateau range) despite variations of the M-wave (see Fig. 1 in Capaday and Stein 1986). The stimulus to the tibial nerve used to elicit the H-reflex during standing and walking was adjusted to give an M-wave whose amplitude was in the plateau range of the H-reflex. The same soleus M-wave amplitude was used throughout the experiment. In some subjects the experiments were done at several different soleus M-wave amplitudes. The H-reflexes associated with these different-sized M-waves were in the range of 25−50% of the maximum M-wave, including standing and walking. The amount of inhibition of H-reflexes in this range is relatively independent of the reflex size (Crone et al. 1990).

The experiments usually began by first studying subjects during quiet standing. The test H-reflex response was determined at several conditioning−testing (C−T) intervals, ranging from 0 to 150 ms. At each C−T interval (time difference between the beginning of the conditioning and testing stimuli) at least four to eight H-reflex responses were averaged in real-time. The rectified soleus background EMG (50 ms prior to the test stimulus) and the TA M-wave were also averaged in real-time. The signals were digitized at a rate of 5000 samples/s. All C−T intervals were tested in real-time in one uninterrupted time period of between 30 s and 2.6 min, depending on the number of C−T intervals tested (range 5−20). The C−T intervals were equiprobable and the stimulus pairs delivered in pseudorandom order every 2−4 s. The following conditioning stimulus strengths were used: 0.9, 1.0, 1.5, 2.0, and 2.5 times the threshold of the TA motor fibres (MT).

During walking the conditioning stimulus strength most often used was 1.5 × MT. At this stimulus intensity the TA M-wave is nearly constant during all phases of the step cycle, in marked contrast to the M-wave of the soleus (Capaday et al. 1990). The test stimulus intensity to the tibial nerve was adjusted during walking to give an M-wave of the same amplitude as during standing. This required continual adjustment based on the real-time calculations of the soleus M-wave amplitude (see details below). The test stimulus was always delivered at 150 or 170 ms following heel contact (Fig. 1). The test H-reflex was, therefore, evaluated at the same point in the step cycle, early in the stance phase. We chose to make our measurement at this point in the step cycle for several practical and physiological reasons. Firstly, the level of background EMG in this part of the step cycle is comparable with that during quiet standing (Fig. 1). Therefore, all our measurements are made at nearly the same level of background α-motoneuron pool activity in the two tasks. In cases where the mean level of background EMG differed by more than a few microvolts between the two tasks, the experiment was repeated during standing with the heels slightly raised. In this situation, the subject was required to generate the same level of soleus motor activity as during walking by viewing a display of his mean soleus EMG level on a suitably calibrated analog meter. In this task, as in quiet standing, only the soleus was active, the TA was silent. The second reason for making the measurements in the early part of the stance phase of the step cycle is that the foot is flat on the ground and the ankle angle is approximately the same as during standing. Finally, the difference in H-reflex amplitude is greatest between standing and walking in the early part of the stance phase of the step cycle (Capaday and Stein 1986). Therefore, any change of the neural circuitry underlying the task-dependent change of the H-reflex, such as a change of presynaptic inhibition, should be most apparent in this part of the step cycle.

During walking, the conditioning stimulus to the CP nerve was delivered in the early part of the stance phase, as shown in Fig. 1. Five to seven C−T intervals, between 0 and

150 ms, were typically tested during walking. The strength of the stimulus to the CP nerve was adjusted during walking to elicit a TA M-wave of the sample amplitude as during standing. This usually required little adjustment, and once set, the TA M-wave remained essentially constant during the walking episodes, which typically lasted from 3 to 7 min.

Data acquisition and analysis

The data were acquired, processed, and analyzed in real-time by a 386-PC microcomputer, with each experiment (e.g., standing) done in one uninterrupted time period as described above. This allowed us to make very rapid measurements of the effects of the conditioning stimulus on the test H-reflex response. Thus, the measurements were done in conditions that were as stationary as is physiologically possible. The real-time data acquisition and analysis system allowed us to adjust the stimulus strength to the tibial and CP nerves, as required, so as to elicit constant-amplitude M-waves in the soleus and the TA, at each C−T interval and in each task. A significant new feature of the present experiments was that the computer only accepted test H-reflex responses whose M-waves had an amplitude that fell within a specified time−amplitude window (e.g., 0.5 ± 0.1 mV, between 5 and 15 ms after the stimulus). Therefore, the individual records that were used to compute the average responses at each C−T interval, and in each task, were evoked by stimuli of very nearly the same intensity. Consequently, the coefficients of variation (CV) of the averaged soleus M-waves were typically between 0.1 and 0.15.

The percent change of the H-reflex relative to the control value was calculated to compare the inhibition of the H-reflex produced by the conditioning stimulus in each task.

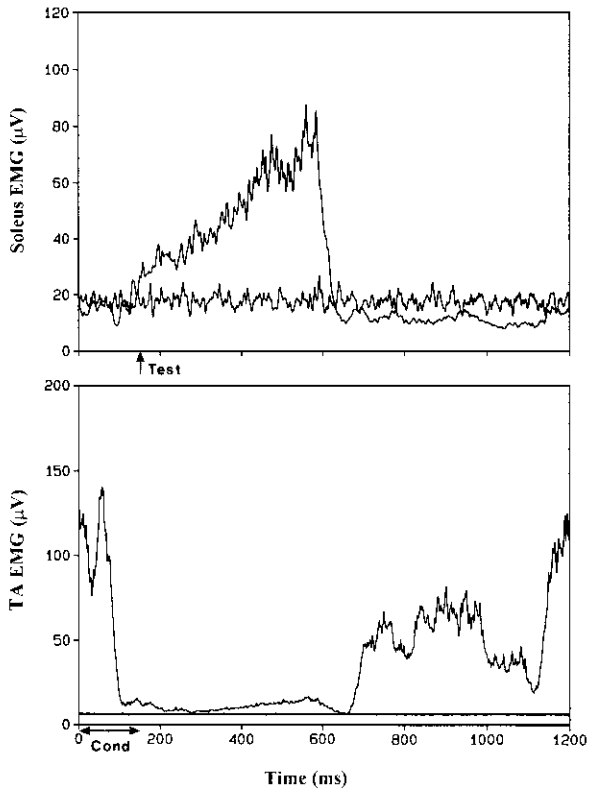
Results

The results section is divided into two parts. In the first part, the effects of the conditioning stimulus to the CP nerve on the soleus H-reflex during standing are presented. These effects are also correlated with the changes in the background soleus EMG induced by the conditioning stimulus. In the second part results comparing the effects of the conditioning stimulus during walking versus standing are presented.

Effects of the conditioning stimulus on the soleus H-reflex during standing

The effects of a single conditioning stimulus to the CP nerve at 1.5 × MT on the soleus H-reflex during quiet standing are shown in Fig. 2, along with the amplitude of the TA M-wave and the mean soleus background EMG. Note the constancy of the soleus and TA M-wave amplitudes as well as the constancy of their wave form at all C−T intervals (Fig. 2). A clear inhibition of the soleus H-reflex can be observed starting at about 50 ms following the conditioning stimulus and the recovery to the control level beginning at about 140 ms. The rectified soleus EMG (middle column) was sampled for 50 ms just before the test stimulus was given. The time of delivery of the conditioning stimulus relative to the test stimulus, for C−T intervals of 50 ms or less, can be inferred in the EMG records from the cross-talk artifacts due to the conditioning stimulus and TA M-wave. It is clear from inspection of Fig. 2 that the duration of these cross-talk

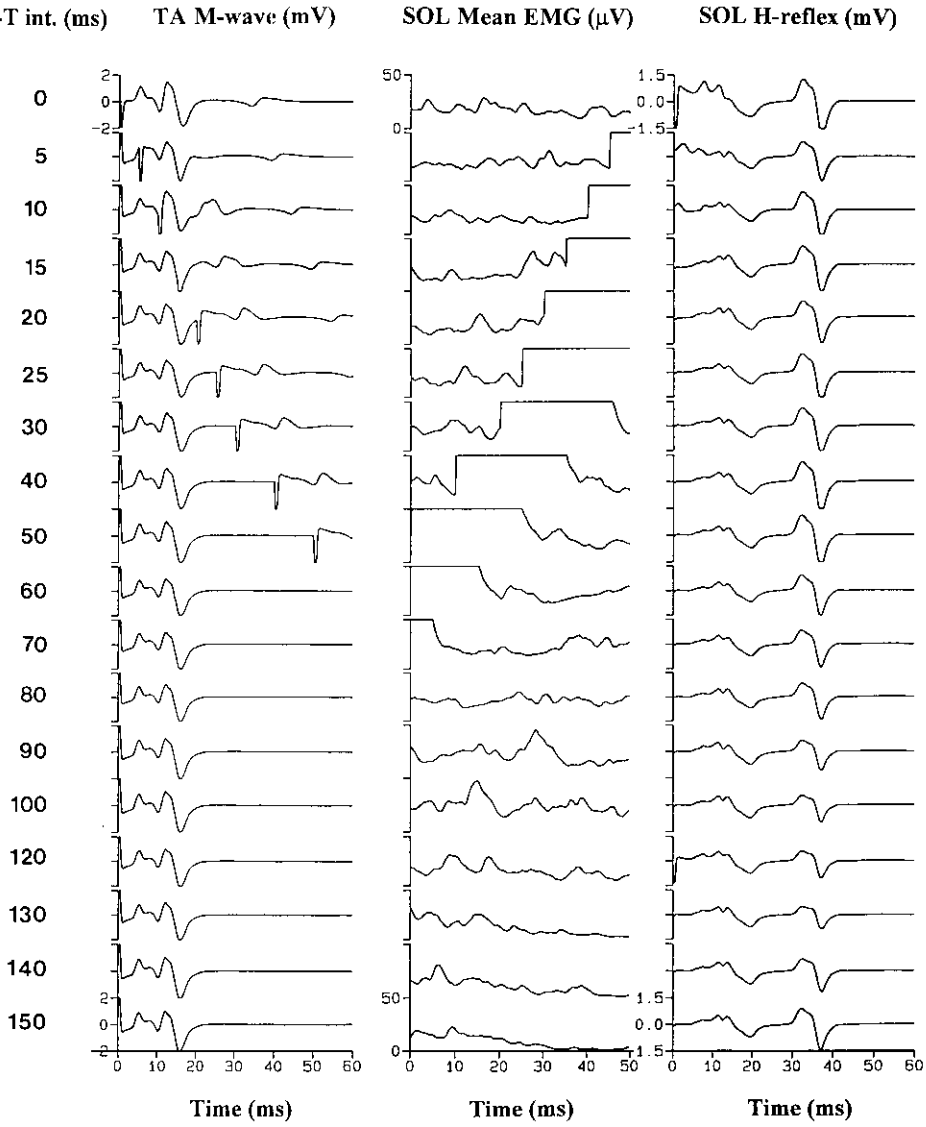
Fig. 1. The average (n = 100 step cycles, subject 1) rectified EMG activity of the soleus and TA muscles in the step cycle are shown starting at heel contact. The times of delivery of the test stimulus to the tibial nerve (150 or 170 ms after heel contact) and the conditioning stimulus to the CP nerve are marked by arrows. Also shown superimposed on the same graph is the mean soleus EMG activity during quiet standing. The reader should note the similarity of the mean soleus EMG activity in the early part of the stance phase with the mean level during standing. It should also be noted that the test stimulus was always given at the same point in the step cycle, 150 or 170 ms, after heel contact. The conditioning (Cond) stimulus preceded the test stimulus by various times (C−T intervals) as indicated by the horizontal double-headed arrow under the TA EMG.



artifacts (typically some 25 ms) and the close temporal proximity of the test stimuli prevented making measurements of the background soleus EMG at short C−T intervals, typically between 0 and 30 ms (Fig. 2). To obtain a measure of the mean level of soleus EMG activity at these short C−T intervals the soleus rectified EMG was averaged following delivery of the conditioning stimulus given alone, examples of which are shown in Figs. 4 and 5. The average value of the soleus EMG at short time intervals following the conditioning stimulus was estimated from such records (Capaday et al. 1990; Widmer and Lund 1989), allowing for a delay of about 30 ms due to afferent and efferent conduction times of the H-reflex.

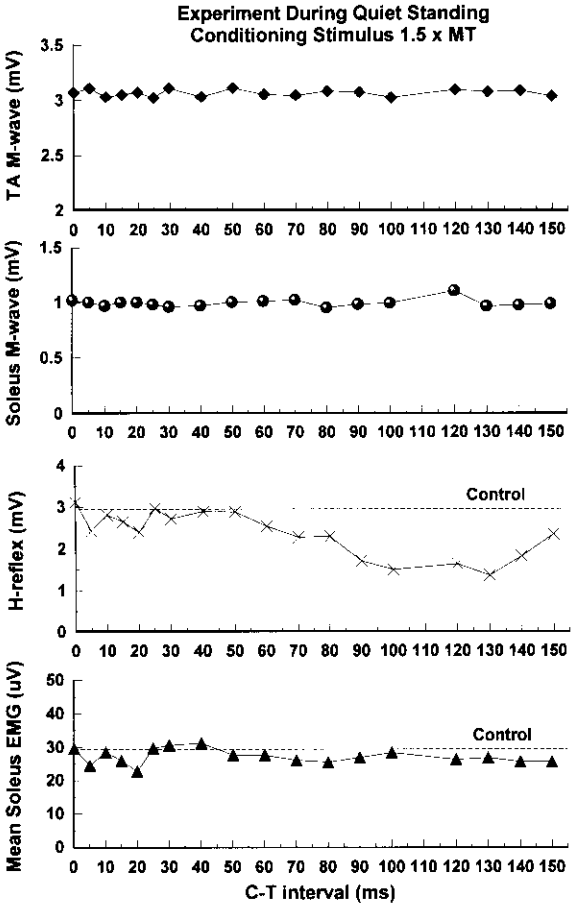
The various measurements made from the traces in Fig. 2 are plotted in the graphs of Fig. 3. There are two main observations presented in the summary graphs of Fig. 3. The first is the clear long latency inhibition of the H-reflex, which

Fig. 2. Examples of typical recordings (subject 2) from the TA and soleus in response to stimulation of their respective nerve during quiet standing. Each trace is the average of eight responses. The three sets of traces, from top to bottom, correspond to increasing C−T intervals (int.) ranging from 0 to 150 ms, as indicated. Note the marked reduction of the test H-reflex beginning at a C−T interval of about 50−60 ms. The soleus (SOL) rectified EMG traces were recorded over a 50-ms time period immediately before the test stimulus. The occurrence of abrupt plateaus in some of the rectified EMG traces is due to cross-talk produced by the conditioning stimulus artifact and subsequent TA M-wave. For example, in the third trace from the top the plateau begins 10 ms before the test stimulus, corresponding to a C−T interval of 10 ms. Note that the amplitude scale of the rectified EMG recordings is in microvolts. The very beginning of the soleus H-reflex recording in the topmost record (C−T interval of 0 ms) is also perturbed by the stimulus artifact produced by the conditioning stimulus.



begins, in this example, at about 50 ms after the conditioning stimulus and reaches its maximum at about 100 ms. The average onset latency of this inhibition was 68 ms (SD = 13.3 ms, n = 14 subjects) following the conditioning stimulus. The maximum value of the long latency inhibition was observed at C−T intervals between 100 and 120 ms (mean = 109 ms, SD = 15.2 ms, n = 14 subjects). The inhibition at these long C−T intervals reduced the test H-reflex by an average of 45.8% compared with its control value (range 21−80%, n = 14 subjects). In the example of Fig. 3, the background level of soleus EMG at C−T intervals between 100 and 120 ms was within 2−3 μV of the control value, whereas the conditioning stimulus reduced the H-reflex by 50%. In this subject, the sensitivity of the H-reflex to the background level of soleus EMG during standing was 0.09 mV/μV (r = 0.98); therefore the reduction of the

Fig. 3. An example, in one subject (subject 2), of the effects of a single conditioning stimulus to the CP nerve on the soleus test H-reflex. Each point on the various graphs is the average of eight responses. Note the nearly identical intenity, at all C−T intervals, of the conditioning and test stimuli as measured from the amplitudes of the respective M-waves of the TA and soleus muscles. The control values of the soleus H-reflex and the background soleus EMG during quiet standing are shown as broken lines on the respective graphs. The conditioning stimulus produced a weak inhibition of the H-reflex starting at C−T intervals between 10 and 20 ms, and a second phase of very pronounced inhibition starting, in this subject, at about 50 ms. Note that the inhibition at long C−T intervals was not accompanied by any inhibition of the background soleus EMG, measured over a time period of 20−50 ms before the test stimulus. The background soleus EMG level at short C−T intervals (0−20 ms) was estimated from averages of the rectified surface EMG in response to the conditioning stimulus given alone. The data points in the graphs of this figure are taken from the recordings shown in Fig. 2.



H-reflex was not due to a commensurate reduction of the background EMG. Another example of the long latency inhibition of the H-reflex without any significant change in the background EMG is shown in Fig. 4. In this example, H-reflexes were obtained during quiet standing at various C−T intervals and plotted in real-time along with the mean rectified soleus EMG following the delivery of the conditioning stimulus (1 × MT). This allows for a direct comparison of the H-reflex and the background EMG activity. The averaged soleus EMG in response to the conditioning stimulus alone was obtained just before the C−T trial. The mean soleus EMG during quiet standing, without any stimulus given, is also shown on the same graph for comparison. In summary, in all subjects tested during standing the inhibition of the H-reflex at long C−T intervals (>60 ms) was more than could be accounted for by changes in the background EMG.

Fig. 4. Another example (subject 1) of how the conditioning stimulus to the CP nerve (1 × MT) given during quiet standing produces a marked inhibition of the H-reflex (upper graph), starting at a C−T interval of 60 ms, without any significant effect on the mean (n = 32) background soleus EMG (continuous trace). The mean (n = 32) soleus background EMG during quiet standing, with no conditioning stimulus applied (dotted trace), is superimposed on the same graph. Each point in the upper graph is the average of four responses. In this and subsequent graphs the error bars represent ±1 SD. The time axis in this figure is in real-time, not relative C−T times as in Fig. 3. The conditioning stimulus was given 50 ms after time 0, and the times of occurrence of the H-reflex responses following the conditioning stimulus are plotted on this same real-time axis by adding to the C−T interval the 50-ms stimulus delay and the H-reflex latency of 30 ms (afferent + efferent conduction time). The C−T intervals of the data points in the upper graph are 50, 60, 70, 100, and 120 ms, respectively.

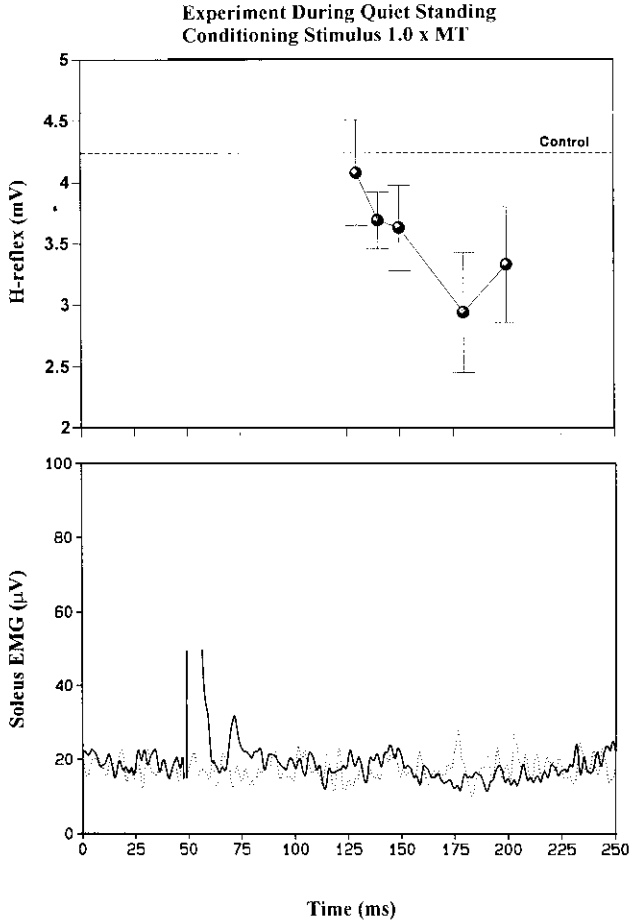
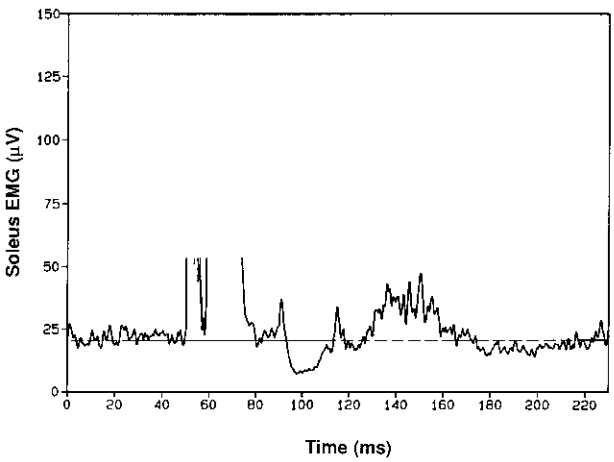


Fig. 5. This figure shows an example (subect 3) of how a single conditioning stimulus (1.5 × MT) to the CP nerve may perturb the ongoing soleus rectified EMG during standing. The trace is the average of 32 responses. The first 50 ms are the average control background level; the stimulus is given 50 ms after time 0. There are three points to be noted in this trace. First, the decrease below the control background value, beginning about 35–40 ms after the stimulus and lasting for about 20 to 25 ms. Second, the increase above the control background value, which follows the period of inhibition and lasts for about 40 ms. For conditioning test intervals of 100–120 ms the background level of EMG corresponds to the time interval between 180 and 200 ms in this trace (50 ms of background + 30 ms for afferent and efferent conduction time), at which time the EMG has returned to within a few microvolts of the control value (broken line).



In contrast to the long latency inhibition, the one observed at short C–T intervals (approximately between 0 and 15 ms), when it occurred, was always associated with a decrease in the background EMG (Figs. 3 and 5). The inhibition observed at these short C–T intervals in the active soleus is due to the well-known disynaptic reciprocal inhibitory pathway (Agarwal and Gottlieb 1972; Capaday et al. 1990; cf. Mizuno et al. 1971; Crone et al. 1987). The inhibition at long C–T intervals (100–120 ms) was usually more prominent than the reciprocal inhibition (C–T intervals 0–15 ms). In the 10 subjects in which both short (0–15 ms) and long (100–120) C–T intervals were tested using a conditioning stimulus of 1.5 × MT, the long latency inhibition averaged 45.6% (range 21–80%), whereas the one at short C–T intervals averaged 25.5% (range 11–45%). The difference between the short latency and the long latency inhibition is statistically highly significant (one-tailed t test, $t = 2.77, p < 0.01$). Not only was the inhibition at long C–T intervals of greater amplitude than the one at short C–T intervals but it was also more robust. It occurred in all subjects tested, whereas the inhibition at short C–T intervals occurred in 7 of 10 subjects tested.

Several more observations on the long latency inhibition of the soleus H-reflex during standing may be of interest. In many subjects (12 of 16) an increase of the EMG above the control background level, ranging from slight to prominent (as in Fig. 5), occurred at C–T intervals between about 30 and 70 ms and followed the period of reciprocal inhibition. The reader should note that these C–T intervals correspond to between 110 and 150 ms on the real-time axis of Fig. 5. This increase of EMG activity, at average C–T intervals between 32.2 ms (SD = 6 ms) and 68.6 ms (SD = 17.6 ms), is due to the increased motor unit spike density that inevitably follows a period of inhibition (e.g., see the appendix in Capaday et al. 1990). It is also possible that some of this increased activity may be due to a cutaneous, or other, reflex pathway (Hultborn et al. 1987*a*, 1987*b*). In any case, the activity of the α-motoneuron pool is increased during this period. Therefore, any increase of inhibition of the H-reflex occurring at a premotoneuronal level during this time interval would be underestimated in magnitude, as well as in latency, because of the simultaneous increase of α-motoneuron activity. Augmenting the strength of the conditioning stimulus increases the amplitude and duration of the period of increased α-motoneuron activity, making it sometimes difficult to compare the effects of weak and strong conditioning stimuli.

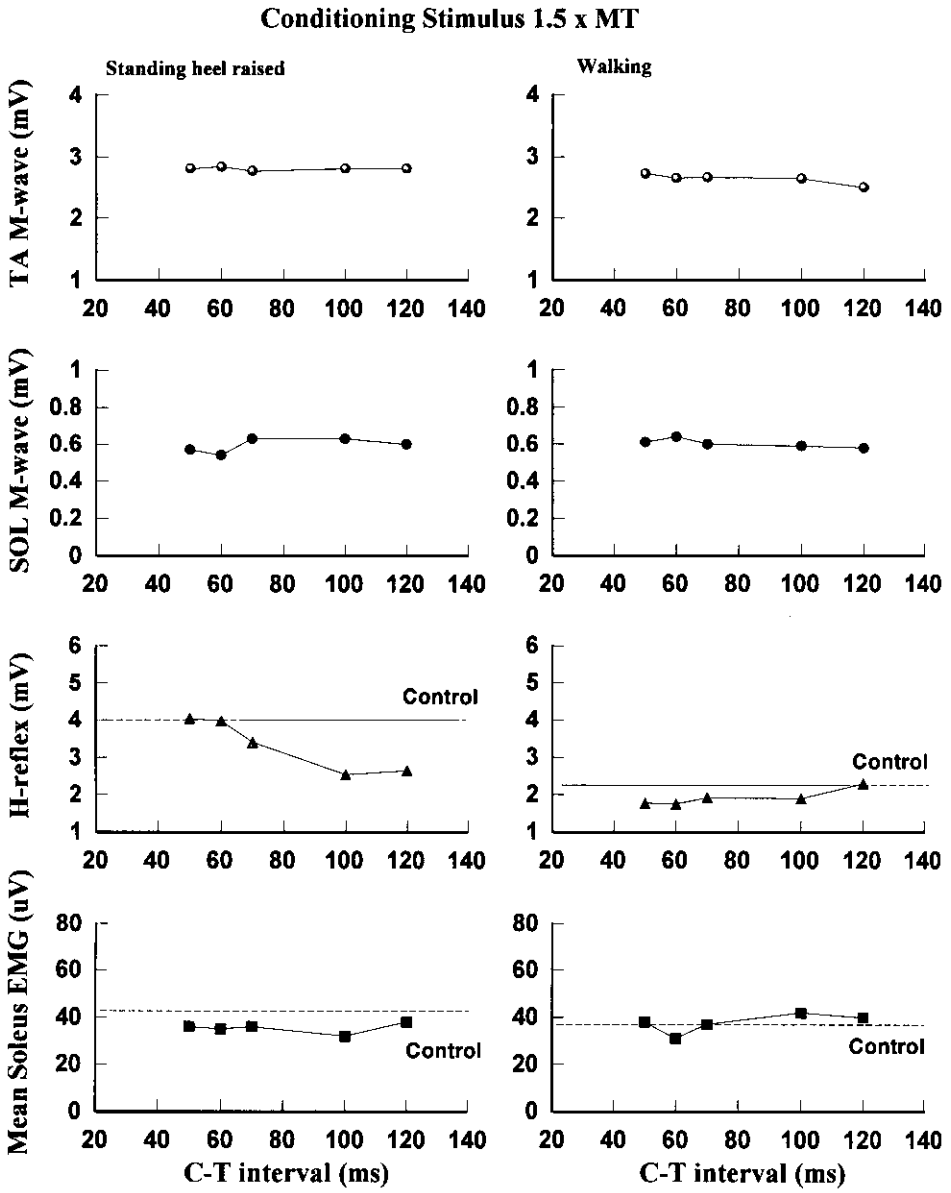
It should be noted that the twitch contraction of the TA produced by the conditioning stimulus (1.5 × MT) was small. It did not produce sufficient torque to dorsiflex the ankle in a standing subject and thus stretch the ankle extensors, as determined by goniometric recordings. Therefore, none of the effects of the conditioning stimulus during standing, or indeed during walking, can be attributed to stretch of the ankle extensors.

Effects of the conditioning stimulus on soleus H-reflex during walking

The main, and most striking, result obtained in the present experiments was that the conditioning stimulus always produced a clear long latency inhibition of the H-reflex during standing, but in contrast it produced little or no inhibition in the early part of the stance phase of walking (Figs. 6, 7, and 8). In this task, the conditioning stimulus (1.5 × MT, C–T intervals of 100–120 ms) reduced the test H-reflex by an average of 11.6% (range 0–53%, n = 14 subjects). This small amount of inhibition is statistically significant at the 95% level of confidence. However, in seven subjects no inhibition was observed at these C–T intervals during walking, yet they all showed a clear inhibition during standing (mean inhibition of 41.4%). The inhibition obtained during standing was compared with that during walking; the difference was highly statistically significant (one-tailed paired t test, $t = 6.1, p < 0.001$). It is emphasized that the comparison between standing and walking was done, for each subject, at nearly the same level of soleus background EMG, soleus M-wave, and TA M-wave (e.g., Fig. 6). Therefore, the difference in the results obtained between the two tasks cannot be due to uncontrolled variations of the variables that most significantly affect the H-reflex.

An example comparing the conditioned inhibition of the H-reflex during walking versus standing in the same subject is shown in Fig. 6. For practical reasons only five to seven C–T intervals (typically 40, 60, 70, 100, and 120 ms) were tested during walking. The C–T intervals of 40–70 ms were used as controls to ensure that the increased activity of the α-motoneurons in this time period was comparable in the two tasks, as we have in fact found (Fig. 6). The control and con-

Fig. 6. During walking the same conditioning stimulus that produced an inhibition of the soleus H-reflex during standing, at C−T intervals of 100−120 ms, did not produce any inhibition during walking. The format of this figure is the same as that in Fig. 3. Each data point in the graphs is the average of eight responses. The results obtained in the same subject (subject 1), during the same experimental session, are shown side by side for each task. Note that in the experiments comparing standing and walking fewer C−T intervals were tested than in the standing experiments alone. Also, in this example the subject stood with his heels slightly raised from the ground so as to generate approximately the same level of soleus EMG activity as in the early part of the stance phase of walking. The natural inhibition of the H-reflex in going from standing to walking is readily apparent, as can be seen from the amplitude of the control H-reflex response in each task.



ditioned H-reflexes were evaluated at the same point in the step cycle, 150 or 170 ms following heel contact (Fig. 1), depending on the time at which the EMG was most comparable with that during standing. In the example shown in Fig. 6 the maximum inhibition of the H-reflex during standing occurred at a C−T interval of 100 ms, a reduction of 37%. During walking, the amplitude of the control H-reflex decreased by 46% compared with its amplitude during standing, an example of the natural inhibition of the H-reflex that occurs during walking compared with standing. Note, however, that during walking the same conditioning stimulus to the CP nerve produced no significant inhibition of the test H-reflex (Fig. 6). Furthermore, there was no shift of the optimal C−T interval at which inhibition could be observed. In the example shown in Fig. 6 the C−T intervals used were between 50 and 120 ms, but shorter and longer C−T intervals

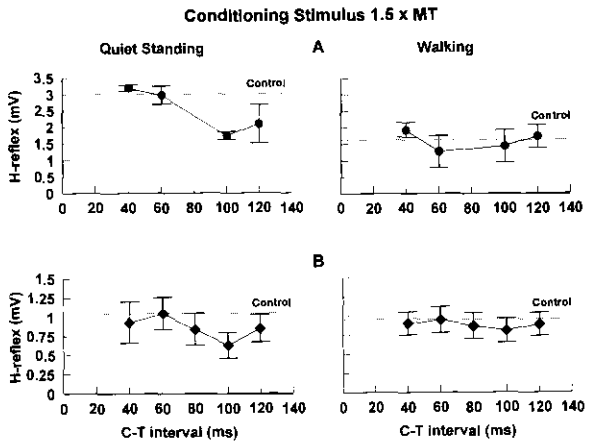


Fig. 7. Further examples of the decreased effectiveness of the conditioning stimulus during walking. Each data point in the figures is the average of eight responses. In Fig. 7A (subject 4) note the natural inhibition of the H-reflex that occurred in the early part of the stance phase of walking and the reduced effectiveness of the conditioning stimulus at inhibiting the H-reflex in this task. However, the main point illustrated in Fig. 7B of the figure is that the conditioning stimulus is less effective at inhibiting the H-reflex during walking even when its size is nearly the same as in standing (subject 5). Additional details are given in the text.

were also tested in other subjects to confirm this point. It is also apparent from the measurements of the background EMG in Fig. 6 that at C−T intervals between 50 and 70 ms there was no difference of α-motoneuron activity between walking and standing. These observations, taken together, make it unlikely that any inhibition that may have occurred during walking was underestimated.

Two more examples of the reduced effectiveness of the conditioning stimulus during walking compared with standing are shown in Fig. 7. The main point illustrated in that figure is that the decreased effectiveness of the conditioning stimulus during walking does not depend on the amplitude of the test H-reflex. In the example of Fig. 7A the conditioning stimulus decreased the H-reflex by 43% during standing, but it had no significant effect during walking. In this example the control H-reflex was nearly 50% smaller during walking than standing. In Fig. 7B the test H-reflex was delivered at about 25−30% of the stance phase of walking. Because the EMG is greater in this part of the stance phase than during quiet standing, it was possible, in some subjects, to obtain control H-reflexes of nearly the same amplitude in the two tasks. As can be seen in that figure, it is clear that the effectiveness of the conditioning stimulus is markedly reduced during walking, despite the fact that the control H-reflexes are comparable in size in the two tasks. Finally, the reduced effectiveness of the conditioning stimulus during walking could not be offset by increasing, or indeed decreasing, its strength. During standing the inhibition of the H-reflex increased with the intensity of the conditioning stimulus up to about 2 × MT (Fig. 8). In contrast, for an H-reflex of similar amplitude, the inhibition was greatly reduced at all conditioning stimulus strengths during walking, including a weak stimulus of 1 × MT (Fig. 8).

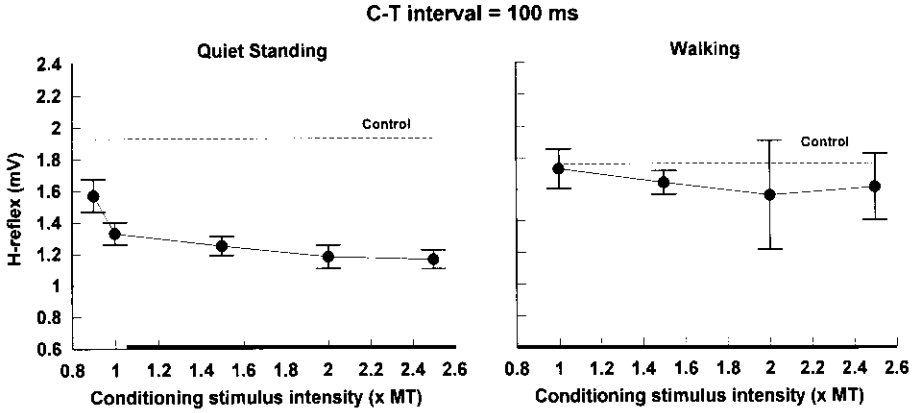
Discussion

Two main observations are reported in the present paper. Firstly, we have shown that the inhibition of the soleus H-reflex by a conditioning stimulus to the CP nerve, at C−T intervals of 100−120 ms, occurs with little change in the background level of α-motoneuron pool activity, as measured by the mean rectified EMG signal. Secondly, we found that the inhibition of the H-reflex by the conditioning stimulus was very robust during standing, but that its effectiveness was markedly reduced during the early part of the stance phase of walking. Thus, the same peripheral conditioning stimulus produced very different effects during standing compared with walking. The possible neural mechanisms and the implications of this observation for studies employing conditioning−testing paradigms are discussed below. It should be recognized that the decreased effectiveness of the conditioning stimulus during walking was not due to the fact the test H-reflex was smaller in this task. When test H-reflexes of comparable amplitude were obtained in the two tasks, the conditioning stimulus remained less effective during walking (Figs. 8 and 9). Perhaps more importantly, the present results are completely opposite to what may be predicted from the nonlinear relation between H-reflex amplitude and stimulus strength (Crone et al. 1990). This relation is sigmoidal in nature, and it can be demonstrated that in such a case the percent change of the test H-reflex, due to either an excitatory or an inhibitory conditioning stimulus of fixed strength, is biggest for small test H-reflexes (see details in Crone et al. 1990). What is reported in this paper is precisely the opposite; the percent change of smaller test H-reflexes produced by the conditioning stimulus during walking is smaller than for the larger test H-reflexes obtained during standing.

Most of the measurements reported here were done in the early part of the stance phase of walking. It is in this part of the step cycle that we expected the neural mechanisms that contribute to the natural inhibition of the H-reflex to be most active. It is possible that the activity of these modulatory mechanisms (e.g., presynaptic inhibition) changes throughout the stance phase, for example, decreasing from a maximum at heel contact, as suggested by Yang and Whelan (1993). Therefore, the conditioning stimulus may have different effects in other parts of the stance phase. However, the same result was obtained in a few experiments in which the test H-reflex was delivered in a later part (25−30%) of the stance phase when the EMG level is higher than in the early part of the stance phase (Figs. 8 and 9). Such experiments are more difficult to do because they require the subjects to exert relatively large tonic contractions for prolonged periods of time during standing. In addition, as the level of contraction increases, it is often difficult to maintain a contant soleus M-wave, because the stimulating electrode is displaced away from the nerve by stiffening of the underlying tissues.

In the following discussion we present the reasons for suggesting that the long latency inhibition of the H-reflex produced by the conditioning stimulus during standing may be due, for the most part, to presynaptic inhibition of the Ia-afferent terminals in the spinal cord. We then discuss the possible neural mechanisms that may underlie the task-

Fig. 8. Conditioning stimuli of 0.9−2.5 × MT to the CP nerve produced a graded inhibition of the soleus H-reflex (C−T intervals of 100 ms) during quiet standing (subject 6). However, remarkably these same stimuli produced little, or no, long latency inhibition in the early part of the stance phase of walking. Each data point in the figures is the average of four to eight responses.



dependent changes of the effectiveness of the conditioning stimulus.

Presynaptic inhibition of the H-reflex

To interpret the observation that during standing the inhibition soleus H-reflex occurred without a commensurate reduction of the background EMG in terms of presynaptic inhibition of the Ia afferent terminals requires that the H-reflex pathway be essentially monosynaptic. The early studies, based on measurements of conduction latencies at various points along the reflex arc (Magladery et al. 1951; Paillard 1955), provided good evidence in favour of this point. In more recent studies, using the method of facilitation of single motor unit discharge, it has been estimated that excitatory postsynaptic potential (EPSP) rise time may be less than 2 ms (Mao et al. 1984; Fournier et al. 1986; Hultborn et al. 1987*a*; Miles et al. 1989). This would hardly allow time for an oligosynaptic contribution, as has been suggested by Burke et al. (1984), unless the rise time of the EPSP in the putative interneurons is faster than in the α-motoneurons, or their threshold much lower. It should also be considered that, since the rate of rise of an EPSP is directly related to the stimulus strength, the method of facilitation may well overestimate the EPSP rise time, because it requires using weak (0.6−0.8 × MT) nerve stimuli. The H-reflex is typically elicited by much stronger stimuli. Finally, although there is evidence for the existence of excitatory Ia interneurons in humans, they may not contribute to the H-reflex because it is produced by an EPSP of brief rise time, as suggested by Fournier et al. (1986). In summary, the current evidence is that the H-reflex pathway is essentially monosynaptic (Mao et al. 1984; Fournier et al. 1986; Miles et al. 1989). Therefore, excluding the possible effects of remote dendritic inhibition (for a discussion see Rudomin 1990) and those of neuromodulators acting on the motoneurons (for a discussion see Heckman 1994), it seems reasonable to suggest that the inhibition observed at C−T intervals of 100−120 ms was due, for the most part, to presynaptic inhibition of the Ia-afferent terminals in the spinal cord. It should also be noted that the C−T intervals used in the present study are comparable with those used in animal experiments (e.g., Schmidt 1971; Hultborn et al. 1987*a*; Stuart and Redman 1991). These rather long C−T intervals should not be interpreted as representing the onset latency of presynaptic inhibition; rather, they reflect its protracted duration (Eccles 1964) and the fact that at shorter C−T intervals presynaptic and postsynaptic effects overlap (Rudomin 1990; Stuart and Redman 1991).

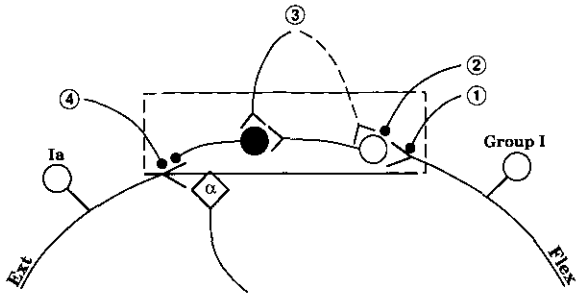
It is also interesting to consider that, if the Ia afferents were providing some synaptic drive to the α-motoneurons during standing, a transient increase of presynaptic inhibition induced by the conditioning stimulus should have also transiently decreased the ongoing soleus EMG, in addition to reducing the soleus H-reflex. The fact that it did not do so to any significant extent may indicate that the Ia afferents do not contribute to the low level tonic activity during quiet standing. It may be that only when forward body sway occurs, thereby stretching the ankle extensors and increasing the Ia-afferents discharge, that these afferents contribute synaptic drive to the α-motoneurons. It would be interesting to elucidate the origin of the tonic ankle extensor activity during quiet standing.

Possible neural mechanisms

There are at least two explanations of the observed differences between standing and walking (Fig. 9). These explanations are not mutually exclusive and may in fact be complementary. Firstly, during walking the intraspinal terminals of the afferent fibres (group Ia and Ib) conducting the conditioning volley may be presynaptically inhibited, or their input gated at the interneuronal level. Secondly, on the assumption that the conditioning stimulus is acting via the presynaptic inhibitory network in the spinal cord, it is possible that during walking this network is saturated as a result of increased central or peripheral synaptic inputs. Each of these mechanisms is discussed, in turn, below.

Studies using C−T paradigms have tacitly assumed that the conditioning stimulus is, itself, not modulated as a function of the task being studied. Indeed, we had assumed at the outset of the present experiments, that the afferent conditioning volley would be the same in each task. It is quite possible

Fig. 9. Schematic diagram showing the possible neural mechanisms that may explain the present experimental results. The presynaptic inhibitory network is minimally disynaptic (see text for details) and is enclosed in the broken rectangular outline. The first mechanism (1) is increased presynaptic inhibition of the flexor group afferents (Ia and Ib) during walking. Mechanism 2 represents the possibility that during walking a central control mechanism inhibits the access of the flexor group I afferents to the presynaptic inhibitory network by inhibiting the excitatory interneuron. The third possibility is that during walking the presynaptic inhibitory network is driven to saturation by central commands. Finally, it may be argued that whatever system may be producing the hypothesized presynaptic inhibition of the soleus Ia afferents, it uses a different presynaptic inhibitory network (mechanism 4) than the one used by the flexor group I inputs.



① Presynaptic inhibition of flexor group I afferents

② Inhibition of access of group I afferents to the presynaptic inhibitory network

③ Occlusion (saturation) of central and peripheral inputs

④ A different presynaptic inhibitory network is used to inhibit the soleus Ia afferents

that the intraspinal terminals of the afferent fibres (group Ia and Ib) conducting the conditioning volley are presynaptically inhibited to a greater extent during walking compared with standing, or their input gated at the interneuronal level (Fig. 9, mechanisms 1 and 2). The conditioning volley would not, therefore, be equally effective in the two tasks. Such task-dependent changes in interneuronal excitability and presynaptic inhibition have been reported to occur during cocontraction of antagonist muscles (Nielsen and Kagimara 1992, 1993). The possibility of presynaptic inhibition of the flexor group I afferents during walking receives some experimental support from the findings of Gossard et al. (1991). They reported that during fictive locomotion in the cat flexor muscle afferents (e.g., from the TA) are especially prone to discharge antidromically during the flexion phase, as a result of intense depolarization of their intraspinal terminals (PAD). Extensor group I terminals have also been shown to undergo changes in PAD during fictive cat locomotion (Baev and Kostyuk 1982; Duenas and Rudomin 1988; Gossard et al. 1991; see also Shefshyk et al. 1984). However, these studies could not, by their very nature, determine how presynaptic inhibition changes in going from one motor task to another, nor clearly establish the functional significance of the PAD.

The idea that the flexor afferents are strongly presynaptically inhibited during locomotion may seem contradictory to the results of a previous study of the reciprocal disynaptic inhibitory pathway (Capaday et al. 1990). In that study, it was shown that the reciprocal inhibitory pathway was equally effective during standing and walking. This result implies that at least the flexor group Ia afferent terminals are not presynaptically inhibited during walking, unless it is possible to presynaptically inhibit one group of terminals (e.g., those projecting to the presynaptic inhibitory interneurons), while not affecting others of the same fibre (e.g., those projecting to the Ia inhibitory interneurons). Some evidence for differential presynaptic inhibitory control of the different intraspinal terminals of the same afferent fibre has been recently obtained (Eguibar et al. 193). Various other possibilities can also be conjectured, for example, differential control of presynaptic inhibition on the group Ia and Ib terminals (Duenas and Rudomin 1988; Gossard et al. 1991). Only further experiments can bring light to these various possibilities.

On the assumption that during standing the conditioning stimulus was acting via the presynaptic inhibitory network in the spinal cord, it may be that this network was saturated by central, or peripheral, synaptic inputs during walking (Fig. 9, mechanism 3). This suggestion is compatible with the changes in the input–output properties of the H-reflex observed between walking and running (Capaday and Stein 1987*a*). The main difference is that, during running, the slope of the relation between the H-reflex amplitude and the background level of EMG decreases. In other words, the H-reflex is equally, and perhaps maximally, inhibited in the early part of the stance phase of walking and running. Therefore, any additional input, such as the conditioning volley used in the present experiments, would not produce a further increase of inhibition. On the other hand, it may be argued that saturation is an unlikely explanation because the same result was obtained with a relatively weak conditioning stimulus (e.g., Fig. 8, 1 × MT). However, since we have no detailed quantitative information on the input–output properties of this pathway, it is difficult to evaluate this possibility. In any case, the idea of saturation is consistent with our hypothesis that presynaptic inhibition of the Ia-afferent terminals increases during walking. However, corroboration or refutation of this hypothesis will require new approaches that circumvent the potential difficulties outlined above.

The possibility that different systems may utilize different presynaptic inhibitory circuits must also be considered as an explanation of the present results. There is in fact evidence that peripheral and descending inputs converge onto common presynaptic inhibitory circuits in the spinal cord. For example, the presynaptic inhibition of extensor Ia-afferent fibres produced by flexor group I afferents can be decreased by conditioning stimulation of the sural nerve, or of the motor cortex. These two inputs (and others, see for example Rudomin 1990) thus converge onto the same presynaptic inhibitory network used by the flexor group I fibres. Like other spinal cord interneurons, those involved in presynaptic inhibition receive convergent inputs from a variety of central and peripheral sources. It is therefore not unreasonable to think that different pathways do utilize common presynaptic inhibitory interneurons (as they seem to use, for example, Ia

inhibitory interneurons). Nonetheless, it can be argued that whatever system may be producing the hypothesized presynaptic inhibition of the soleus Ia afferents it uses a different presynaptic inhibitory network that the one used by the flexor group I inputs (Fig. 9, mechanism 4). Thus, the present findings may reflect changes in the presynaptic inhibitory network used by the flexor group I afferents, rather than the activity of the presynaptic inhibitory network responsible for the inhibition of the soleus Ia afferents during walking.

The possibility of peripheral occlusion (refractoriness of peripheral afferents), whereby the stimulus to the CP nerve fails to discharge the same number of group I afferents during walking compared with standing, must also be considered. It is clear that refractoriness of peripheral afferents to the conditioning stimulus would only occur when their discharge rate is at, or near, the maximum. There is little reason to believe that the group Ia and Ib afferents in the CP nerve, or indeed other afferents, are discharging anywhere near their maximum rate in the early part of the stance phase. For example, the burst of activity in the TA muscle at the time of heel contact (Fig. 1) is about 5–10% of the maximum TA M-wave; it would be surprising if the Ib afferents were discharging anywhere near their maximum rate for such a low level of intramuscular force. The Ia afferents are also not expected to be discharging at, or near, their maximum rate in the early part of the stance phase of walking. The TA muscle at this time is either slowly stretched, as the ankle gradually begins to bear weight, or is beginning to shorten (see Fig. 5 in Capaday et al. 1990). Nonetheless, it is possible that, for example, a burst of activity in these afferents at the time of heel contact may be a source of homonymous presynaptic inhibition, or postactivation depression (Crone and Nielsen 1989). Indeed, it has been suggested that movement-related afferent activity may be an important source of the inhibition of the H-reflex during pedaling (McIlroy et al. 1992). Cutaneous afferents are one source of peripheral activity that may be involved in a task-dependent change of presynaptic inhibition. These afferents inhibit the presynaptic inhibition (i.e., reduce it) produced by flexor group I afferents onto extensor group Ia afferents (Schmidt 1971; Rudomin 1990). Thus, increased cutaneous activity (see Duysens et al. 1993), or interneuronal transmission of this activity, may have reduced the effectiveness of presynaptic inhibition during walking (e.g., by mechanism 2 in Fig. 9).

Finally, as stated in the introduction, other mechanisms may be used to explain the changes in the input–output properties of the H-reflex during walking compared with standing. For example, it may be that the relation between motoneuron firing rate and synaptic current is modified during walking (Brownstone et al. 1992), or that the recruitment gain of the motoneuron pool is changed during walking (Kernell and Hultborn 1990; see a quantitative evaluation of this possibility in Heckman 1994). Thus, it may be that several neural mechanisms contribute to the phenomenon. Unraveling the contribution of each of these possible mechanisms, quantitatively, will be a challenging endeavor.

Conclusions

Regardless of what the exact mechanisms turn out to be, it is clear that a strong task-dependent modulation of a reflex pathway from a flexor nerve has been demonstrated in the present study. The reasons for this may prove to be of importance for understanding the neural mechanisms of human walking. Our results also raise an important methodological issue. Neurophysiological studies using C–T paradigms depend on maintaining a constant conditioning stimulus. This criterion can usually be met when dealing, for example, with anesthetized animal preparations. However, when this paradigm is used during natural motor tasks, as in the present study, the possibility that the conditioning stimulus may be modulated by the task being studied will need to be considered in the design of the experiments. From the functional point of view, our results hint at the fact that the neural networks of the spinal cord subserving motor functions may be dynamically reorganized, in a task-dependent manner (see relevant discussions by Pearson 1985; Loeb et al. 1990; Stein et al. 1991).

Acknowledgments

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