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THE UNIVERSITY OF ALBERTA

MODULATION OF EXCITATORY AND INHIBITORY REFLEXES DURING LOCOMOTION

BY

© Charles Capaday

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF Doctor of Philosophy.

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Dedicated with affection to my parents and grandparents.

ABSTRACT.

During walking (4 km/h), the amplitude of the Soleus H-reflex was strongly modulated. It increased progressively during the stance phase, reaching its maximum value at about the time of the peak Soleus EMG. It then abruptly decreased at the end of the stance phase. The H-reflex was usually [illegible] very small during the swing phase. The pattern of modulation was qualitatively similar during running (8 km/h). However, the reflexes obtained during running were significantly smaller than those obtained during walking. Furthermore, the slope of the line fitted to a plot of H-reflex amplitude vs the mean value of the background Soleus EMG was always steeper for the walking data than for the running data. The H-reflex was also investigated in a postural task, ranging from quiet standing to shifting progressively more of the body weight onto the experimental leg. During quiet standing, despite a smaller level of Soleus EMG activity the amplitude of the H-reflex was 3-5 times greater than that during the early part of stance. In fact, the H-reflex was greater, at the same level of Soleus EMG activity, in the postural task than during walking. From these findings, it is concluded that the CNS can control the efficacy of synaptic

transmission between the Ia-afferents and the motoneurons, independently of the level of motor activity. This would allow for the adaptive control of the stretch reflex stiffness.

A computer model was developed to study the factors that can affect the amplitude of the monosynaptic reflex. It was found that presynaptic inhibition is the only mechanism that can alter the size of the monosynaptic reflex independently of the level of activity in the motoneuron pool. This finding was confirmed by experiments done in the cat.

The Soleus motor activity, as measured from the intramuscular EMG, can be inhibited at all times during the stance phase of walking, as well as during voluntary tonic activity. Therefore, the Ia-interneurons projecting to the Soleus motoneurons are not shut off during activity of the Soleus motoneuron pool. Moreover, there was no difference in the efficacy of the inhibition in the two tasks.

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First and foremost I wish to express my sincere gratitude to my teacher Dick Stein. He has been truly inspirational during my stay in his laboratory and will continue to be for a long time to come. While I am a little sad to leave, I am also very happy to have been a part of his laboratory. I thank Robert Rolf for his outstanding technical assistance and help with the production of this thesis. The members of my advisory committee have made many excellent suggestions to improve this thesis. I extend to them many thanks, as well as to Dr Pang for his advice and genuine caring. Finally, my best regards go to all my colleagues in the department.

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I. INTRODUCTION

The study of physiological systems can be viewed as consisting of analysis at four different but strongly interrelated levels. The structural organization of the system, ranging from classical anatomy to studies involving immunohistochemical localizations of cell groups, is at the most basic level. With regards to the nervous system this includes identification of the major subdivisions, the pathways for afferent and efferent activity and those linking the major subdivisions. The details of cell types, their interconnections in a network and possible neurotransmitter content are provided by various histological techniques. The next level of analysis consists of identifying the basic physiological processes that underlie the activity of the system under study and determining the mechanisms behind these processes. As an example, in the nervous system nerve conduction and synaptic transmission across nerve cells are the basic physiological processes underlying the transfer of information in this system. Many years of effort have gone into elucidating the mechanisms of the action potential and synaptic transmission (Hodgkin, 1964; Katz, 1969). At the third level of analysis one tries to identify by physiological means, usually in reduced preparations,

the underlying neural circuits that subserve a particular function. For example, Eccles and his many colleagues using microelectrodes in the cat spinal cord identified many of the pathways that link muscle receptors to motoneurons as well as the types of synaptic connections, excitatory or inhibitory, within those pathways (Eccles, 1964). This sets the stage for the fourth level of analysis which may be referred to as systems Physiology. Here the issue is the role of the identified neural pathways in normal function. Questions such as, which of the identified mechanisms operates during normal activity, and what qualitative and quantitative contributions do they make to that activity, are fundamental. In simple terms, at this level of analysis one is concerned with the functional role of putative neural circuits in a particular physiological activity.

The Renshaw cell, the first identified interneuron in the mammalian spinal cord (Renshaw, 1941), can serve as an example. This neuron receives a major excitatory input directly from the axon collaterals of motoneurons and in turn monosynaptically inhibits motoneurons, thus making a recurrent negative feedback type of connection with the motoneurons (Renshaw, 1941; Granit, 1972). Because the Renshaw cell axon branches extensively to innervate widely separated motoneurons and does not usually contact the

motoneurons that synapse upon them (Granit, 1972) one may ask whether their role during maintained contractions is to overcome the possible synchronization of motoneurons and hence reduce the tendency for tremor. Some evidence for this has been obtained in reduced cat preparations (Adam, Windhorst, and Inbar, 1978) and certainly warrants further investigation during voluntary contractions.

The various studies contained in this thesis were all attempts at understanding the functional role of various basic spinal cord mechanisms during natural motor tasks such as walking, running and standing. The emphasis is placed on the term natural motor task or activity, because as happens all too often in motor Physiology the task investigated is somewhat contrived. Conclusions derived from such studies may not, therefore, have general applicability. In figure 1.1 the basic spinal cord circuits that are the subject of this thesis are shown. The diagram represents a summary of what is known based mainly on studies of the cat spinal cord and to some extent that of the monkey (Baldissera, Hultborn, and Ilert, 1981; Jankowska, Padel, and Tanaka, 1976). The basic connections shown in the diagram are described below and some ideas on the possible functional significance of each circuit are presented. Following this, a

more detailed discussion of the pathways that have been directly investigated in the present studies is given.

The basic spinal cord motor circuits

The monosynaptic nature of the connection between the Ia muscle afferents and the motoneurons was first demonstrated by Lloyd (1943). It was later confirmed by intracellular recordings from motoneurons (Lundberg and Winsbury, 1960). This connection subserves the well known stretch reflex, but as discussed below it may not be the only pathway contributing to the stretch reflex. An excellent historical account of the work done on this pathway starting with the discovery of the stretch reflex by Liddell and Sherrington is given by Matthews (1972). The first clear demonstration that the Ia afferents may excite motoneurons via polysynaptic pathways was made by Hultborn et al. (1975). These polysynaptic connections may account for such phenomena as the so called medium latency stretch reflex responses (M2) and the tonic vibration reflex (see, Baldissera, Hultborn and Illert, 1981). Related to these polysynaptic connections, it was shown that in the human the rise time of the monosynaptic epsp in motoneurons, in response to an electrical nerve stimulus, may be relatively slow, about 2.4 ms (Burke,

Gandevia and McKeon, 1984). These authors have argued, therefore, that the relatively prolonged duration of the monosynaptic epsp allows for possible oligosynaptic inputs to affect the motoneurons before they reach threshold. This suggestion is examined further and evaluated in the general discussion. Finally, there may be an autogenic inhibitory effect from the Ia afferents to the motoneurons mediated by a disynaptic or trisynaptic connection (Fetz, Jankowska, Johannisson and Lipski, 1979).

The motoneurons have collaterals that innervate small inhibitory interneurons, located in the ventral horn, which in turn inhibit motoneurons (Renshaw, 1946). This recurrent inhibitory pathway may have several functional roles. As already discussed, it may serve to desynchronize the discharges of motoneurons (Adam et al., 1978), as well as to slow the discharge rates of the motoneurons (Granit, 1972). Hultborn, Lindstrom, and Wigstrom (1979) hypothesized that the Renshaw cells, which are under supraspinal control, may also contribute to the regulation of the motor output as follows. If the gain of this pathway is high, that is the Renshaw cells are very excitable, then large variations of the supraspinal input onto the motoneurons will produce relatively small variations of the motor output. This would allow for

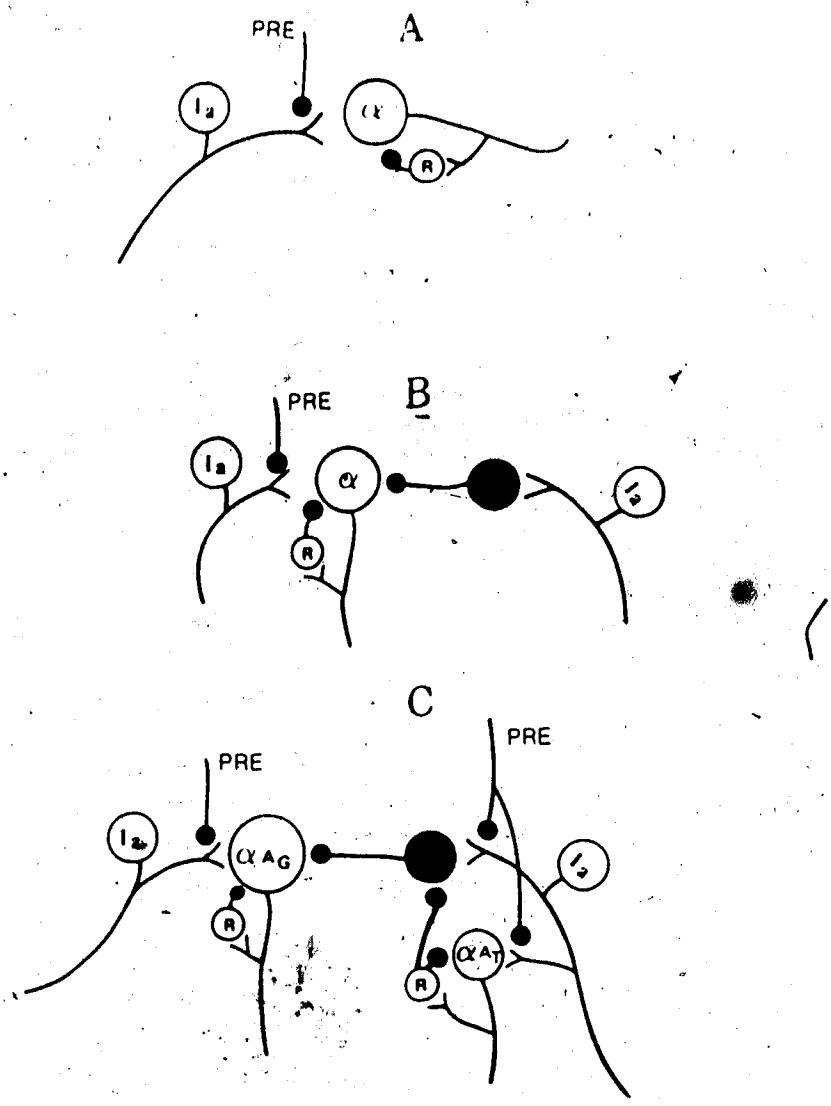

Figure 1.1: The basic spinal cord motor circuits. The alpha motoneurons are labeled with the symbol "α", the Renshaw cells are labeled with the symbol "R". The Ia inhibitory interneurons are shown in solid black, presynaptic inhibition of the Ia terminals is labeled as "PRE". Inhibitory contacts are shown as

small black circles, the excitatory ones are shown as a forked bifurcation. The diagram shown in part C is symmetrical, but only the connections on the right side are shown in their entirety for clearness of illustration. The details of the diagrams are described in the text.

the very fine control of the motor output. If, on the other hand, the gain of this pathway is low, then large variations of the supraspinal input onto the motoneurons will produce relatively large variations in the motor output. This would allow for high levels of force output when needed. In addition, Renshaw cells inhibit the Ia inhibitory interneurons that project onto the antagonist motoneurons (Hultborn, Jankowska and Lindstrom, 1971). The function of this inhibitory connection is not known, but clearly it would tend to reduce the effectiveness of the inhibition of antagonist motoneurons in parallel with the level of motor output. This issue is discussed in detail in chapter 5.

The other two major pathways shown in figure 1.1 are the presynaptic inhibition of the Ia terminals within the spinal cord (Schmidt, 1971), and the well known Ia inhibitory interneurons projecting to the motoneurons (Eccles, 1964). Presynaptic inhibition of the Ia afferents may be produced from either supraspinal stuctures, such as the red nucleus (Rudomin, 1980), or as a result of activation of other groups of afferent fibers. For example, stimulation of Ia afferents in flexor nerves presynaptically inhibits Ia afferent terminals of extensor nerves (Schmidt, 1971; Eccles, 1964).

Issues pertinent to the work done in this thesis

concerning the monosynaptic pathway, the disynaptic inhibitory pathway, and the presynaptic inhibitory pathway(s) are further discussed in the next three sections.

The monosynaptic reflex connection

The monosynaptic connection between the primary (Ia) spindle afferents and the motoneurons has been investigated as an example of integration of information in the CNS, specifically the integration of descending and afferent inputs to the motoneurons (Lloyd, 1941; Phillips and Porter, 1977). It has also served as a model system for the study of the mechanisms of synaptic transmission in the mammalian nervous system (Eccles, 1964; Mendell and Henneman, 1971). The stretch reflex pathway(s) has also been extensively studied from the functional point of view, that is what role it may have during motor activity (Liddell and Sherrington; 1924; Merton 1953; Matthews, 1972).

Two views on this pathway stand out in my mind. First, although it can be regarded as a negative feedback pathway tending to oppose changes in muscle length due to internal or external perturbations, it appears that it does not have sufficient gain, or more correctly stiffness, for it to work as an effective position servo-system. The best experiment

on this was done by Peter Matthews several years ago (Matthews, 1959) in the decerebrate cat, a preparation with a good stretch reflex compared to other common preparations. He measured the stiffness of the soleus muscle from tension/extension measurements and found it to be rather low. Typically, the stiffness measured in response to large slow stretches was 75-90 g/mm or some 5% of maximum tetanic tension for each millimeter of stretch. Values up to 200 g/mm were also observed. However, when small stretches are used (0.2 mm) the measured stiffness is some 400 g/mm. Thus, the stretch reflex behaves in a manner reminiscent of the Ia-spindle ending which possesses a markedly greater sensitivity to small stretches as opposed to large ones (Matthews and Stein, 1969).

It appears, therefore, that the stiffness of the stretch reflex is low to moderate. However, it should be noted that despite this it can nevertheless generate a substantial amount of tension in response to a large stretch especially when compared to what may be required in a motor act such as walking. Allum, Mauritz, and Vogele (1982) have attempted to measure in normal humans the contribution of the short latency (approximately 40 ms) stretch reflex response in subjects instructed to resist a dorsiflexing torque

applied to the foot. They found that the torque produced by the short latency stretch reflex response was about 5 Nm. This represents a moderate amount of muscle tension when the torque to force conversion is made. Walking is an energetically efficient motor activity requiring small levels of muscle activation despite relatively large limb displacements (Basmajian, 1967; Winter and Robertson, 1978; Pedotti, 1977). Thus, the small to moderate contributions made by the stretch reflex may be sufficient to assist locomotor activity.

In contrast to the view that the short latency stretch reflex may be useful in assisting locomotion, Dietz et al. have reported that this reflex response may be absent in normal humans during locomotion (Dietz, Quintern and Berger, 1984). They attributed their observation to a suppression of the monosynaptic pathway. This is contrary to the findings reported in this thesis. In chapters 2 and 3 it is shown that the monosynaptic reflex pathway is not shut off during locomotion, in fact it is strongly modulated in amplitude during the step cycle. The fact that this reflex is strongly modulated during the locomotor cycle may account for the observations of Dietz et al. (1984). In their study, the stretch of the ankle extensors is applied at the moment of heel contact. As will be described in the following two chapters,

the sensitivity of the reflex is low in this phase of the step cycle and the ankle extensors relatively slack. Both of these factors mitigate obtaining stretch reflex responses in that phase of the step cycle. A perturbation applied later in the step cycle, when the sensitivity of the reflex is relatively higher, should produce an observable reflex response. This argument is strengthened by the observation that the same perturbation applied during quiet standing is followed by a short latency stretch reflex response (Dietz et al., 1984). As will be shown in chapter 2 we have found that the sensitivity of the monosynaptic reflex is very high in this task.

The other clear observation in Matthews' study was that the muscle under stretch reflex control behaves very much like an ideal spring (i.e., a spring of constant stiffness at all extensions). This point was later emphasized by Nichols and Houk who showed that, in addition, a muscle under stretch reflex control behaves symmetrically to stretch and release (Nichols and Houk, 1976). The linear and symmetrical (i.e., no hysteresis) behaviour of muscle under stretch reflex control may ease the required neural control. What I wish to emphasize is that the stretch reflex provides a mechanism by which the stiffness of the muscle whithin this closed loop may be modified independently

of the level of motor output. This would allow the stiffness to be set to a value appropriate to the motor task. For example, increased stiffness in a task such as standing where position needs to be controlled, and greater compliance in a task such as walking to allow for a fluid stride. In addition adjustments of the stiffness of the extensors would provide a sort of tunable suspension for shock absorption during locomotion, which is clearly important in running and downhill walking. Furthermore, the value at which the stiffness is set will determine the extent to which Ia afferent activity will contribute via the stretch reflex pathway to the total motor output. It should be noted that the view presented here, that the reflex stiffness of a muscle may be modified to suit the requirements of the motor task, is quite different from that of Nichols and Houk (1976). They suggested that the muscle stiffness was regulated in the same sense that position or temperature are regulated in a suitably designed control system. In other words, in their view, the function of the stretch reflex was to insure that the overall stiffness of a muscle does not depart from a set level. In fact, Houk (1976) argued that this set point was constant and invariable at all levels of motor output (see also Berkinblit, Feldman, and Fukson, 1986).

This brings us to the second point; the stretch reflex, especially its monosynaptic component, has traditionally been viewed as a stereotyped response with little or no scope for modification. Indeed, it has been hypothesized that the adaptive capacity of the organism to respond to muscle stretch produced by a perturbation to a limb is due to a transcortical loop involving the motor cortex (Phillips, 1969; Wiesendanger, Ruegg, and Lucier, 1975). To date there is no general agreement that such a transcortical reflex operates during natural conditions (Darton et. al, 1985; Matthews, 1984; Houk, 1978), although the connections are known to exist (Cheney and Fetz 1984; Phillips et. al, 1971; Hore, et. al, 1976). In fact there is no good evidence that the so called "long latency" responses are modifiable on a moment to moment basis (see for example Houk 1978; Marsden et al., 1978). One of the major points of this thesis is that the above view is incorrect. The short latency essentially monosynaptic responses are modifiable by a central mechanism, on a moment to moment basis, independently of the level of motor activity, and they are specifically adapted to the motor task. Furthermore, the changes in the amount of presynaptic inhibition acting on the Ia afferent terminals in the spinal cord is the primary central mechanism

responsible for this adaptive capacity. Fusimotor activity, as will be discussed in the body of the thesis, would tend to reinforce the central effects.

Thus, such a capacity to control the efficacy of synaptic transmission between the Ia-afferents and the motoneurons, on a moment to moment basis, would allow for the adjustment of the stiffness of the stretch reflex to a value appropriate to the motor task. Indeed, this may account for such observations as the increase of stretch reflex stiffness in man when the motor task involves stabilizing the position of an unstable load (Akazawa, Milner, and Stein, 1983). Furthermore, this adaptive benefit would not be delayed by having to traverse long loop pathways (e.g., transcortical).

The disynaptic inhibitory pathway

The well known short latency inhibition of motoneurons by electrical stimulation of the antagonist nerve (Lloyd, 1941, 1946) has been shown by Eccles and colleagues (Araki, Eccles, and Ito, 1960; Eccles, 1964) to be due to an interneuron interposed between the Ia-afferents and the motoneurons of the antagonist muscle. This was contrary to the view of Lloyd that this inhibitory pathway was monosynaptic. Eccles in his book the "The Physiology of Synapses" (Eccles, 1964) summarizes the evidence obtained from a

series of experiments showing that there exists an interneuron in this simplest of inhibitory pathways of the mammalian CNS. Briefly, the Ia ipsp has a time course comparable to that of the inhibition of reflex discharge (Brock, Coombs, and Eccles, 1952), the latency of the ipsp is 1 ms longer than that of the epsp. Furthermore, this latency is comparable to that of the first detectable sign of inhibition of ventral root reflexes (Araki, Eccles and Ito, 1960). The next major progress was the finding by Lundberg (1966) that the Ia-inhibitory interneuron was under supraspinal control. This led to the hypothesis of "*a*-linked inhibition" whereby activation of motoneurons was linked to the simultaneous excitation of the Ia inhibitory interneurons projecting to the motoneurons of the antagonist muscle. This hypothesis implied a potentiation of inhibitory action at this synapse preceding as well as during a movement. Support for this hypothesis was obtained in the early seventies (Tanaka, 1974) in experiments on the ankle musculature of human subjects. However, recent reexamination of this issue has failed to confirm a potentiation of the inhibitory action at this synapse accompanying voluntary activation of the ankle extensors (Iles, 1984; Crone, Hultborn and Jespersen, 1985). This issue is more fully discussed in the fifth chapter of this thesis.

Another important point on this pathway is that all the known inhibitory projections onto the Ia inhibitory interneurons are from other inhibitory interneurons in the spinal cord. There are no known direct supraspinal inhibitory connections onto the Ia-interneurons. They are inhibited by Renshaw cells whose motoneurons receive the same Ia-afferent input. They are also inhibited by the Ia inhibitory interneurons associated with the motoneurons of the antagonist muscle. This is referred to as mutual inhibition of opposite Ia inhibitory interneurons (Baldissera, Hultborn and Illert, 1981). The two interneurons providing inhibition onto the Ia inhibitory interneurones are under supraspinal control, thus allowing for the supraspinal inhibition of Ia inhibitory interneurons.

The presynaptic inhibitory pathway

The literature on presynaptic inhibition in the spinal cord is extensive (reviewed by Burke and Rudomin, 1977; Rudomin, 1980) and goes back to Barron and Matthews (Barron and Matthews, 1938) who studied the related phenomenon of dorsal root potentials in the frog spinal cord resulting from high frequency stimulation of afferent fibres. Here I want to make three points on this mechanism that controls the efficacy of synaptic transmission.

The first is that it can produce its effects sufficiently rapidly to be capable of modulating reflex transmission on a moment to moment basis. For example stimulation of flexor group I fibres produces within a few milliseconds presynaptic inhibition of extensor group Ia-afferents (Frank and Fuortes, 1957) the same is true when presynaptic inhibition of afferent fibres is produced by supraspinal structures (Rudomin, 1980). The second point is that presynaptic inhibition can be very specifically directed onto certain types of terminals at the exclusion of others which are in the same vicinity. For example, vestibulospinal fibre terminals projecting to motoneurons are adjacent to those of the Ia-afferents since the interaction between their epsps in the motoneuron soma is nonlinear. Stimulation of a flexor nerve at group I strength produces presynaptic inhibition of the Ia-afferent fibre terminals but has no effect on those of the vestibulospinal fibre terminals (Rudomin, 1980). This specificity has also been shown for presynaptic inhibition of terminals in the spinal cord produced by supraspinal structures such as the red nucleus, Deiters's nucleus, and the sensorimotor cortex (Rudomin, 1980). The speed and specificity of action are due no doubt to the existence of specific interneurons mediating

presynaptic inhibition (Jimenez, Rudomin, Solodkin, and Vyklicky, 1984). Finally, if during a natural motor activity a change in reflex transmission is found to be due to presynaptic inhibition, the source of this inhibition may be of either central or peripheral origin.

Reflex activity during locomotion

The modern view on the generation of locomotor activity in the mammal has been summarized by Grillner in three recent reviews (Grillner, 1985; Grillner and Wallen, 1985; Grillner, 1986). In Grillners' view the basic locomotor pattern, that is the timing relations between the activities of the various muscles, is produced by a so called central pattern generator (CPG) located in the spinal cord. The CPG can, apparently in the total absence of afferent inputs, produce appropriately timed motor bursts in the various muscle groups. Grillner, however, has repeatedly stressed that in the intact animal the observed locomotor pattern is a resultant of both central and peripheral factors acting in concert. A clear example of how afferent activity from the leg can influence the motor output is provided by the entrainment of locomotor rhythm produced by hip afferent inputs. During normal locomotion in the cat if the hip is prevented from extending during the

early part of stance the discharge of all leg extensors is prolonged until the leg is released (Grillner and Rossignol, 1978). If on the other hand the hip joint is extended in the same phase the leg will flex and this at about the same hip joint angle as would occur naturally. Furthermore, in the curarized fictive locomotion preparation, if the hip is moved sinusoidally by an externally applied force the fictive motor pattern is entrained by the applied hip movements (Andersson and Grillner, 1983). Loading the cat during the stance phase produces enhanced extensor activity and delays the initiation of the swing phase; conversely, unloading the animal at the end of stance promotes limb flexion (Duysens and Pearson, 1980). These examples clearly demonstrate that afferent inputs can directly influence the CPG. They serve to reinforce the point that the pattern of motor output observed in the intact animal is a resultant of both central activity and movement related feedback. These ideas are in agreement with those of Pearson (1985) who argues that the concept of a CPG is misleading, since the motor output pattern in the intact animal may be different from that in the deafferented animal. He shows that in locust flight and cockroach locomotion the motor output is different in the intact animal compared to the deafferented preparation (Pearson, 1985). In particular, the

timing relations between the motor burts of the various muscles is altered in the deafferented animal. In these two systems the concept of the CPG as described by Grillner is not applicable (see, Grillner and Zangger, 1975). Whether the concept of a CPG, as an entity in the spinal cord that can appropriately time the motor outputs to the various locomotor muscles in the absence of peripheral feedback, is applicable to the human is not known. This is, obviously, of scientific as well as clinical interest.

The counterpart of the above phenomenon, namely the selective control by the CPG of the effects of afferent inputs on the motor output, has also been observed. For example, if the foot encounters an obstacle during the swing phase, that is when it is in the air, this results in hyperflexion of the leg so as to pass over the obstacle (Forssberg, 1979). The same stimulus during the stance phase does not cause a leg flexion as this might cause the animal to fall. Instead, it increases the extensor activity presumably until the other leg is placed on the ground. This is a classic example of the central control of the effects of afferent input on motor output.

The above examples involved for the most part afferent inputs from joint and skin afferents. The effects of the Ia muscle spindle afferents on the

motor output during locomotion have been much less studied. In general, the reflex effects of the cutaneous and joint afferents influence the timing of locomotor activity. In contrast, muscle afferents influence the amplitude of locomotor activity, and may in addition have some effect in determining the exact duration of a motor burst depending on the exact kinematic events as will be explained in the final chapter of this thesis. However, like cutaneous and joint influences on the locomotor output, those of muscle afferents must also be regulated by a central mechanism(s). Referring to extensor muscles of the leg, a stretch reflex would reinforce activity during the stance phase, where these muscles yield under the weight of the body, whereas it would oppose the flexors during the swing phase when the extensors are stretched by the flexor activity (Akazawa et. al, 1982; chapters 1 and 2). Prior to the present studies only that of Akazawa et al. (1982) had systematically investigated the reflex effects of Ia-spindle afferents during the various phases of the locomotor cycle of the mesencephalic cat. This thesis takes its origins in part from that initial study.

Outline of thesis

The chapters of this thesis are ordered in a logical sequence rather than in the chronological

sequence in which the experiments were done. Each of the studies described in the following chapters was done to answer one or more of the following questions:

1) Is the short latency, essentially monosynaptic, reflex response of the soleus muscle modulated in amplitude during the step cycle?

2) Is the modulation specific to and of functional importance for the task being performed?

3) Can the amplitude of this reflex be controlled independently of the level of motor activity?

4) If so, what is the mechanism(s)?

5) Is the segmental inhibitory pathway (Ia inhibitory interneuron pathway) to the soleus motoneurons shut off during their active phase in the locomotor cycle? What is the quantitative relation between the amount of inhibition and the amount of motor activity?

The results obtained in answer to the first three questions are contained in the next two chapters. As mentioned above my interest was in identifying a central factor that may be responsible for any possible reflex modulation during natural motor activities. Therefore, experimental manipulations such as stretching a muscle produce responses that depend on the state of the fusimotor system and hence the sensitivity of the muscle spindles, a peripheral factor. Electrical stimulation of a nerve was therefore used since it is largely independent of

peripheral factors such as the sensitivity of muscle spindles (see Chapter 2 for further details). Thus, the monosynaptic reflex was elicited in humans by applying an electrical stimulus to the tibial nerve and recording the direct muscle response (M-wave) and the subsequent reflex response of the Soleus (H-reflex) electromyographically. The Soleus muscle was used for several physiological and methodological reasons. It is a major ankle extensor and thus is one of the most important muscles providing forward thrust and lifting of the body during normal locomotion. It also has a well developed stretch reflex which manifests itself in an easily obtainable H-reflex. Finally, one can record the electromyographic reponses of this muscle in relative isolation from those of other ankle extensors (Hugon, 1973). The method was first developed by Hoffmann (Hoffmann, 1922), hence the designation Hoffmann reflex (H-reflex) in his honour. It has been used to test the so called excitability of the motoneurons under either resting conditions, preceding voluntary activation of the ankle extensors (Kots, 1969; Paillard, 1959) and during tonic contractions in the sitting position (Gottlieb, Agarwal, and Stark, 1970).

Until the present study, and except for a short abstract (Garrett et al., 1984) and a short paper

(Morin et al., 1982) it had never been used to study a natural, dynamic, motor task. The technical details concerning its application during human locomotor activity are fully described in the various chapters of this thesis. It is often suggested that the technique tests the excitability of the motoneurons, which is a factor intrinsic to the motoneurons themselves. The method inevitably also tests for the state of transmission between the Ia-afferents and the motoneurons. Furthermore, as will be described in chapter 4 the method may in fact be independent of the intrinsic excitability of the motoneurons when comparisons between reflexes are made at the same level of motor output. In fact, the fourth chapter is a theoretical analysis of what central factors (presynaptic vs postsynaptic) may be involved in changing the input-output relations in the monosynaptic pathway and thus adresses the fourth question. It should be pointed out that the conclusions reached in that study are contrary to those in chapter 2 which were based on a qualitative analysis of the problem.

Finally, the results relating to the last question are presented in the fifth chapter. The state of the Ia-inhibitory pathway to the soleus motoneurons was tested by its effect on the naturally occurring motor

activity, as measured from the rectified intramuscular e.m.g., as opposed to the traditional conditioning/ test reflex paradigm (e.g., Tanaka, 1974).

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II. AMPLITUDE MODULATION OF THE SOLEUS H-REFLEX IN THE HUMAN DURING WALKING AND STANDING

It was reported recently that the stretch reflex of the soleus muscle was strongly modulated in amplitude during the walking cycle of the mesencephalic cat (Akazawa et al., 1982). Moreover, the modulation of the amplitude of the stretch reflex was not simply a function of the level of activity in the soleus muscle. This demonstration depended on comparing reflexes obtained during locomotion to those obtained during similar levels of tonic activity which occur spontaneously in the mesencephalic cat. Therefore, it is possible that the efficacy of the synaptic transmission between the Ia afferents and the motoneurons may be modulated by central neural mechanisms independently of the level of motoneuronal activity (Akazawa et al., 1982). However, because the study used a reduced preparation and relied on spontaneous changes of activity, the utilization and functional value of such a modulation during voluntary activity remains unknown.

A version of this chapter has been published.
Capaday, C. & Stein, R.B. (1986)
Journal of Neuroscience 6, 1308-1313.

Does a functional modulation of the stretch reflex occur in normal human subjects, and if so, what is its origin? Surprisingly, these questions have been the subject of only brief reports (Capaday and Stein, 1985; Garrett et al., 1984; Morin et al., 1982). Walking and standing were chosen to investigate these questions in more detail, because the stretch reflex is of functional value in both tasks (Dietz et al, 1980; Dietz et al, 1979; Nashner 1976) and may be used to a different extent in each task. Walking requires a certain amount of compliance (Houk 1976), whereas standing may require a more rigid control of ankle position. In principle, a modulation of the amplitude of the stretch reflex can be produced by a shift of reflex threshold (i.e., the curve relating reflex output to stimulus input is shifted along the abcissa without changing its slope; Crago et al, 1976; Houk, 1976, 1979) or by a change in reflex sensitivity which would change the slope of the input-output relation. These two possibilities may result from quite different neural mechanisms.

There are obvious technical difficulties in applying, during walking, perturbations that would stretch a muscle group of a normally moving limb. However, Akazawa et al. (1982) found that in the mesencephalic walking cat the amplitude of the H-reflex and the stretch reflex were modulated in

essentially the same way. It was also found in this preparation, that during spontaneous states of tonic contractions the amplitude of the H-reflex paralleled that of the stretch reflex (Akazawa et al., 1982; see also, Aldridge and Stein, 1982). Furthermore, while the H-reflex and the stretch reflex are not identical (Burke et al., 1983, Burke, 1984), both depend in large part on the synaptic connections between the Ia muscle afferents and the α-motoneurons. Therefore, the amplitude of the H-reflex and the stretch reflex may have similar temporal profiles during the course of a movement or postural state, although the extent of facilitation or depression of each reflex may not be exactly the same. To the extent that the H-reflex is less dependent on the peripheral effects of the fusimotor system on muscle spindles, it should provide a better measure of any change in synaptic efficacy between the muscle afferents and the α-motoneurons. There is, however, a problem in maintaining a constant electrical stimulus to the tibial nerve at all phases of the step cycle, but this can be minimized (see Methods).

In this paper it is shown that the H-reflex is deeply modulated during walking in humans and that this modulation is dependent on central mechanisms of which the level of α-motoneuron excitation is only one

component. The modulation is accompanied by changes in both reflex sensitivity and reflex threshold.

MATERIALS and METHODS

EXPERIMENTAL PROCEDURES

H-reflexes were obtained from 6 human subjects during level walking on a treadmill at a comfortable speed (0.6-0.8 m/s). The average cycle time was about 1.4 s/step. A silver disc stimulus electrode (diameter of active area = 0.7 cm) was placed over the tibial nerve in the popliteal fossa , fastened to the skin with adhesive tape, and secured by a velcro strap around the leg. The stimulus ground electrode was placed either above the patella or above the popliteal fossa. Care was taken in the placement of electrodes to avoid restricting normal movement of the knee joint. Similar surface electrodes were placed over the soleus and tibialis anterior (T.A.) muscles to record the EMG activity. The tibial nerve was electrically stimulated in a pseudorandom sequence at a strength that elicited both an M-wave (direct stimulation of α-motoneuron axons) and an H- wave (reflex response to stimulation of Ia muscle afferents). The minimum inter-stimulus interval was 400 ms, and the maximum was 2 s. Although some H-reflex depression can occur at inter-stimulus intervals in the lower part of this range (Taborikova and Sax, 1969), these rather short intervals were used to minimize fatigue in the walking subjects during the

course of prolonged experiments. Moreover, any potential effects of the inter-stimulus interval were minimized by randomizing the intervals and by averaging the individual responses (further described below).

The EMG signals of the soleus and tibialis anterior muscles, were amplified, high pass filtered (10 Hz RC-filter) and recorded on FM magnetic tape along with the stimulus marker. The data was later analysed on a computer. Because of changes in distance between the nerve and the stimulating electrode during walking, the effective stimulus strength (current density) was not constant throughout the walking cycle. However, by repeating the experiment at several stimulus intensities and using the M-wave as a measure of the effective stimulus strength, H-reflexes occurring at various phases of the step cycle could be compared at equal stimulus intensities. Moreover, the data were selected from a range in which the H-reflex was relatively independent of the stimulus strength (Fig. 2.1); this range was similar during walking and during standing. A further problem is that the size of the EMG response to a constant electrical stimulus to the muscle nerve may vary significantly at different muscle lengths (Inman et al., 1952). However, both M and H waves are affected in the same way, so maintaining a constant M-wave should largely overcome

this problem.

It may be argued that a stronger stimulus is required to produce the same M-wave when the muscle is active . However, the relative refractory period of human nerves is between 4-5 msec, whereas the highest discharge rates of soleus motor units is between 10-15 spikes/s (i.e., one spike every 60-100 ms). Therefore, only a small fraction of motor units will be refractory at any time and the procedure of matching the amplitudes of M-waves as a measure of stimulus strength is justified. In fact, an essentially maximal M-wave can be obtained even during a maximum voluntary contraction.

In a second series of experiments, subjects were instructed to maintain tonic contractions of the soleus muscle at various levels while standing. To increase the level of the contraction subjects shifted progressively more of their body weight onto the leg used for experimentation and went onto their toes. During these maintained tonic contractions electrical stimuli were applied to the tibial nerve in the same pseudorandom sequence as during walking. The whole range of maintainable voluntary activity of the soleus was investigated.

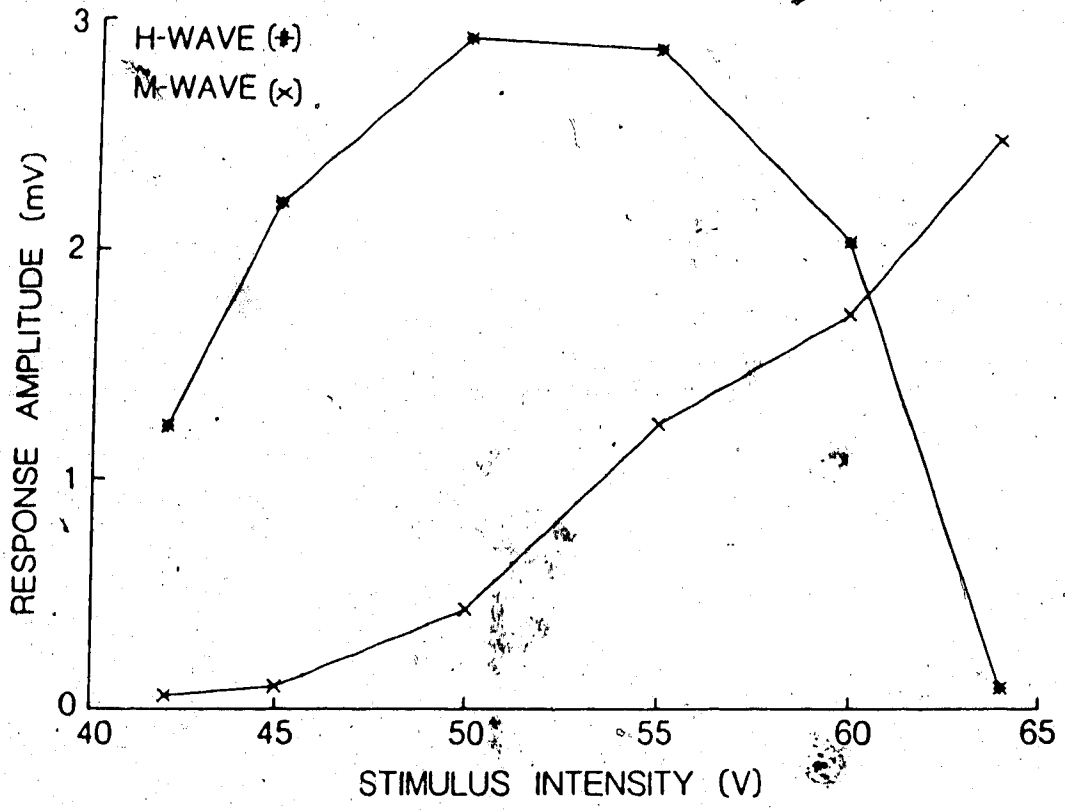

Figure 2.1: H-reflex and M-wave amplitude recorded from the soleus muscle as a function of the intensity of the stimuli applied to the tibial nerve. Note the range in which the H-reflex amplitude is relatively constant in spite of a large variation of M-wave amplitude.

DATA ANALYSIS

The data was analysed on a digital computer as follows. The EMG activity of the tibialis anterior (T.A.) muscle was full-wave rectified, low-pass filtered (20 Hz RC-filter), Paynter filtered (3 Hz cutoff), and then passed through a Schmitt trigger to generate a pulse which served as a step marker. An EMG signal was preferred as a step marker because fitting shoes with heel contacts or strain gauges could affect the walking. The large and randomly occurring stimulus evoked EMG in the soleus made this signal unusable as a step marker, so the EMG activity of the antagonist (T.A.) was therefore used.

The computer used the latency between a step marker and a stimulus marker to determine in which of 16 possible intervals (or phases of the step cycle) the stimulus occurred (a detailed description of the analysis procedure can be found in Akazawa et al., 1982). Responses occurring in the same phase of the step cycle were averaged together. The duration of each average was 76.8 ms from the time of stimulation, which was sufficient to include the M-wave and H-reflex. The amplitude of the H-reflex as a function of the phase in the step cycle (16-phases) was thus obtained. As explained above, H-reflexes occurring at various phases of the step cycle were grouped for comparison by matching the averaged amplitude of the

M-wave.

The peak to peak amplitude of the H-reflex obtained in each of the 16 phases of the step cycle was plotted against the mean level of EMG activity in each of the phases. These results were compared to those obtained during steadily maintained contractions.

In a few experiments walking subjects were videotaped. Using a special effects generator the full-wave rectified and smoothed EMG activity of the soleus and T.A. muscles during walking was superimposed in real-time on the videotape of the walking subject. Thus, the EMG activity could be directly compared to changes in ankle angle and hence changes in soleus muscle length (see Fig. 2.2).

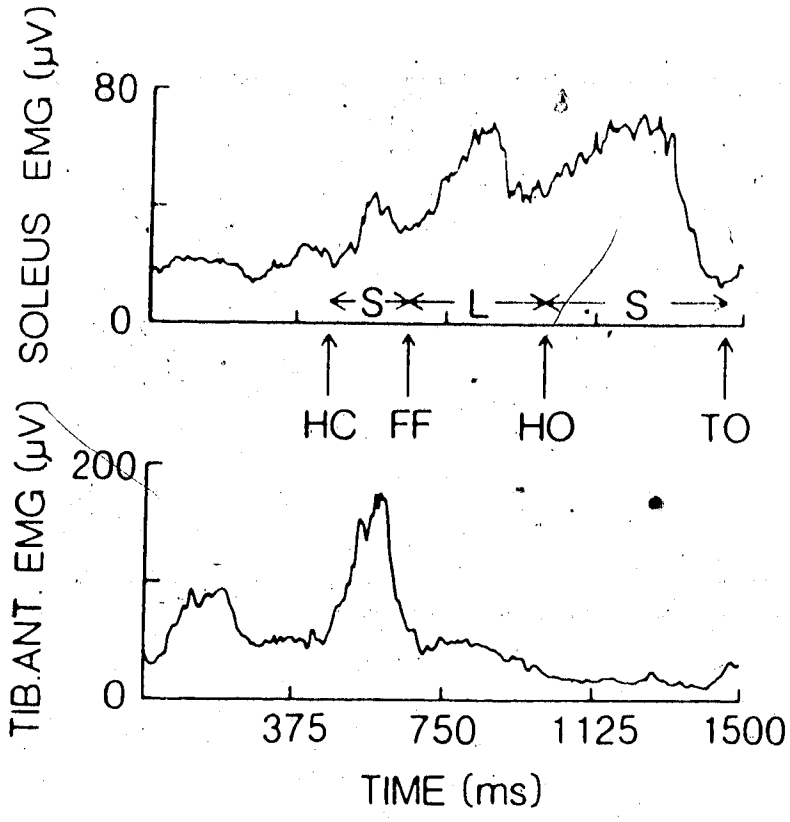

Figure 2.2: Full wave rectified, filtered, and averaged (n = 100) EMG activity of the soleus and T.A. muscles of the ankle during walking. The EMG during individual steps was superimposed on a video recorded image of the walking subject, so that the EMG could be correlated with various kinematic features of the step cycle which are indicated by arrows (further details in results). Abbreviations: heel contact (HC), foot flat on the ground (FF), heel off (HO), toe off (TO), muscle shortening (S), muscle lengthening (L). The background EMG level of 10-20 uV is mainly attributable to amplifier noise and perhaps some DC offset in the rectifier circuit.

RESULTS

EMG ACTIVITY OF SOLEUS AND T.A. DURING WALKING

The full wave rectified, RC-filtered, and averaged (n = 100) EMG activity of an ankle extensor, soleus, and an ankle flexor, T.A., during walking are shown in Fig. 2.2 (see also Fig. 2.4D). In this experiment the subject was videotaped during walking and the various step markers commonly used in human locomotion studies were correlated with the EMG activity of the soleus and T.A. muscles. The EMG activity of soleus usually began before the heel touched the ground (heel contact = HC), increased during most of the stance phase, and terminated abruptly just before the toes were lifted off the ground (TO). After heel contact the soleus muscle shortens (S) until the foot is flat on the ground (FF), it then lengthens (L) until the heel comes off the ground (HO), and finally, it shortens (S) between HO and TO. The length changes of T.A. during this period are of course in the opposite direction.

The T.A. EMG activity consisted of two prominent bursts. The first burst, in Fig. 2.2, was associated with the ankle dorsiflexion which occurs late in the swing phase. The second, usually larger burst began at about the same time as HC and continued until about the time the foot was flat on the ground. Since the soleus muscle was also active during this time, HC was

followed by co-contraction of these two antagonistic muscles. The extent of this co-contraction may differ from subject to subject. Some have relatively little (see Fig. 5.4) others considerably more (Fig. 2.2, 2.4).

AMPLITUDE MODULATION OF THE H-REFLEX DURING WALKING

The amplitude of the soleus H-reflex in each of the phases of the step cycle of one subject is shown in Fig. 2.3. The first phase in this example occurs at about the time of HC and the period of analysis (1.5 s) occupies approximately one step cycle. Each of the traces in Fig. 2.3 was selected as described in the Methods section. The reader should note that despite a relatively constant amplitude of the M-wave (mean = 1.31 mV, S.D = 0.31) the H-reflex is strongly modulated throughout the cycle. The H-reflex was small at the time of foot contact, but increased rapidly to a maximum value and then decreased very abruptly after TO.

In Fig. 2.4 the peak to peak (P-P) amplitude of the H-reflex was plotted against the phase in the step cycle. The P-P amplitude of the M-wave was also plotted against the phase in the step cycle. The average (n = 70) rectified and filtered EMG activities of the soleus and T.A. are also shown in Fig. 2.4. In this example, the amplitude of the soleus H-reflex

covaries directly with the EMG activity in this muscle.

In the example shown in Fig. 2.4 the amplitude of the soleus H-reflex is closely related to the EMG activity of the muscle. However, such a close correlation between the EMG activity and the reflex amplitude was observed in only three of the six subjects. In the other three subjects, the soleus H-reflex amplitude was strongly modulated in amplitude, but the variation was not as closely correlated with the EMG activity of the muscle. Two such examples are shown in Fig. 2.5. In Fig. 2.5A the peak reflex amplitude occurs prior to the peak EMG level. Another example is shown in Fig. 2.5B in which the reflex amplitude is not closely related to the EMG activity, being high throughout the stance phase. In this and other subjects, the peak reflex amplitude attained during walking was not the maximum possible (see following section). Therefore, the broad, relatively flat reflex peak seen in Fig. 2.5B is not due to a saturation phenomenon.

It seems unlikely that the observed pattern of amplitude modulation of the H-reflex during the walking cycle is due to changes in the refractoriness of the Ia-afferent fibers. There are two phases in the walking cycle in which the Ia-afferents discharge at high frequency and hence where these afferents may

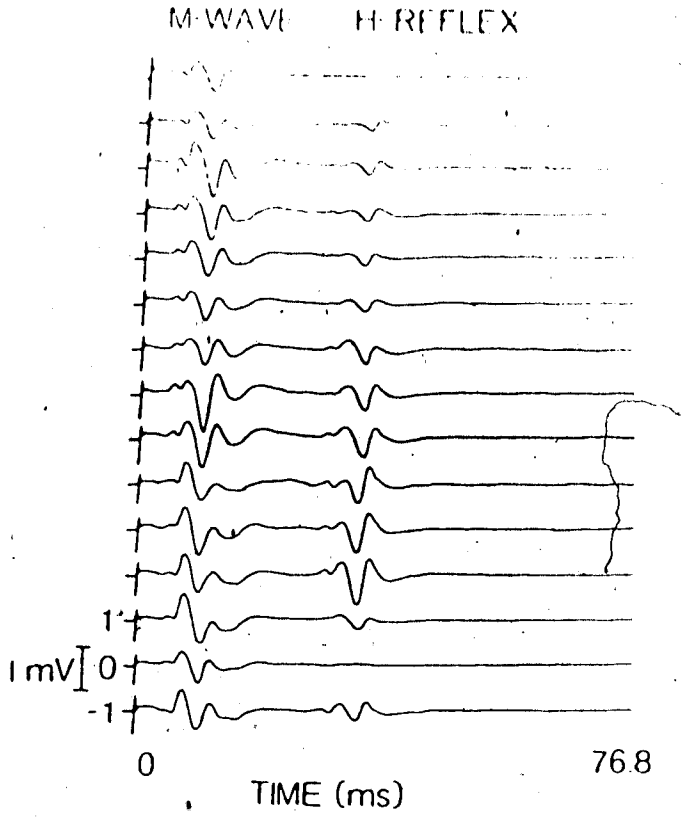

Figure 2.3: M-wave and H-reflex response to tibial nerve stimulation at various phases of the step cycle. The topmost trace represents the response of soleus in the first phase of the step cycle (i.e., the average of 14 responses occurring in the first 94 ms after the step marker, which was set for this subject at about the time of dorsiflexion). Subsequent traces are responses which occurred progressively later in the step cycle. The third trace from the bottom occurs at about the time of TO.

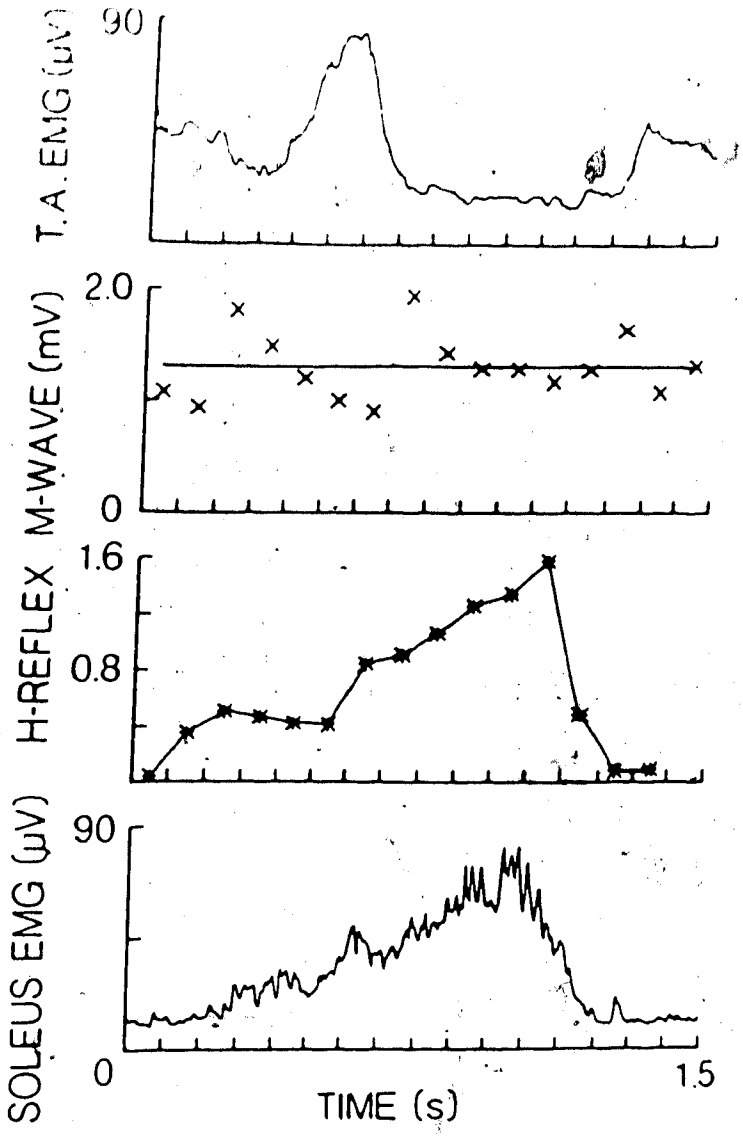

Figure 2.4: Amplitude of the H-reflex (P-P) as a function of the phase, or time, in the step cycle. The amplitude of the M-wave (mean = 1.31 mV, S.D = .31) in the various phases of the step cycle is also shown as well as the EMG activity of soleus and T.A. muscles.

show the greatest degree of refractoriness. During the swing phase the soleus is stretched by the ankle dorsiflexion and the Ia-afferents consequently discharge at high frequency (Prochazka et al., 1976). The same afferents also discharge at high frequency during the stance phase when the soleus is stretched between FF and HO as the body rotates over the ankles (Prochazka et al., 1976). However, during stance the H-reflex is relatively high, whereas during swing it is low. The H-reflex is also low in the period between HC and FF when the soleus is both actively contracting and shortening and therefore the discharge rate of the Ia-afferents is relatively low and so too their degree of refractoriness. Therefore, if changes in the degree of refractoriness was the only factor contributing to the observed amplitude modulation of the H-reflex, the H-reflex should be high during low refractoriness (e.g., between HC and FF) and low during high refractoriness (e.g., between FF and HO), but exactly the opposite was observed. In summary, changes in the degree of refractoriness of the Ia-afferents may influence the magnitude but not the pattern of the observed amplitude modulation of the H-reflex during walking.

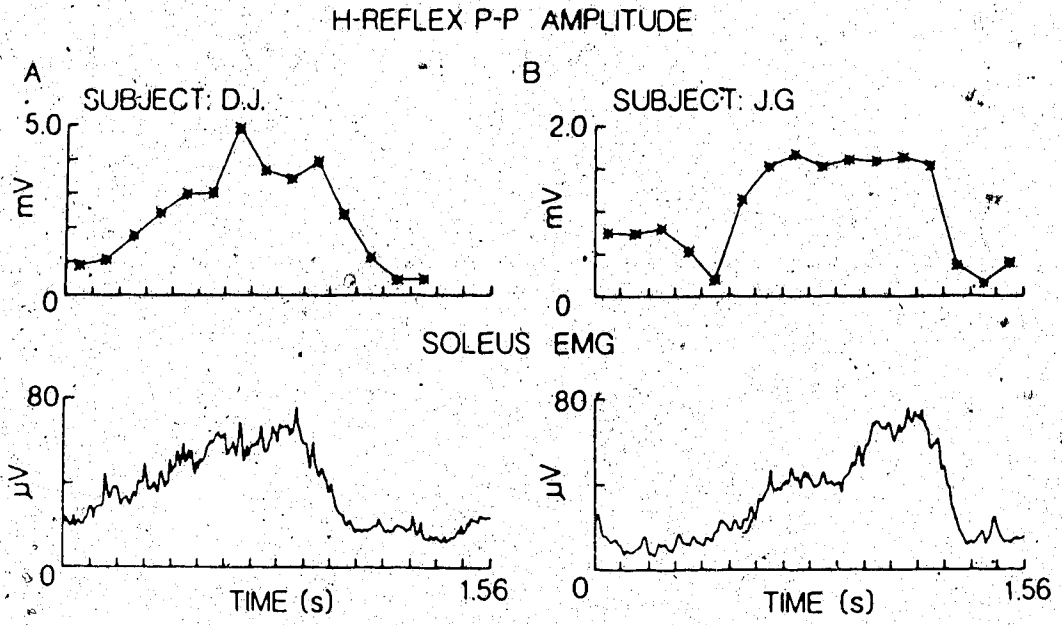

Figure 2.5: Other examples of H-reflex amplitude as a function of the phase in the step cycle. In each case the corresponding soleus EMG activity is also shown for comparison. Details are given in the text.

COMPARING H-REFLEXES IN TONIC CONTRACTIONS AND WALKING

The amplitude of the H-reflex, obtained while the subject was standing and steadily maintaining contractions of the soleus muscle at various levels, was compared with that obtained during walking. The subject relied on a chart recorder display of the rectified and smoothed soleus EMG activity to maintain a steady contraction at the required level for a period of about 20-30 s. The amplitude of the H-reflexes obtained, in one subject during steadily maintained contractions, is plotted in Fig. 2.6 as a function of the mean level of the soleus EMG activity. The amplitude of the H-reflex obtained, in the same subject, during walking is also plotted in Fig. 2.6 as a function of the mean EMG level (i.e., the mean EMG level during the phase in which the reflex occurred). It can be seen that the amplitude of the reflex was larger during maintained contractions (referred to as standing below) than during walking, and that the difference was greatest during low-level activity. In this example, the slope of the best fitting straight line, in the least squares sense, was 0.015 mV/ μV (S.E = 0.016) for standing, and 0.075 mV/ μV (S.E = 0.012) for walking; thus, there was a highly statistically significant difference between the slopes in the two conditions. Of particular interest

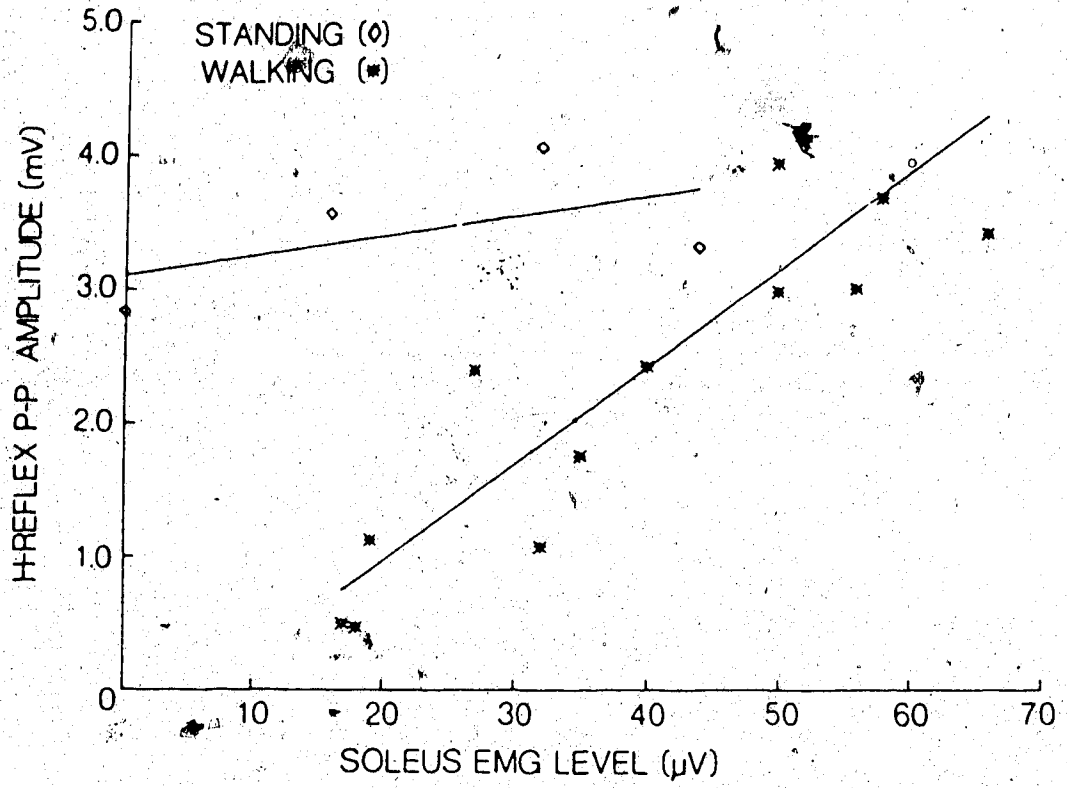

Figure 2.6: Soleus H-reflex amplitude during walking (*) and standing ( ) as a function of EMG level. Note the marked difference in the slopes (m = 0.075 walking, m = 0.015 standing) and y-intercepts (b = -0.54 walking, b = 3.1 standing) of the straight lines which were computed to minimize the mean square errors.

is the large amplitude of the H-reflex at "zero" EMG level (y-intercept) which will be referred to as "quiet" standing. Thus, the reflex sensitivity (i.e., the slope of the line relating H-reflex amplitude to EMG level) and the reflex threshold (x-intercept) were lower during standing than during walking. Both effects (i.e., decrease in sensitivity and threshold) were observed in the 4 subjects tested.

In the example of Fig. 2.6, the mean value of the M-wave was 1.25 mV (S.D =0.16) during walking and 1.23 mV (S.D =0.09) during the isometric contractions. Therefore, the difference in the amplitude of the H-reflex between the two conditions was not due to the stimulus strength. Moreover, the data was taken from a range in which the H-reflex was relatively independent of the stimulus strength (see Methods).

A potential problem in comparing EMG levels during walking and standing is that the EMG activity recorded by the soleus electrodes may include a component (due to cross-talk) from the other ankle extensors, medial and lateral gastrocnemius. For example, if as in the cat (Walmsley et al., 1978), the human soleus is predominantly, if not exclusively, active during standing and the gastrocnemius becomes more active during walking, then the H-reflexes recorded during walking would thus appear smaller than those recorded during standing because the activity level of the

soleus is in fact less than that indicated by the recording electrodes. However, the recording electrodes were placed over the soleus muscle just above the insertion of the gastrocnemius into the Achilles tendon, a site where soleus EMG activity can be selectively recorded (Hugon, 1973). Secondly, the largest difference between the H-reflexes elicited during walking and standing occurs at the lowest levels of activity, where a fast-twitch muscle like the gastrocnemius is least active and therefore the effects of cross-talk, if any, are least significant.

DISCUSSION

The major new findings reported here are the strong modulation of the H-reflex during locomotion in normal human subjects and the difference in the strength of the modulation of this reflex between walking and standing. Clearly, the modulation of the reflex is not simply a passive consequence of the excitation level of α-motoneurons, but depends on central mechanisms of which the level of α-motoneuron excitation is only one component. The change in the slope and x-intercept of the curve in the two states is also important, because it means that the sensitivity of the reflex as well as its threshold can be changed. Some previous authors have suggested that only the reflex threshold could be changed by central commands (Crago et al., 1976; Houk, 1976; Feldman and Orlovsky, 1972). Possible neural mechanisms underlying these reflex changes and their functional implications for the two types of motor activities studied will be dealt with, in turn, in the following sections.

Neural mechanisms. The neural mechanisms by which the modulation of the H-reflex is brought about during walking and standing are difficult to determine in human experiments, but some suggestions can be made which are illustrated in the schematic diagram of Fig. 2.7. The H-reflex increases more or less in parallel with the level of EMG activity, curve 1 in Fig. 2.7A.

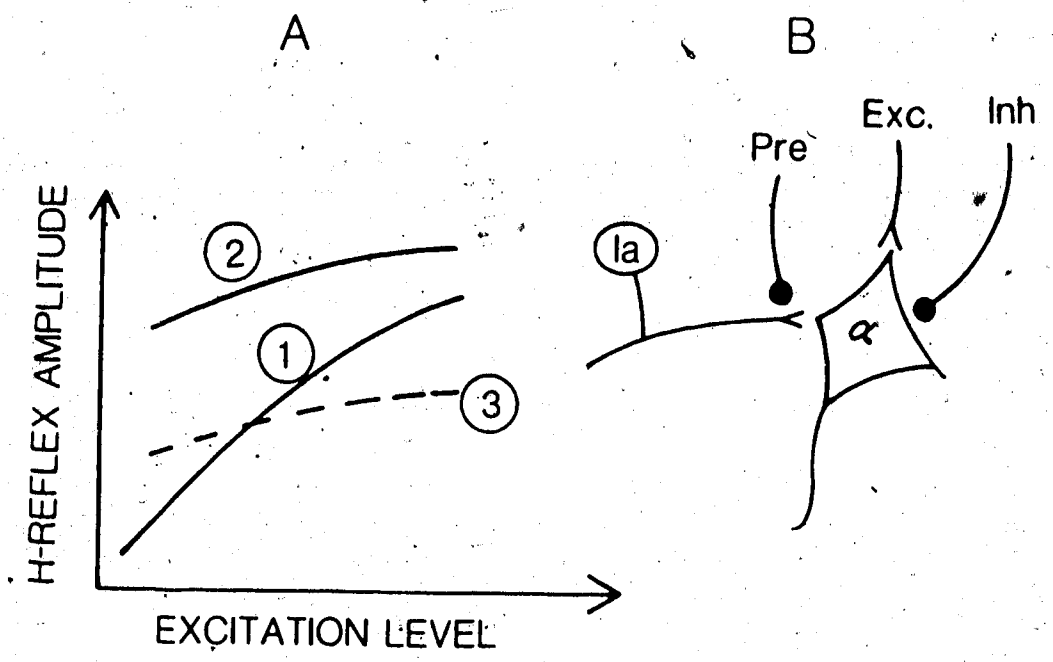

Figure 2.7: (A) Expected relation between the H-reflex amplitude and the level of α-motoneuron excitation for different combinations of excitatory, inhibitory, and presynaptic inputs to the motoneurons (B). Further explanation in Discussion.

If the same mechanisms are used as in the cat, α-motoneurons are depolarized by a combination of added excitation (Exc. in Fig. 2.7B) and decreased post-synaptic inhibition (Inh.), such that the resistance of the cell body is little affected (Shefchyk et al., 1984). The EPSP from primary muscle spindle receptors (Group Ia fibers) is then relatively constant at all phases of the cycle (Shefchyk et al., 1984) and the size of the H-reflex will therefore reflect the percentage of voluntarily activated α-motoneurons.

The much larger H-reflex in quiet standing could arise if weak excitatory inputs are active and inhibitory inputs are inactive, or greatly decreased compared to the levels during walking. Therefore, the size of the EPSP would be large during quiet standing because less shunting would be produced by inhibitory inputs. However, the EPSP would decrease in size with increasing excitation, because of the additional conductance produced by more excitatory inputs (i.e., decreased resistance). Therefore, as the number of active motoneurons increases with increasing excitation, the H-reflex would increase more slowly during standing (curve 2 in Fig. 2.7A) than during walking (curve 1 in Fig. 2.7A).

Morin et al. (1982) suggested that the differences between the two states might arise from presynaptic inhibition (Pre. in Fig. 2.7B). This

mechanism would reduce the Ia EPSP by a constant factor at all levels of excitation, without affecting postsynaptic conductance, and therefore produce a proportional reduction in the H-reflex (compare the dashed curve 3 in Fig. 2.7A with the solid curve 2). Clearly, if walking and standing are compared at only one level of excitation, presynaptic inhibition can appear to be an explanation for the results. Morin et al. (1982) used only one level of excitation and so did not anticipate the change in slope. One could of course postulate that the level of presynaptic inhibition is also tied to the level of EMG in just the right way to produce the observed change in shape between curves 1 and 2, but the post-synaptic mechanisms suggested above are far simpler to envisage. These suggestions should also be directly testable by intracellular recording from α-motoneurons in paralyzed decerebrate cats during fictive walking and tonic states with comparable levels of α-motoneuron excitation. Once data is obtained from these experiments, a mathematical model of how motoneurons are controlled in various types of motor activities may be formulated.

Another possible explanation for the difference between the amplitude of the H-reflex during walking and standing is that the size of the EPSP's during

walking are smaller than during standing because the high frequency discharge of the Ia-afferents during walking results in a depression of transmitter release and hence smaller EPSP's (Curtis and Eccles, 1960). However, if the depression lasted throughout the step cycle, it would be functionally equivalent to presynaptic inhibition, which can not explain our results (see above). If the depression only occurred when the afferents were firing fastest, it would have an analoguous effect to that of refractoriness which was also ruled out as an explanation of the results (see Results). In conclusion, while changes in the amplitude of the EPSP's due to this well known depression phenomenon may have occurred, postsynaptic factors such as those described above must also be considered.

Functional implications. The large difference in the y-intercepts (Fig. 2.6) of the H-reflex vs EMG curves between walking and standing is of functional importance. During standing, most of the body weight is supported by the skeleton, so the activity of the leg and other muscles during quiet standing is minimal (Basmajian, 1967). The large value of the H-reflex during quiet standing implies that even a small body sway will result in a relatively large stretch reflex in the soleus which will tend to counteract the sway. Thus, the large reflexes when the subjects were

standing, are consistent with the control of ankle angle and hence body position in this task. However, a comparably large stretch reflex during the swing phase of walking, where the EMG activity of the soleus is also minimal, would impede ankle dorsiflexion and would therefore be inappropriate. As discussed in the Introduction the stretch reflex of a muscle will be much more influenced by fusimotor effects than will the H-reflex, and possibly, because of the temporal dispersion of the afferent volley (Burke, 1983), also by the state of certain spinal interneurons (e.g., Ib interneurons, and Renshaw cells). However, at least in the mesencephalic walking cat, peripheral fusimotor effects add to and reinforce the modulation produced centrally (Murphy et al., 1984; Taylor et al., 1985), and both the stretch reflex and the H-reflex are modulated in essentially the same way (Akazawa et al., 1983).

Foot contact with the ground (HC) occurred during co-contraction of the ankle flexors and extensors, at a time when the amplitude of the H-reflex was relatively low. Therefore, the reflex was not adjusted to help overcome the loading of the foot at the time of HC. Indeed, it has been suggested that the stretch reflex would occur too late to contribute force to counteract the increased loading at the time

of foot contact (Grillner, 1972; Melvill Jones and Watt 1971; but see Stuart et al., 1973). The sudden impact and loading of the foot at the time of HC is compensated by a stiffening of the ankle resulting from a co-contraction of the ankle flexors and extensors which may be pre-programmed (Engberg and Lundberg, 1969).

The H-reflex increased rapidly to a maximum value during stance and then abruptly decreased to a low value after TO. The highest values of the stretch reflex during walking are therefore timed to resist the stretch of the ankle extensors while the foot is flat on the ground and the body rotates over this fixed support and to assist the "push-off" phase (i.e., the ankle extension which occurs late in the stance phase). This extends the finding of Dietz and his collaborators who showed that the stretch reflex of the triceps surae contributes significantly to the tension required for the "push-off" phase of running (Dietz et al., 1979). Thus, the stretch reflex amplitude appears to be appropriately adjusted in each phase of the step cycle to the requirements of locomotion.

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III. DIFFERENCE IN THE AMPLITUDE OF THE HUMAN SOLEUS H-REFLEX DURING WALKING AND RUNNING

In a previous publication (Capaday & Stein, 1986) we reported that the H-reflex of the human soleus muscle was strongly modulated in amplitude during the step cycle in a manner appropriate to the requirements of locomotion. The reflex output was largest late in the stance phase when it would assist in lifting the body off the ground. The same reflex was absent during the swing phase when it would oppose ankle dorsiflexion. The size of the H-reflex was also much larger at an equivalent level of e.m.g. during standing than during walking. In particular, during quiet standing the background e.m.g. activity of the soleus is nominally zero as it is also during ankle dorsiflexion in the swing phase of locomotion. However, during quiet standing the amplitude of the reflex is very large which would make it useful in counteracting forward body sway, but during the swing phase of walking the reflex is shut-off when it would oppose ankle doriflexion. We therefore concluded that during walking the modulation of the amplitude of the H-reflex was not simply a passive consequence of the

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α-motoneurone excitation level (measured experimentally as the rectified surface e.m.g.) and that it depended on other central neural mechanisms.

Is the pattern and extent (minimum to maximum) of modulation of the H-reflex similar in running and walking, and is the relation between the size of the H-reflex and the background e.m.g. the same in the two locomotor tasks? A priori, a difference in the pattern of modulation may be expected since, for example, the impact force on the ankle at the time of Heel contact (HC) during running is larger than during walking and therefore a larger reflex response may be desirable to further increase the stiffness of the ankle. If the relation between the H-reflex amplitude and the e.m.g. were different in the two tasks, it would be further evidence that the size of the H-reflex depends on central neural mechanisms other than the excitation level of the α-motoneurones. Furthermore, any such change in the relationship between these two variables may provide some clues on how the stretch reflex is adapted to the motor task. The validity of inferring changes in the short latency stretch reflex from changes in the H-reflex is discussed in detail in Capaday & Stein (1986). Briefly, while the extent of potentiation or depression of the H-reflex may not be identical to that of the stretch reflex (Van Boxtel, 1986) the two

never undergo changes in the opposite direction (Akazawa, Aldridge, Steeves & Stein, 1982; Aldridge & Stein, 1982). Furthermore, during locomotion, the effects of the fusimotor system on the muscle spindles tend to reinforce the effects of the modulation of the H-reflex (Taylor, Stein & Murphy, 1985; Loeb & Hoffer, 1985).

The contribution of the stretch reflex to sprinting, which is a digitigrade locomotor was investigated by Dietz and colleagues (Dietz, Shmidtbleicher & Noth, 19[illegible]). They showed that, during sprinting, the stretch reflex produces a large increase of (e.m.g.) activity in the triceps surae g[illegible] following contact of the foot with the ground. The reflex also contributes significantly to the muscular tension exerted by this group during the short (150-200 ms) stance phase.

In this study, we have investigated the modulation of the H-reflex in various phases of running, in which the locomotor pattern is plantigrade (heel to toe), and compared it to that during walking in the same subject.

METHODS

The details of the experimental procedures and the data analysis methods were described in detail in a previous publication (Capaday & Stein, 1986). Here, we briefly describe these as well as some of the modifications that were made in the present experiments.

H-reflexes of the soleus muscle were obtained from 8 human subjects during level walking (4 km/hr) and running (8 km/hr) on a treadmill. The average walking cycle time was 1100 ms and that for running was 640 ms. The e.m.g.'s of the soleus and the tibialis anterior muscles were recorded with surface silver disc electrodes. A similar silver disc electrode was used to stimulate the tibial nerve in the popliteal fossa. The stimulus return electrode was placed either above the patella or above the popliteal fossa.

The major problem with electrical stimulation of the tibial nerve during locomotion using surface electrodes is that the distance between the stimulating electrode and the nerve changes because of the large displacements at the knee joint. Therefore, the effective stimulus strength (the current density) is not constant throughout the locomotor cycle. However, by repeating the experiment at several stimulus intensities and using the M-wave

(which is the electrical response of the muscle to electrical stimulation of its nerve) as a measure of the effective stimulus strength, H-reflexes occuring at various phases of the step cycle could be compared at essentially the same stimulus intensity (details in Capaday & Stein, 1986). The M-waves were also closely matched in comparing the walking and running data of each subject. We tried to select values of the M-wave which fell on the relatively flat region of the curve relating H-reflex amplitude and stimulus intensity (Capaday & Stein, 1986). The position of this flat region of the curve did not seem to change between walking and running (i.e., it occurred at about the same range of values of the M-wave as in standing). In some subjects, however, the M-waves could only be matched at high amplitudes (i.e., in the portion of the curve where the H-reflex decreases). In all cases the results were qualitatively similar.

It is important to have a good measure of the average e.m.g. activity in each of the two locomotor tasks so that the reflex responses can be compared at corresponding levels of activity. The average e.m.g. activity of the soleus and the tibialis anterior muscles during the locomotor cycle was measured by triggering the averaging computer from the suitably conditioned output of a switch placed under the heel

inside the subject's shoe. The switch closed and hence triggered the computer at about the time when the foot was flat on the ground. Typically, the e.m.g. activity of each muscle during the locomotor cycles (high pass RC-filtered at 10 Hz, full-wave rectified, and low pass RC-filtered at 100 Hz) was averaged in real time (n=100) and the standard error of the mean was also computed.

This procedure was repeated several times during the course of an experiment to ensure that the pattern of activity remained essentially the same throughout the duration of the experiment. The extent of any possible cross-talk between the ankle extensors (medial gastrocnemius (MG), lateral gastrocnemius(LG), and soleus) was determined by direct trans-cutaneous maximal stimulation of the LG or the MG while recording simultaneously the e.m.g. response of the stimulated muscle and its spread over the soleus. This was done to insure that the e.m.g. activity recorded over the soleus muscle was in fact produced for the most part by soleus and not by some combination of soleus activity and that of the other foot extensors. The extent of the cross-talk measured in this way was less than or equal to 10% (0.1 mV of activity picked up at the soleus electrodes for every 1 mV of gastrocnemius activity).

The method of obtaining the reflex responses of the

soleus muscle in the various phases of the step cycle is described in detail in the paper by Capaday & Stein (1986) and by Akazawa et al. (1982). In this study, however, the step marker was obtained from a switch placed under the heel inside the subject's shoe, instead of passing the tibialis anterior e.m.g. through a schmitt trigger circuit. The computer received the step mark, generated by the heel switch, and a stimulus mark. On the occurrence of the stimulus mark the soleus e.m.g. (unrectified, and RC filtered between 10 Hz and 300 Hz) was sampled for approximately 60 ms. The latency between the step mark and the stimulus mark was used to decide in which of 16 phases of the step cycle the stimulus occurred. Having determined this, the sampled signal from soleus was averaged with other signals which occurred in the same phase. By this method the average H-reflex response (usually, n=10-20) of the soleus in each of 16 different phases of the locomotor cycle was obtained.

The reason for dividing the locomotor cycle into 16 phases is that this gives a good temporal resolution of events in the step cycle. The procedure of "phase-dependent" averaging was done in real time and allowed the experimenter to determine, after averaging a suitable number of responses, the size of the M-wave

(effective stimulus strength) in each of the 16-phases of the step cycle. The experimenter could then adjust the output voltage of the stimulator for the next series of averages in order to obtain M-waves in the desired range. By repeating this procedure several times during the course of an experiment M-waves of approximately the same size could be obtained in all 16-phases of the step cycle.

In a few experiments the WATSMART system (Northern Digital, Waterloo, Canada) for reconstruction of the three dimensional kinematics of points in space was used to determine the ankle displacement as a [redacted] of time in each of the two locomotor tasks. Thus, the changes in length of the soleus muscle, which acts only at the ankle joint, were estimated.

RESULTS

The H-reflex of the soleus during the running cycle increased progressively during the stance phase, reaching its peak value usually at about the time of the peak e.m.g. activity. The H-reflex rapidly decreased at the end of the stance phase and was absent during the swing phase (ankle dorsiflexion). An example from one subject of the H-reflex modulation during the running cycle is shown in Fig. 3.1.

In Fig. 3.2 the peak to peak (p-p) amplitude of the H-reflex in each of the 16 phases of the running cycle is plotted, as well as the average soleus e.m.g., the average tibialis anterior e.m.g., and the p-p amplitude of the M-wave in each phase of the cycle. This subject had the largest phase difference between the H-reflex and the e.m.g. (a lag of 2/16 of a cycle). In many subjects little or no phase difference was observed while in others a small phase lead occurred. Overall, no significant phase difference was observed between the peak soleus e.m.g. and the peak H-reflex.

In this subject, heel contact (HC) occurred at about the 14 th phase of the cycle, but the H-reflex was relatively low at this time as it was in other subjects. The e.m.g. level at the time of HC of both the soleus and the tibialis anterior increased on the

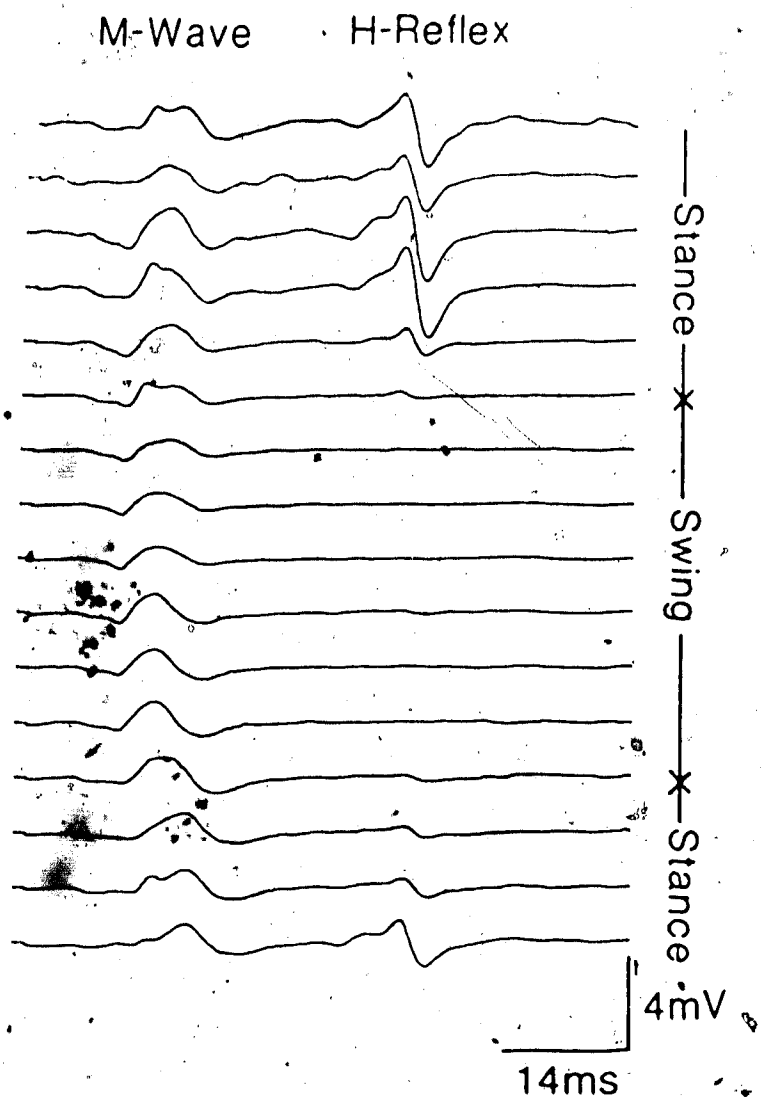

Figure 3.1: Amplitude modulation of the H-reflex during the 16 phases of the running cycle. Each record is the average of about 15 responses of the soleus muscle to stimulation of the tibial nerve. The first record from the top is the response that occurred at about one third of the way through the stance phase. Note how the reflex increases progressively during the stance phase and that it is absent during the swing phase.

average 1.8 times during running compared to walking. The increase of activity in these two muscles at the time of HC serves to stiffen the ankle joint and thus prevent the foot from extending too quickly towards the ground after the HC. Therefore, the adaptation to the higher impact forces on the ankle at the time of HC is at the level of the command signals to the muscles rather than at the reflex level.

In Fig. 3.2 the period in the stance during which the soleus muscle is lengthening is indicated. In running the soleus undergoes a lengthening contraction during most of the stance phase. The same is true during walking (Fig. 3.3), and hence the spindle afferents will be firing at relatively high rates (Loeb, Hoffer & Pratt, 1985; Prochazka, Westerman & Ziccone, 1976). Since the presence of an H-reflex indicates that there is transmission from the Ia-afferents to the α-motoneurones during this phase of locomotion, part of the muscular activity in this phase must be due to the stretch reflex.

The peak value of the H-reflex during running was on the average significantly smaller ($p<0.05$ for a one tailed T-test) than during walking. This finding is especially noteworthy as the peak e.m.g. levels of the soleus attained during running were on the average 2.4 times greater than during walking. An example of the pattern of the H-reflex modulation

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THE UNIVERSITY OF ALBERTA

MODULATION OF EXCITATORY AND INHIBITORY REFLEXES DURING LOCOMOTION

BY

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A THESIS

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Dedicated with affection to my parents and grandparents.

ABSTRACT.

During walking (4 km/h), the amplitude of the Soleus H-reflex was strongly modulated. It increased progressively during the stance phase, reaching its maximum value at about the time of the peak Soleus EMG. It then abruptly decreased at the end of the stance phase. The H-reflex was usually very small during the swing phase. The pattern of modulation was qualitatively similar during running (8 km/h). However, the reflexes obtained during running were significantly smaller than those obtained during walking. Furthermore, the slope of the line fitted to a plot of H-reflex amplitude vs the mean value of the background Soleus EMG was always steeper for the walking data than for the running data. The H-reflex was also investigated in a postural task, ranging from quiet standing to shifting progressively more of the body weight onto the experimental leg. During quiet standing, despite a smaller level of Soleus EMG activity the amplitude of the H-reflex was 3-5 times greater than that during the early part of stance. In fact, the H-reflex was greater, at the same level of Soleus EMG activity, in the postural task than during walking. From these findings, it is concluded that the CNS can control the efficacy of synaptic

transmission between the Ia-afferents and the motoneurons, independently of the level of motor activity. This would allow for the adaptive control of the stretch reflex stiffness.

A computer model was developed to study the factors that can affect the amplitude of the monosynaptic reflex. It was found that presynaptic inhibition is the only mechanism that can alter the size of the monosynaptic reflex independently of the level of activity in the motoneuron pool. This finding was confirmed by experiments done in the cat.

The Soleus motor activity, as measured from the intramuscular EMG, can be inhibited at all times during the stance phase of walking, as well as during voluntary tonic activity. Therefore, the Ia-interneurons projecting to the Soleus motoneurons are not shut off during activity of the Soleus motoneuron pool. Moreover, there was no difference in the efficacy of the inhibition in the two tasks.

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I. INTRODUCTION

The study of physiological systems can be viewed as consisting of analysis at four different but strongly interrelated levels. The structural organization of the system, ranging from classical anatomy to studies involving immunohistochemical localizations of cell groups, is at the most basic level. With regards to the nervous system this includes identification of the major subdivisions, the pathways for afferent and efferent activity and those linking the major subdivisions. The details of cell types, their interconnections in a network and possible neurotransmitter content are provided by various histological techniques. The next level of analysis consists of identifying the basic physiological processes that underlie the activity of the system under study and determining the mechanisms behind these processes. As an example, in the nervous system nerve conduction and synaptic transmission across nerve cells are the basic physiological processes underlying the transfer of information in this system. Many years of effort have gone into elucidating the mechanisms of the action potential and synaptic transmission (Hodgkin, 1964; Katz, 1969). At the third level of analysis one tries to identify by physiological means, usually in reduced preparations,

the underlying neural circuits that subserve a particular function. For example, Eccles and his many colleagues using microelectrodes in the cat spinal cord identified many of the pathways that link muscle receptors to motoneurons as well as the types of synaptic connections, excitatory or inhibitory, within those pathways (Eccles, 1964). This sets the stage for the fourth level of analysis which may be referred to as systems Physiology. Here the issue is the role of the identified neural pathways in normal function. Questions such as, which of the identified mechanisms operates during normal activity, and what qualitative and quantitative contributions do they make to that activity, are fundamental. In simple terms, at this level of analysis one is concerned with the functional role of putative neural circuits in a particular physiological activity.

The Renshaw cell, the first identified interneuron in the mammalian spinal cord (Renshaw, 1941), can serve as an example. This neuron receives a major excitatory input directly from the axon collaterals of motoneurons and in turn monosynaptically inhibits motoneurons, thus making a recurrent negative feedback type of connection with the motoneurons (Renshaw, 1941; Granit, 1972). Because the Renshaw cell axon branches extensively to innervate widely separated motoneurons and does not usually contact the

motoneurons that synapse upon them (Granit, 1972) one may ask whether their role during maintained contractions is to overcome the possible synchronization of motoneurons and hence reduce the tendency for tremor. Some evidence for this has been obtained in reduced cat preparations (Adam, Windhorst, and Inbar, 1978) and certainly warrants further investigation during voluntary contractions.

The various studies contained in this thesis were all attempts at understanding the functional role of various basic spinal cord mechanisms during natural motor tasks such as walking, running and standing. The emphasis is placed on the term natural motor task or activity, because as happens all too often in motor Physiology the task investigated is somewhat contrived. Conclusions derived from such studies may not, therefore, have general applicability. In figure 1.1 the basic spinal cord circuits that are the subject of this thesis are shown. The diagram represents a summary of what is known based mainly on studies of the cat spinal cord and to some extent that of the monkey (Baldissera, Hultborn, and Ilert, 1981; Jankowska, Padel, and Tanaka, 1976). The basic connections shown in the diagram are described below and some ideas on the possible functional significance of each circuit are presented. Following this, a

more detailed discussion of the pathways that have been directly investigated in the present studies is given.

The basic spinal cord motor circuits

The monosynaptic nature of the connection between the Ia muscle afferents and the motoneurons was first demonstrated by Lloyd (1943). It was later confirmed by intracellular recordings from motoneurons (Lundberg and Winsbury, 1960). This connection subserves the well known stretch reflex, but as discussed below it may not be the only pathway contributing to the stretch reflex. An excellent historical account of the work done on this pathway starting with the discovery of the stretch reflex by Liddell and Sherrington is given by Matthews (1972). The first clear demonstration that the Ia afferents may excite motoneurons via polysynaptic pathways was made by Hultborn et al. (1975). These polysynaptic connections may account for such phenomena as the so called medium latency stretch reflex responses (M2) and the tonic vibration reflex (see, Baldissera, Hultborn and Illert, 1981). Related to these polysynaptic connections, it was shown that in the human the rise time of the monosynaptic epsp in motoneurons, in response to an electrical nerve stimulus, may be relatively slow, about 2.4 ms (Burke,

Gandevia and McKeon, 1984). These authors have argued, therefore, that the relatively prolonged duration of the monosynaptic epsp allows for possible oligosynaptic inputs to affect the motoneurons before they reach threshold. This suggestion is examined further and evaluated in the general discussion. Finally, there may be an autogenic inhibitory effect from the Ia afferents to the motoneurons mediated by a disynaptic or trisynaptic connection (Fetz, Jankowska, Johannisson and Lipski, 1979).

The motoneurons have collaterals that innervate small inhibitory interneurons, located in the ventral horn, which in turn inhibit motoneurons (Renshaw, 1946). This recurrent inhibitory pathway may have several functional roles. As already discussed, it may serve to desynchronize the discharges of motoneurons (Adam et al., 1978), as well as to slow the discharge rates of the motoneurons (Granit, 1972). Hultborn, Lindstrom, and Wigstrom (1979) hypothesized that the Renshaw cells, which are under supraspinal control, may also contribute to the regulation of the motor output as follows. If the gain of this pathway is high, that is the Renshaw cells are very excitable, then large variations of the supraspinal input onto the motoneurons will produce relatively small variations of the motor output. This would allow for

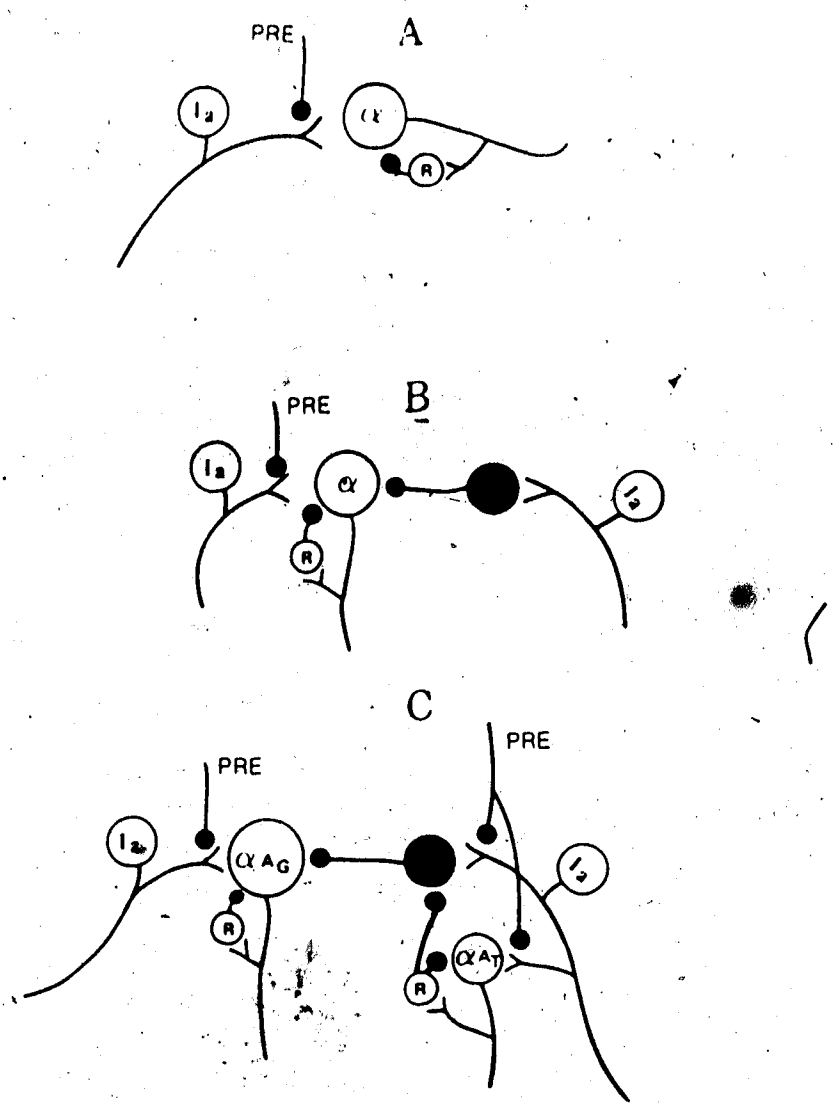

Figure 1.1: The basic spinal cord motor circuits. The alpha motoneurons are labeled with the symbol "α", the Renshaw cells are labeled with the symbol "R". The Ia inhibitory interneurons are shown in solid black, presynaptic inhibition of the Ia terminals is labeled as "PRE". Inhibitory contacts are shown as

small black circles, the excitatory ones are shown as a forked bifurcation. The diagram shown in part C is symmetrical, but only the connections on the right side are shown in their entirety for clearness of illustration. The details of the diagrams are described in the text.

the very fine control of the motor output. If, on the other hand, the gain of this pathway is low, then large variations of the supraspinal input onto the motoneurons will produce relatively large variations in the motor output. This would allow for high levels of force output when needed. In addition, Renshaw cells inhibit the Ia inhibitory interneurons that project onto the antagonist motoneurons (Hultborn, Jankowska and Lindstrom, 1971). The function of this inhibitory connection is not known, but clearly it would tend to reduce the effectiveness of the inhibition of antagonist motoneurons in parallel with the level of motor output. This issue is discussed in detail in chapter 5.

The other two major pathways shown in figure 1.1 are the presynaptic inhibition of the Ia terminals within the spinal cord (Schmidt, 1971), and the well known Ia inhibitory interneurons projecting to the motoneurons (Eccles, 1964). Presynaptic inhibition of the Ia afferents may be produced from either supraspinal stuctures, such as the red nucleus (Rudomin, 1980), or as a result of activation of other groups of afferent fibers. For example, stimulation of Ia afferents in flexor nerves presynaptically inhibits Ia afferent terminals of extensor nerves (Schmidt, 1971; Eccles, 1964).

Issues pertinent to the work done in this thesis

concerning the monosynaptic pathway, the disynaptic inhibitory pathway, and the presynaptic inhibitory pathway(s) are further discussed in the next three sections.

The monosynaptic reflex connection

The monosynaptic connection between the primary (Ia) spindle afferents and the motoneurons has been investigated as an example of integration of information in the CNS, specifically the integration of descending and afferent inputs to the motoneurons (Lloyd, 1941; Phillips and Porter, 1977). It has also served as a model system for the study of the mechanisms of synaptic transmission in the mammalian nervous system (Eccles, 1964; Mendell and Henneman, 1971). The stretch reflex pathway(s) has also been extensively studied from the functional point of view, that is what role it may have during motor activity (Liddell and Sherrington; 1924; Merton 1953; Matthews, 1972).

Two views on this pathway stand out in my mind. First, although it can be regarded as a negative feedback pathway tending to oppose changes in muscle length due to internal or external perturbations, it appears that it does not have sufficient gain, or more correctly stiffness, for it to work as an effective position servo-system. The best experiment

on this was done by Peter Matthews several years ago (Matthews, 1959) in the decerebrate cat, a preparation with a good stretch reflex compared to other common preparations. He measured the stiffness of the soleus muscle from tension/extension measurements and found it to be rather low. Typically, the stiffness measured in response to large slow stretches was 75-90 g/mm or some 5% of maximum tetanic tension for each millimeter of stretch. Values up to 200 g/mm were also observed. However, when small stretches are used (0.2 mm) the measured stiffness is some 400 g/mm. Thus, the stretch reflex behaves in a manner reminiscent of the Ia-spindle ending which possesses a markedly greater sensitivity to small stretches as opposed to large ones (Matthews and Stein, 1969).

It appears, therefore, that the stiffness of the stretch reflex is low to moderate. However, it should be noted that despite this it can nevertheless generate a substantial amount of tension in response to a large stretch especially when compared to what may be required in a motor act such as walking. Allum, Mauritz, and Vogele (1982) have attempted to measure in normal humans the contribution of the short latency (approximately 40 ms) stretch reflex response in subjects instructed to resist a dorsiflexing torque

applied to the foot. They found that the torque produced by the short latency stretch reflex response was about 5 Nm. This represents a moderate amount of muscle tension when the torque to force conversion is made. Walking is an energetically efficient motor activity requiring small levels of muscle activation despite relatively large limb displacements (Basmajian, 1967; Winter and Robertson, 1978; Pedotti, 1977). Thus, the small to moderate contributions made by the stretch reflex may be sufficient to assist locomotor activity.

In contrast to the view that the short latency stretch reflex may be useful in assisting locomotion, Dietz et al. have reported that this reflex response may be absent in normal humans during locomotion (Dietz, Quintern and Berger, 1984). They attributed their observation to a suppression of the monosynaptic pathway. This is contrary to the findings reported in this thesis. In chapters 2 and 3 it is shown that the monosynaptic reflex pathway is not shut off during locomotion, in fact it is strongly modulated in amplitude during the step cycle. The fact that this reflex is strongly modulated during the locomotor cycle may account for the observations of Dietz et al. (1984). In their study, the stretch of the ankle extensors is applied at the moment of heel contact. As will be described in the following two chapters,

the sensitivity of the reflex is low in this phase of the step cycle and the ankle extensors relatively slack. Both of these factors mitigate obtaining stretch reflex responses in that phase of the step cycle. A perturbation applied later in the step cycle, when the sensitivity of the reflex is relatively higher, should produce an observable reflex response. This argument is strengthened by the observation that the same perturbation applied during quiet standing is followed by a short latency stretch reflex response (Dietz et al., 1984). As will be shown in chapter 2 we have found that the sensitivity of the monosynaptic reflex is very high in this task.

The other clear observation in Matthews' study was that the muscle under stretch reflex control behaves very much like an ideal spring (i.e., a spring of constant stiffness at all extensions). This point was later emphasized by Nichols and Houk who showed that, in addition, a muscle under stretch reflex control behaves symmetrically to stretch and release (Nichols and Houk, 1976). The linear and symmetrical (i.e., no hysteresis) behaviour of muscle under stretch reflex control may ease the required neural control. What I wish to emphasize is that the stretch reflex provides a mechanism by which the stiffness of the muscle whithin this closed loop may be modified independently

of the level of motor output. This would allow the stiffness to be set to a value appropriate to the motor task. For example, increased stiffness in a task such as standing where position needs to be controlled, and greater compliance in a task such as walking to allow for a fluid stride. In addition adjustments of the stiffness of the extensors would provide a sort of tunable suspension for shock absorption during locomotion, which is clearly important in running and downhill walking. Furthermore, the value at which the stiffness is set will determine the extent to which Ia afferent activity will contribute via the stretch reflex pathway to the total motor output. It should be noted that the view presented here, that the reflex stiffness of a muscle may be modified to suit the requirements of the motor task, is quite different from that of Nichols and Houk (1976). They suggested that the muscle stiffness was regulated in the same sense that position or temperature are regulated in a suitably designed control system. In other words, in their view, the function of the stretch reflex was to insure that the overall stiffness of a muscle does not depart from a set level. In fact, Houk (1976) argued that this set point was constant and invariable at all levels of motor output (see also Berkinblit, Feldman, and Fukson, 1986).

This brings us to the second point; the stretch reflex, especially its monosynaptic component, has traditionally been viewed as a stereotyped response with little or no scope for modification. Indeed, it has been hypothesized that the adaptive capacity of the organism to respond to muscle stretch produced by a perturbation to a limb is due to a transcortical loop involving the motor cortex (Phillips, 1969; Wiesendanger, Ruegg, and Lucier, 1975). To date there is no general agreement that such a transcortical reflex operates during natural conditions (Darton et. al, 1985; Matthews, 1984; Houk, 1978), although the connections are known to exist (Cheney and Fetz 1984; Phillips et. al, 1971; Hore, et. al, 1976). In fact there is no good evidence that the so called "long latency" responses are modifiable on a moment to moment basis (see for example Houk 1978; Marsden et al., 1978). One of the major points of this thesis is that the above view is incorrect. The short latency essentially monosynaptic responses are modifiable by a central mechanism, on a moment to moment basis, independently of the level of motor activity, and they are specifically adapted to the motor task. Furthermore, the changes in the amount of presynaptic inhibition acting on the Ia afferent terminals in the spinal cord is the primary central mechanism

responsible for this adaptive capacity. Fusimotor activity, as will be discussed in the body of the thesis, would tend to reinforce the central effects.

Thus, such a capacity to control the efficacy of synaptic transmission between the Ia-afferents and the motoneurons, on a moment to moment basis, would allow for the adjustment of the stiffness of the stretch reflex to a value appropriate to the motor task. Indeed, this may account for such observations as the increase of stretch reflex stiffness in man when the motor task involves stabilizing the position of an unstable load (Akazawa, Milner, and Stein, 1983). Furthermore, this adaptive benefit would not be delayed by having to traverse long loop pathways (e.g., transcortical).

The disynaptic inhibitory pathway

The well known short latency inhibition of motoneurons by electrical stimulation of the antagonist nerve (Lloyd, 1941, 1946) has been shown by Eccles and colleagues (Araki, Eccles, and Ito, 1960; Eccles, 1964) to be due to an interneuron interposed between the Ia-afferents and the motoneurons of the antagonist muscle. This was contrary to the view of Lloyd that this inhibitory pathway was monosynaptic. Eccles in his book the "The Physiology of Synapses" (Eccles, 1964) summarizes the evidence obtained from a

series of experiments showing that there exists an interneuron in this simplest of inhibitory pathways of the mammalian CNS. Briefly, the Ia ipsp has a time course comparable to that of the inhibition of reflex discharge (Brock, Coombs, and Eccles, 1952), the latency of the ipsp is 1 ms longer than that of the epsp. Furthermore, this latency is comparable to that of the first detectable sign of inhibition of ventral root reflexes (Araki, Eccles and Ito, 1960). The next major progress was the finding by Lundberg (1966) that the Ia-inhibitory interneuron was under supraspinal control. This led to the hypothesis of "α-linked inhibition" whereby activation of motoneurons was linked to the simultaneous excitation of the Ia inhibitory interneurons projecting to the motoneurons of the antagonist muscle. This hypothesis implied a potentiation of inhibitory action at this synapse preceding as well as during a movement. Support for this hypothesis was obtained in the early seventies (Tanaka, 1974) in experiments on the ankle musculature of human subjects. However, recent reexamination of this issue has failed to confirm a potentiation of the inhibitory action at this synapse accompanying voluntary activation of the ankle extensors (Iles, 1984; Crone, Hultborn and Jespersen, 1985). This issue is more fully discussed in the fifth chapter of this thesis.

Another important point on this pathway is that all the known inhibitory projections onto the Ia inhibitory interneurons are from other inhibitory interneurons in the spinal cord. There are no known direct supraspinal inhibitory connections onto the Ia-interneurons. They are inhibited by Renshaw cells whose motoneurons receive the same Ia-afferent input. They are also inhibited by the Ia inhibitory interneurons associated with the motoneurons of the antagonist muscle. This is referred to as mutual inhibition of opposite Ia inhibitory interneurons (Baldissera, Hultborn and Illert, 1981). The two interneurons providing inhibition onto the Ia inhibitory interneurones are under supraspinal control, thus allowing for the supraspinal inhibition of Ia inhibitory interneurons.

The presynaptic inhibitory pathway

The literature on presynaptic inhibition in the spinal cord is extensive (reviewed by Burke and Rudomin, 1977; Rudomin, 1980) and goes back to Barron and Matthews (Barron and Matthews, 1938) who studied the related phenomenon of dorsal root potentials in the frog spinal cord resulting from high frequency stimulation of afferent fibres. Here I want to make three points on this mechanism that controls the efficacy of synaptic transmission.

The first is that it can produce its effects sufficiently rapidly to be capable of modulating reflex transmission on a moment to moment basis. For example stimulation of flexor group I fibres produces within a few milliseconds presynaptic inhibition of extensor group Ia-afferents (Frank and Fuortes, 1957) the same is true when presynaptic inhibition of afferent fibres is produced by supraspinal structures (Rudomin, 1980). The second point is that presynaptic inhibition can be very specifically directed onto certain types of terminals at the exclusion of others which are in the same vicinity. For example, vestibulospinal fibre terminals projecting to motoneurons are adjacent to those of the Ia-afferents since the interaction between their epsps in the motoneuron soma is nonlinear. Stimulation of a flexor nerve at group I strength produces presynaptic inhibition of the Ia-afferent fibre terminals but has no effect on those of the vestibulospinal fibre terminals (Rudomin, 1980). This specificity has also been shown for presynaptic inhibition of terminals in the spinal cord produced by supraspinal structures such as the red nucleus, Deiters's nucleus, and the sensorimotor cortex (Rudomin, 1980). The speed and specificity of action are due no doubt to the existence of specific interneurons mediating

presynaptic inhibition (Jimenez, Rudomin, Solodkin, and Vyklicky, 1984). Finally, if during a natural motor activity a change in reflex transmission is found to be due to presynaptic inhibition, the source of this inhibition may be of either central or peripheral origin.

Reflex activity during locomotion

The modern view on the generation of locomotor activity in the mammal has been summarized by Grillner in three recent reviews (Grillner, 1985; Grillner and Wallen, 1985; Grillner, 1986). In Grillners' view the basic locomotor pattern, that is the timing relations between the activities of the various muscles, is produced by a so called central pattern generator (CPG) located in the spinal cord. The CPG can, apparently in the total absence of afferent inputs, produce appropriately timed motor bursts in the various muscle groups. Grillner, however, has repeatedly stressed that in the intact animal the observed locomotor pattern is a resultant of both central and peripheral factors acting in concert. A clear example of how afferent activity from the leg can influence the motor output is provided by the entrainment of locomotor rhythm produced by hip afferent inputs. During normal locomotion in the cat if the hip is prevented from extending during the

early part of stance the discharge of all leg extensors is prolonged until the leg is released (Grillner and Rossignol, 1978). If on the other hand the hip joint is extended in the same phase the leg will flex and this at about the same hip joint angle as would occur naturally. Furthermore, in the curarized fictive locomotion preparation, if the hip is moved sinusoidally by an externally applied force the fictive motor pattern is entrained by the applied hip movements (Andersson and Grillner, 1983). Loading the cat during the stance phase produces enhanced extensor activity and delays the initiation of the swing phase; conversely, unloading the animal at the end of stance promotes limb flexion (Duysens and Pearson, 1980). These examples clearly demonstrate that afferent inputs can directly influence the CPG. They serve to reinforce the point that the pattern of motor output observed in the intact animal is a resultant of both central activity and movement related feedback. These ideas are in agreement with those of Pearson (1985) who argues that the concept of a CPG is misleading, since the motor output pattern in the intact animal may be different from that in the deafferented animal. He shows that in locust flight and cockroach locomotion the motor output is different in the intact animal compared to the deafferented preparation (Pearson, 1985). In particular, the

timing relations between the motor burts of the various muscles is altered in the deafferented animal. In these two systems the concept of the CPG as described by Grillner is not applicable (see, Grillner and Zangger, 1975). Whether the concept of a CPG, as an entity in the spinal cord that can appropriately time the motor outputs to the various locomotor muscles in the absence of peripheral feedback, is applicable to the human is not known. This is, obviously, of scientific as well as clinical interest.

The counterpart of the above phenomenon, namely the selective control by the CPG of the effects of afferent inputs on the motor output, has also been observed. For example, if the foot encounters an obstacle during the swing phase, that is when it is in the air, this results in hyperflexion of the leg so as to pass over the obstacle (Forssberg, 1979). The same stimulus during the stance phase does not cause a leg flexion as this might cause the animal to fall. Instead, it increases the extensor activity presumably until the other leg is placed on the ground. This is a classic example of the central control of the effects of afferent input on motor output.

The above examples involved for the most part afferent inputs from joint and skin afferents. The effects of the Ia muscle spindle afferents on the

motor output during locomotion have been much less studied. In general, the reflex effects of the cutaneous and joint afferents influence the timing of locomotor activity. In contrast, muscle afferents influence the amplitude of locomotor activity, and may in addition have some effect in determining the exact duration of a motor burst depending on the exact kinematic events as will be explained in the final chapter of this thesis. However, like cutaneous and joint influences on the locomotor output, those of muscle afferents must also be regulated by a central mechanism(s). Referring to extensor muscles of the leg, a stretch reflex would reinforce activity during the stance phase, where these muscles yield under the weight of the body, whereas it would oppose the flexors during the swing phase when the extensors are stretched by the flexor activity (Akazawa et. al, 1982; chapters 1 and 2). Prior to the present studies only that of Akazawa et al. (1982) had systematically investigated the reflex effects of Ia-spindle afferents during the various phases of the locomotor cycle of the mesencephalic cat. This thesis takes its origins in part from that initial study.

Outline of thesis

The chapters of this thesis are ordered in a logical sequence rather than in the chronological

sequence in which the experiments were done. Each of the studies described in the following chapters was done to answer one or more of the following questions:

1) Is the short latency, essentially monosynaptic, reflex response of the soleus muscle modulated in amplitude during the step cycle?

2) Is the modulation specific to and of functional importance for the task being performed?

3) Can the amplitude of this reflex be controlled independently of the level of motor activity?

4) If so, what is the mechanism(s)?

5) Is the segmental inhibitory pathway (Ia inhibitory interneuron pathway) to the soleus motoneurons shut off during their active phase in the locomotor cycle? What is the quantitative relation between the amount of inhibition and the amount of motor activity?

The results obtained in answer to the first three questions are contained in the next two chapters. As mentioned above my interest was in identifying a central factor that may be responsible for any possible reflex modulation during natural motor activities. Therefore, experimental manipulations such as stretching a muscle produce responses that depend on the state of the fusimotor system and hence the sensitivity of the muscle spindles, a peripheral factor. Electrical stimulation of a nerve was therefore used since it is largely independent of

peripheral factors such as the sensitivity of muscle spindles (see Chapter 2 for further details). Thus, the monosynaptic reflex was elicited in humans by applying an electrical stimulus to the tibial nerve and recording the direct muscle response (M-wave) and the subsequent reflex response of the Soleus (H-reflex) electromyographically. The Soleus muscle was used for several physiological and methodological reasons. It is a major ankle extensor and thus is one of the most important muscles providing forward thrust and lifting of the body during normal locomotion. It also has a well developed stretch reflex which manifests itself in an easily obtainable H-reflex. Finally, one can record the electromyographic reponses of this muscle in relative isolation from those of other ankle extensors (Hugon, 1973). The method was first developed by Hoffmann (Hoffmann, 1922), hence the designation Hoffmann reflex (H-reflex) in his honour. It has been used to test the so called excitability of the motoneurons under either resting conditions, preceding voluntary activation of the ankle extensors (Kots, 1969; Paillard, 1959) and during tonic contractions in the sitting position (Gottlieb, Agarwal, and Stark, 1970).

Until the present study, and except for a short abstract (Garrett et al., 1984) and a short paper

(Morin et al., 1982) it had never been used to study a natural, dynamic, motor task. The technical details concerning its application during human locomotor activity are fully described in the various chapters of this thesis. It is often suggested that the technique tests the excitability of the motoneurons, which is a factor intrinsic to the motoneurons themselves. The method inevitably also tests for the state of transmission between the Ia-afferents and the motoneurons. Furthermore, as will be described in chapter 4 the method may in fact be independent of the intrinsic excitability of the motoneurons when comparisons between reflexes are made at the same level of motor output. In fact, the fourth chapter is a theoretical analysis of what central factors (presynaptic vs postsynaptic) may be involved in changing the input-output relations in the monosynaptic pathway and thus adresses the fourth question. It should be pointed out that the conclusions reached in that study are contrary to those in chapter 2 which were based on a qualitative analysis of the problem.

Finally, the results relating to the last question are presented in the fifth chapter. The state of the Ia-inhibitory pathway to the soleus motoneurons was tested by its effect on the naturally occurring motor

activity, as measured from the rectified intramuscular e.m.g., as opposed to the traditional conditioning/ test reflex paradigm (e.g., Tanaka, 1974).

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II. AMPLITUDE MODULATION OF THE SOLEUS H-REFLEX IN THE HUMAN DURING WALKING AND STANDING

It was reported recently that the stretch reflex of the soleus muscle was strongly modulated in amplitude during the walking cycle of the mesencephalic cat (Akazawa et al., 1982). Moreover, the modulation of the amplitude of the stretch reflex was not simply a function of the level of activity in the soleus muscle. This demonstration depended on comparing reflexes obtained during locomotion to those obtained during similar levels of tonic activity which occur spontaneously in the mesencephalic cat. Therefore, it is possible that the efficacy of the synaptic transmission between the Ia afferents and the motoneurons may be modulated by central neural mechanisms independently of the level of motoneuronal activity (Akazawa et al., 1982). However, because the study used a reduced preparation and relied on spontaneous changes of activity, the utilization and functional value of such a modulation during voluntary activity remains unknown.

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Capaday, C. & Stein, R.B. (1986)
Journal of Neuroscience 6, 1308-1313.

Does a functional modulation of the stretch reflex occur in normal human subjects, and if so, what is its origin? Surprisingly, these questions have been the subject of only brief reports (Capaday and Stein, 1985; Garrett et al., 1984; Morin et al., 1982). Walking and standing were chosen to investigate these questions in more detail, because the stretch reflex is of functional value in both tasks (Dietz et al, 1980; Dietz et al, 1979; Nashner 1976) and may be used to a different extent in each task. Walking requires a certain amount of compliance (Houk 1976), whereas standing may require a more rigid control of ankle position. In principle, a modulation of the amplitude of the stretch reflex can be produced by a shift of reflex threshold (i.e., the curve relating reflex output to stimulus input is shifted along the abcissa without changing its slope; Crago et al, 1976; Houk, 1976, 1979) or by a change in reflex sensitivity which would change the slope of the input-output relation. These two possibilities may result from quite different neural mechanisms.

There are obvious technical difficulties in applying, during walking, perturbations that would stretch a muscle group of a normally moving limb. However, Akazawa et al. (1982) found that in the mesencephalic walking cat the amplitude of the H-reflex and the stretch reflex were modulated in

essentially the same way. It was also found in this preparation, that during spontaneous states of tonic contractions the amplitude of the H-reflex paralleled that of the stretch reflex (Akazawa et al., 1982; see also, Aldridge and Stein 1982). Furthermore, while the H-reflex and the stretch reflex are not identical (Burke et al., 1983, Burke, 1984), both depend in large part on the synaptic connections between the Ia muscle afferents and the [illegible]motoneurons. Therefore, the amplitude of the H-[illegible] and the stretch reflex may have similar temporal [illegible]files during the course of a movement or postural state, although the extent of facilitation or depression of each reflex may not be exactly the same. To the extent that the H-reflex is less dependent on the peripheral effects of the fusimotor system on muscle spindles, it should provide a better measure of any change in synaptic efficacy between the muscle afferents and the α-motoneurons. There is, however, a problem in maintaining a constant electrical stimulus to the tibial nerve at all phases of the step cycle, but this can be minimized (see Methods).

In this paper it is shown that the H-reflex is deeply modulated during walking in humans and that this modulation is dependent on central mechanisms of which the level of α-motoneuron excitation is only one

component. The modulation is accompanied by changes in both reflex sensitivity and reflex threshold.

MATERIALS and METHODS

EXPERIMENTAL PROCEDURES

H-reflexes were obtained from 6 human subjects during level walking on a treadmill at a comfortable speed (0.6-0.8 m/s). The average cycle time was about 1.4 s/step. A silver disc stimulus electrode (diameter of active area = 0.7 cm) was placed over the tibial nerve in the popliteal fossa , fastened to the skin with adhesive tape, and secured by a velcro strap around the leg. The stimulus ground electrode was placed either above the patella or above the popliteal fossa. Care was taken in the placement of electrodes to avoid restricting normal movement of the knee joint. Similar surface electrodes were placed over the soleus and tibialis anterior (T.A.) muscles to record the EMG activity. The tibial nerve was electrically stimulated in a pseudorandom sequence at a strength that elicited both an M-wave (direct stimulation of α-motoneuron axons) and an H- wave (reflex response to stimulation of Ia muscle afferents). The minimum inter-stimulus interval was 400 ms, and the maximum was 2 s. Although some H-reflex depression can occur at inter-stimulus intervals in the lower part of this range (Taborikova and Sax, 1969), these rather short intervals were used to minimize fatigue in the walking subjects during the

course of prolonged experiments. Moreover, any potential effects of the inter-stimulus interval were minimized by randomizing the intervals and by averaging the individual responses (further described below).

The EMG signals of the soleus and tibialis anterior muscles, were amplified, high pass filtered (10 Hz RC-filter) and recorded on FM magnetic tape along with the stimulus marker. The data was later analysed on a computer. Because of changes in distance between the nerve and the stimulating electrode during walking, the effective stimulus strength (current density) was not constant throughout the walking cycle. However, by repeating the experiment at several stimulus intensities and using the M-wave as a measure of the effective stimulus strength, H-reflexes occurring at various phases of the step cycle could be compared at equal stimulus intensities. Moreover, the data were selected from a range in which the H-reflex was relatively independent of the stimulus strength (Fig. 2.1); this range was similar during walking and during standing. A further problem is that the size of the EMG response to a constant electrical stimulus to the muscle nerve may vary significantly at different muscle lengths (Inman et al., 1952). However, both M and H waves are affected in the same way, so maintaining a constant M-wave should largely overcome

this problem.

It may be argued that a stronger stimulus is required to produce the same M-wave when the muscle is active . However, the relative refractory period of human nerves is between 4-5 msec, whereas the highest discharge rates of soleus motor units is between 10-15 spikes/s (i.e., one spike every 60-100 ms). Therefore, only a small fraction of motor units will be refractory at any time and the procedure of matching the amplitudes of M-waves as a measure of stimulus strength is justified. In fact, an essentially maximal M-wave can be obtained even during a maximum voluntary contraction.

In a second series of experiments, subjects were instructed to maintain tonic contractions of the soleus muscle at various levels while standing. To increase the level of the contraction subjects shifted progressively more of their body weight onto the leg used for experimentation and went onto their toes. During these maintained tonic contractions electrical stimuli were applied to the tibial nerve in the same pseudorandom sequence as during walking. The whole range of maintainable voluntary activity of the soleus was investigated.

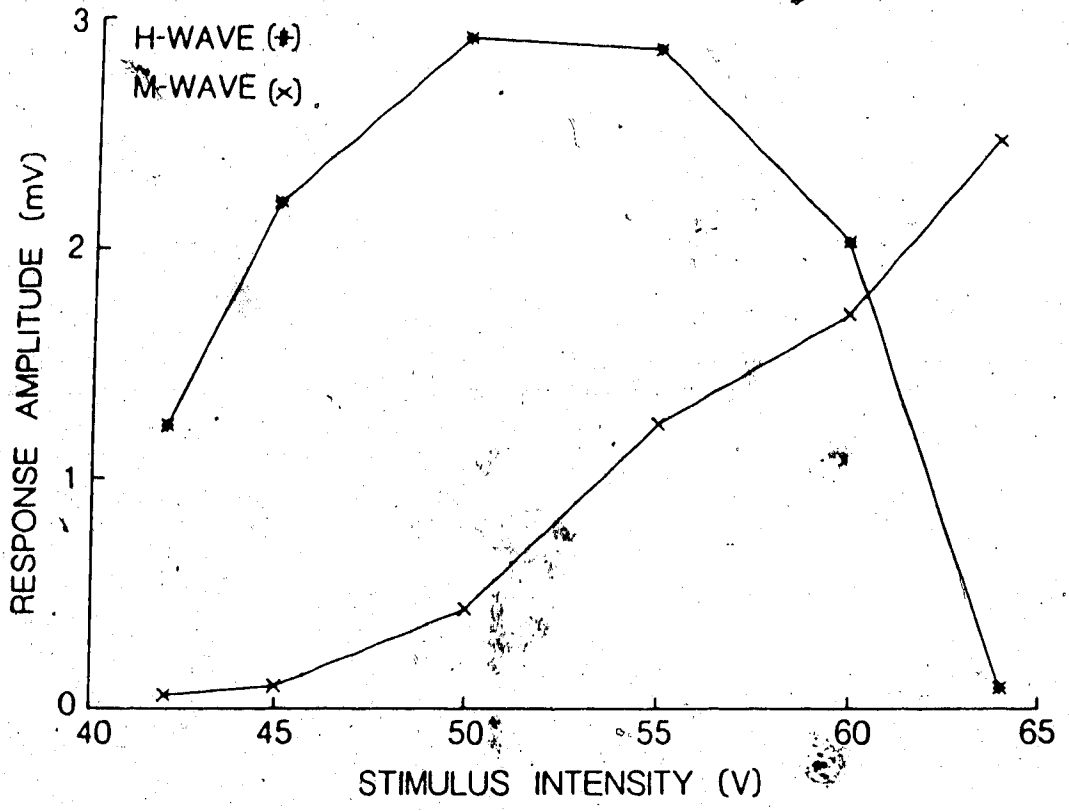

Figure 2.1: H-reflex and M-wave amplitude recorded from the soleus muscle as a function of the intensity of the stimuli applied to the tibial nerve. Note the range in which the H-reflex amplitude is relatively constant in spite of a large variation of M-wave amplitude.

DATA ANALYSIS

The data was analysed on a digital computer as follows. The EMG activity of the tibialis anterior (T.A.) muscle was full-wave rectified, low-pass filtered (20 Hz RC-filter), Paynter filtered (3 Hz cutoff), and then passed through a Schmitt trigger to generate a pulse which served as a step marker. An EMG signal was preferred as a step marker because fitting shoes with heel contacts or strain gauges could affect the walking. The large and randomly occurring stimulus evoked EMG in the soleus made this signal unusable as a step marker, so the EMG activity of the antagonist (T.A.) was therefore used.

The computer used the latency between a step marker and a stimulus marker to determine in which of 16 possible intervals (or phases of the step cycle) the stimulus occurred (a detailed description of the analysis procedure can be found in Akazawa et al., 1982). Responses occurring in the same phase of the step cycle were averaged together. The duration of each average was 76.8 ms from the time of stimulation, which was sufficient to include the M-wave and H-reflex. The amplitude of the H-reflex as a function of the phase in the step cycle (16-phases) was thus obtained. As explained above, H-reflexes occurring at various phases of the step cycle were grouped for comparison by matching the averaged amplitude of the

M-wave.

The peak to peak amplitude of the H-reflex obtained in each of the 16 phases of the step cycle was plotted against the mean level of EMG activity in each of the phases. These results were compared to those obtained during steadily maintained contractions.

In a few experiments walking subjects were videotaped. Using a special effects generator the full-wave rectified and smoothed EMG activity of the soleus and T.A. muscles during walking was superimposed in real-time on the videotape of the walking subject. Thus, the EMG activity could be directly compared to changes in ankle angle and hence changes in soleus muscle length (see Fig. 2.2).

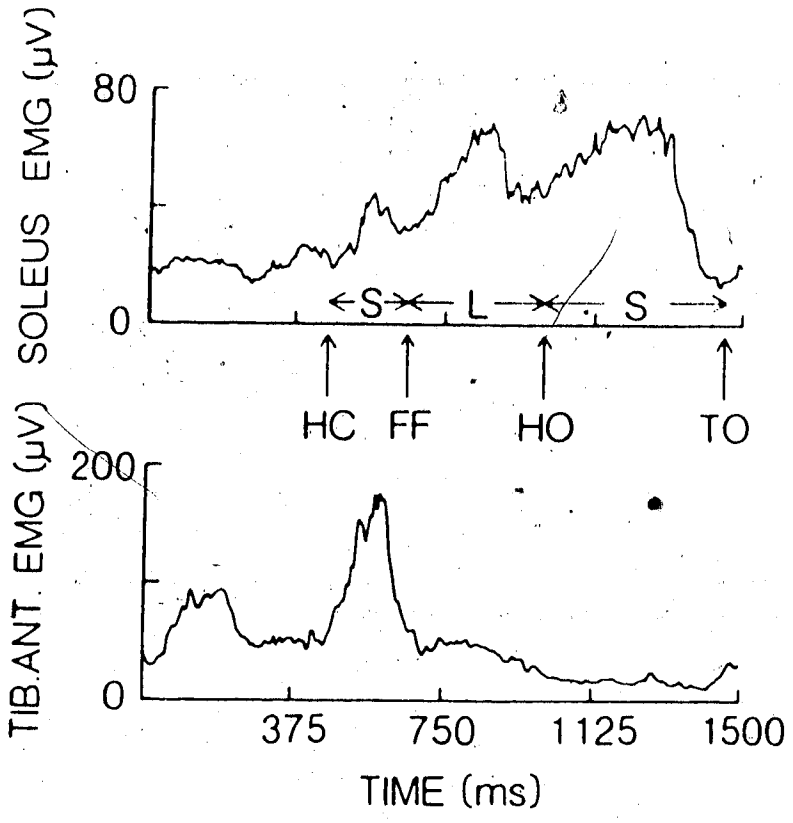

Figure 2.2: Full wave rectified, filtered, and averaged (n = 100) EMG activity of the soleus and T.A. muscles of the ankle during walking. The EMG during individual steps was superimposed on a video recorded image of the walking subject, so that the EMG could be correlated with various kinematic features of the step cycle which are indicated by arrows (further details in results). Abbreviations: heel contact (HC), foot flat on the ground (FF), heel off (HO), toe off (TO), muscle shortening (S), muscle lengthening (L). The background EMG level of 10-20 uV is mainly attributable to amplifier noise and perhaps some DC offset in the rectifier circuit.

RESULTS

EMG ACTIVITY OF SOLEUS AND T.A. DURING WALKING

The full wave rectified, RC-filtered, and averaged (n = 100) EMG activity of an ankle extensor, soleus, and an ankle flexor, T.A., during walking are shown in Fig. 2.2 (see also Fig. 2.4D). In this experiment the subject was videotaped during walking and the various step markers commonly used in human locomotion studies were correlated with the EMG activity of the soleus and T.A. muscles. The EMG activity of soleus usually began before the heel touched the ground (heel contact = HC), increased during most of the stance phase, and terminated abruptly just before the toes were lifted off the ground (TO). After heel contact the soleus muscle shortens (S) until the foot is flat on the ground (FF), it then lengthens (L) until the heel comes off the ground (HO), and finally, it shortens (S) between HO and TO. The length changes of T.A. during this period are of course in the opposite direction.

The T.A. EMG activity consisted of two prominent bursts. The first burst, in Fig. 2.2, was associated with the ankle dorsiflexion which occurs late in the swing phase. The second, usually larger burst began at about the same time as HC and continued until about the time the foot was flat on the ground. Since the soleus muscle was also active during this time, HC was

followed by co-contraction of these two antagonistic muscles. The extent of this co-contraction may differ from subject to subject. Some have relatively little (see Fig. 5.4) others considerably more (Fig. 2.2, 2.4).

AMPLITUDE MODULATION OF THE H-REFLEX DURING WALKING

The amplitude of the soleus H-reflex in each of the phases of the step cycle of one subject is shown in Fig. 2.3. The first phase in this example occurs at about the time of HC and the period of analysis (1.5 s) occupies approximately one step cycle. Each of the traces in Fig. 2.3 was selected as described in the Methods section. The reader should note that despite a relatively constant amplitude of the M-wave (mean = 1.31 mV, S.D = 0.31) the H-reflex is strongly modulated throughout the cycle. The H-reflex was small at the time of foot contact, but increased rapidly to a maximum value and then decreased very abruptly after TO.

In Fig. 2.4 the peak to peak (P-P) amplitude of the H-reflex was plotted against the phase in the step cycle. The P-P amplitude of the M-wave was also plotted against the phase in the step cycle. The average (n = 70) rectified and filtered EMG activities of the soleus and T.A. are also shown in Fig. 2.4. In this example, the amplitude of the soleus H-reflex

covaries directly with the EMG activity in this muscle.

In the example shown in Fig. 2.4 the amplitude of the soleus H-reflex is closely related to the EMG activity of the muscle. However, such a close correlation between the EMG activity and the reflex amplitude was observed in only three of the six subjects. In the other three subjects, the soleus H-reflex amplitude was strongly modulated in amplitude, but the variation was not as closely correlated with the EMG activity of the muscle. Two such examples are shown in Fig. 2.5. In Fig. 2.5A the peak reflex amplitude occurs prior to the peak EMG level. Another example is shown in Fig. 2.5B in which the reflex amplitude is not closely related to the EMG activity, being high throughout the stance phase. In this and other subjects, the peak reflex amplitude attained during walking was not the maximum possible (see following section). Therefore, the broad, relatively flat reflex peak seen in Fig. 2.5B is not due to a saturation phenomenon.

It seems unlikely that the observed pattern of amplitude modulation of the H-reflex during the walking cycle is due to changes in the refractoriness of the Ia-afferent fibers. There are two phases in the walking cycle in which the Ia-afferents discharge at high frequency and hence where these afferents may

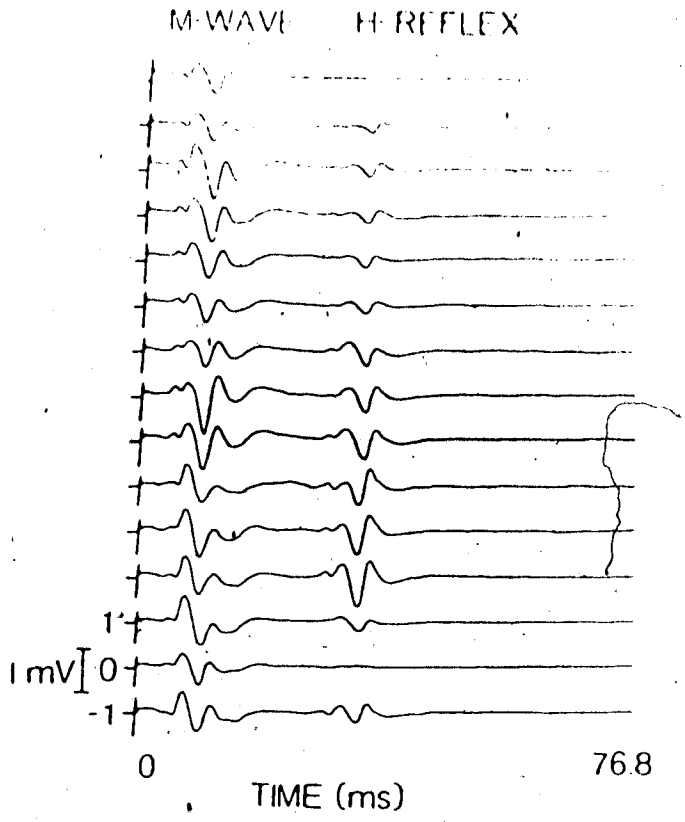

Figure 2.3: M-wave and H-reflex response to tibial nerve stimulation at various phases of the step cycle. The topmost trace represents the response of soleus in the first phase of the step cycle (i.e., the average of 14 responses occurring in the first 94 ms after the step marker, which was set for this subject at about the time of dorsiflexion). Subsequent traces are responses which occurred progressively later in the step cycle. The third trace from the bottom occurs at about the time of TO.

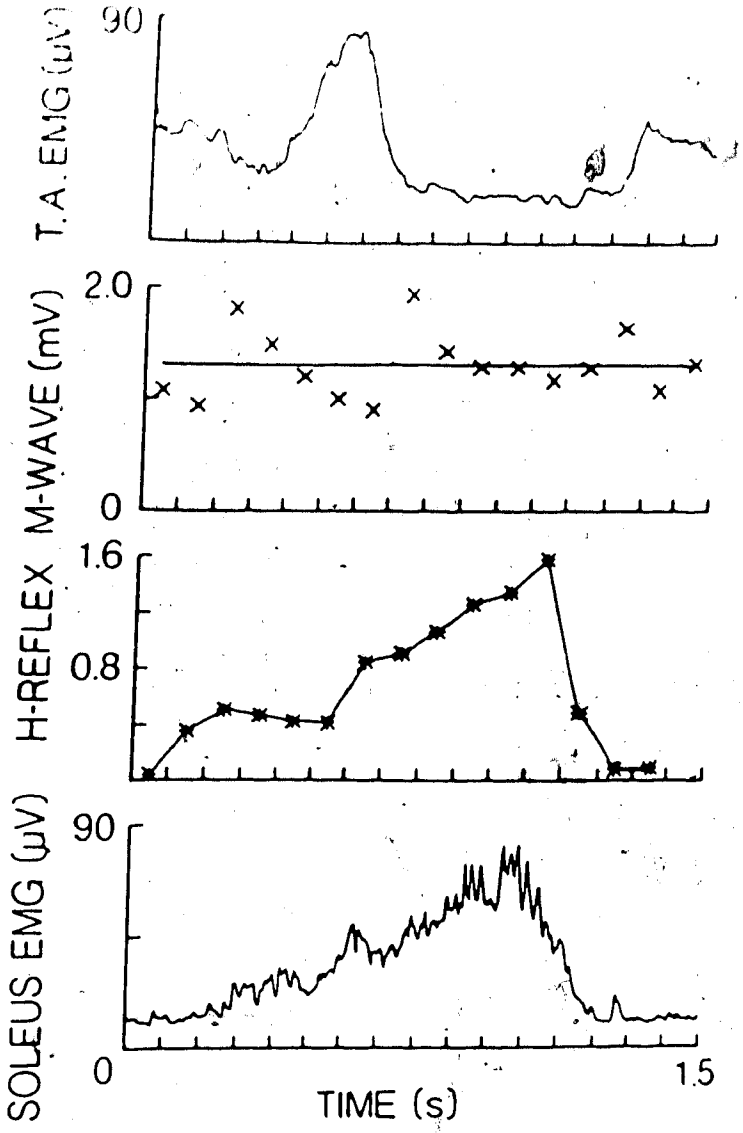

Figure 2.4: Amplitude of the H-reflex (P-P) as a function of the phase, or time, in the step cycle. The amplitude of the M-wave (mean = 1.31 mV, S.D = .31) in the various phases of the step cycle is also shown as well as the EMG activity of soleus and T.A. muscles.

show the greatest degree of refractoriness. During the swing phase the soleus is stretched by the ankle dorsiflexion and the Ia-afferents consequently discharge at high frequency (Prochazka et al., 1976). The same afferents also discharge at high frequency during the stance phase when the soleus is stretched between FF and HO as the body rotates over the ankles (Prochazka et al., 1976). However, during stance the H-reflex is relatively high, whereas during swing it is low. The H-reflex is also low in the period between HC and FF when the soleus is both actively contracting and shortening and therefore the discharge rate of the Ia-afferents is relatively low and so too their degree of refractoriness. Therefore, if changes in the degree of refractoriness was the only factor contributing to the observed amplitude modulation of the H-reflex, the H-reflex should be high during low refractoriness (e.g., between HC and FF) and low during high refractoriness (e.g., between FF and HO), but exactly the opposite was observed. In summary, changes in the degree of refractoriness of the Ia-afferents may influence the magnitude but not the pattern of the observed amplitude modulation of the H-reflex during walking.

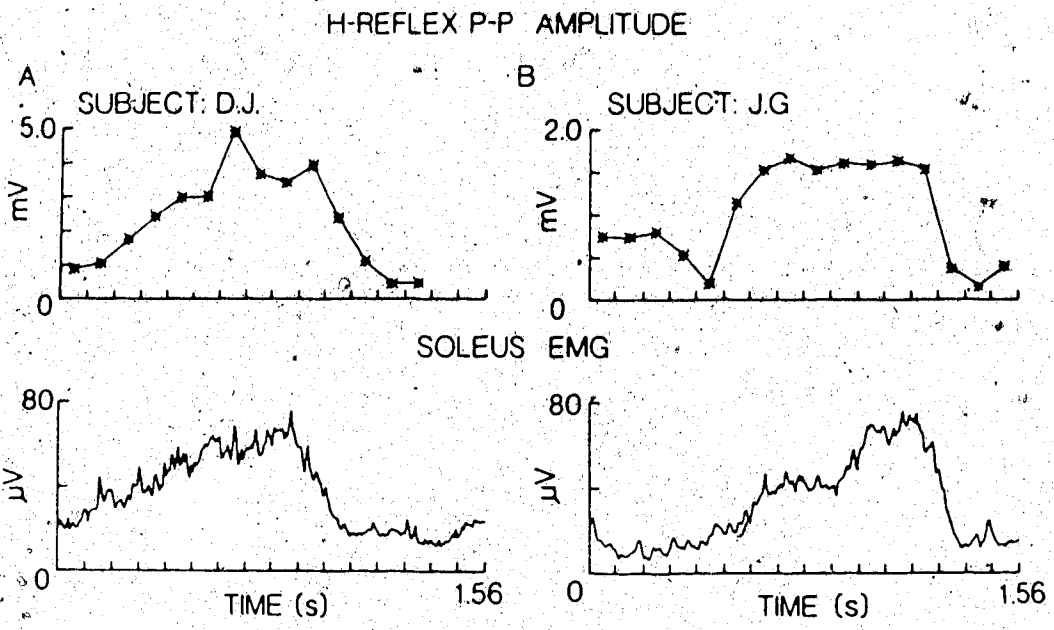

Figure 2.5: Other examples of H-reflex amplitude as a function of the phase in the step cycle. In each case the corresponding soleus EMG activity is also shown for comparison. Details are given in the text.

COMPARING H-REFLEXES IN TONIC CONTRACTIONS AND WALKING

The amplitude of the H-reflex, obtained while the subject was standing and steadily maintaining contractions of the soleus muscle at various levels, was compared with that obtained during walking. The subject relied on a chart recorder display of the rectified and smoothed soleus EMG activity to maintain a steady contraction at the required level for a period of about 20-30 s. The amplitude of the H-reflexes obtained, in one subject during steadily maintained contractions, is plotted in Fig. 2.6 as a function of the mean level of the soleus EMG activity. The amplitude of the H-reflex obtained, in the same subject, during walking is also plotted in Fig. 2.6 as a function of the mean EMG level (i.e., the mean EMG level during the phase in which the reflex occurred). It can be seen that the amplitude of the reflex was larger during maintained contractions (referred to as standing below) than during walking, and that the difference was greatest during low-level activity. In this example, the slope of the best fitting straight line, in the least squares sense, was 0.015 mV/ μV (S.E = 0.016) for standing, and 0.075 mV/ μV (S.E = 0.012) for walking; thus, there was a highly statistically significant difference between the slopes in the two conditions. Of particular interest

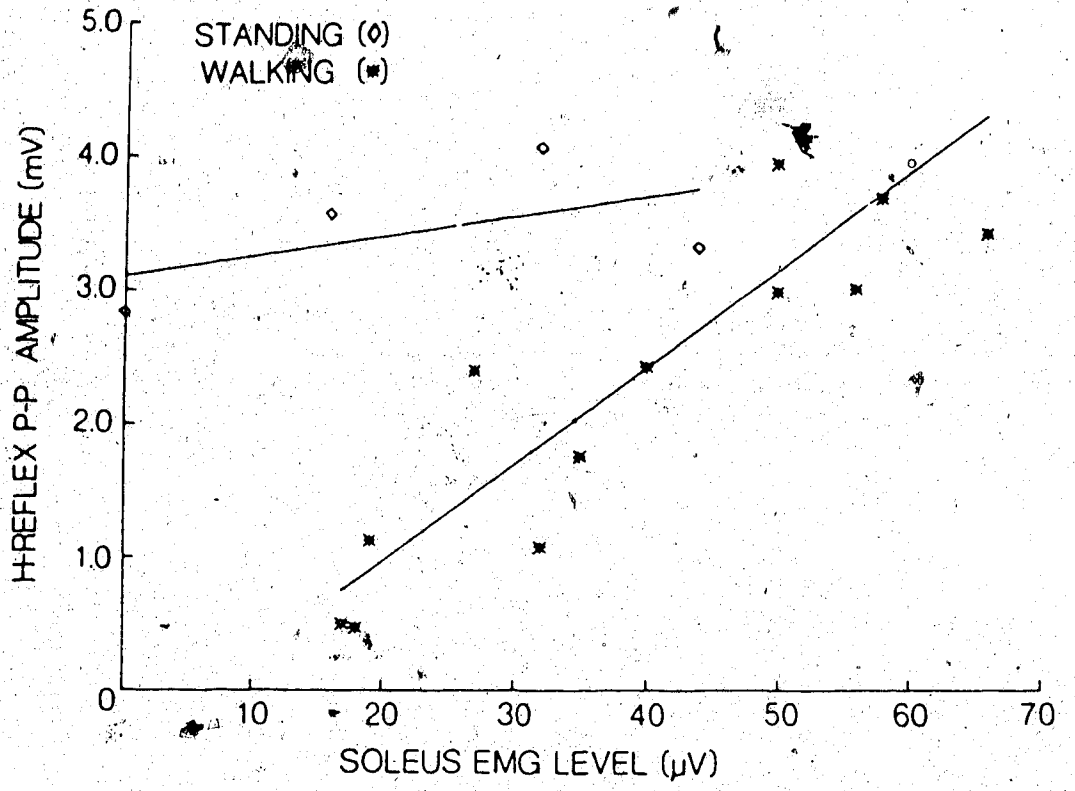

Figure 2.6: Soleus H-reflex amplitude during walking (*) and standing ( ) as a function of EMG level. Note the marked difference in the slopes (m = 0.075 walking, m = 0.015 standing) and y-intercepts (b = -0.54 walking, b = 3.1 standing) of the straight lines which were computed to minimize the mean square errors.

is the large amplitude of the H-reflex at "zero" EMG level (y-intercept) which will be referred to as "quiet" standing. Thus, the reflex sensitivity (i.e., the slope of the line relating H-reflex amplitude to EMG level) and the reflex threshold (x-intercept) were lower during standing than during walking. Both effects (i.e., decrease in sensitivity and threshold) were observed in the 4 subjects tested.

In the example of Fig. 2.6, the mean value of the M-wave was 1.25 mV (S.D =0.16) during walking and 1.23 mV (S.D =0.09) during the isometric contractions. Therefore, the difference in the amplitude of the H-reflex between the two conditions was not due to the stimulus strength. Moreover, the data was taken from a range in which the H-reflex was relatively independent of the stimulus strength (see Methods).

A potential problem in comparing EMG levels during walking and standing is that the EMG activity recorded by the soleus electrodes may include a component (due to cross-talk) from the other ankle extensors, medial and lateral gastrocnemius. For example, if as in the cat (Walmsley et al., 1978), the human soleus is predominantly, if not exclusively, active during standing and the gastrocnemius becomes more active during walking, then the H-reflexes recorded during walking would thus appear smaller than those recorded during standing because the activity level of the

soleus is in fact less than that indicated by the recording electrodes. However, the recording electrodes were placed over the soleus muscle just above the insertion of the gastrocnemius into the Achilles tendon, a site where soleus EMG activity can be selectively recorded (Hugon, 1973). Secondly, the largest difference between the H-reflexes elicited during walking and standing occurs at the lowest levels of activity, where a fast-twitch muscle like the gastrocnemius is least active and therefore the effects of cross-talk, if any, are least significant.

DISCUSSION

The major new findings reported here are the strong modulation of the H-reflex during locomotion in normal human subjects and the difference in the strength of the modulation of this reflex between walking and standing. Clearly, the modulation of the reflex is not simply a passive consequence of the excitation level of α-motoneurons, but depends on central mechanisms of which the level of α-motoneuron excitation is only one component. The change in the slope and x-intercept of the curve in the two states is also important, because it means that the sensitivity of the reflex as well as its threshold can be changed. Some previous authors have suggested that only the reflex threshold could be changed by central commands (Crago et al., 1976; Houk, 1976; Feldman and Orlovsky, 1972). Possible neural mechanisms underlying these reflex changes and their functional implications for the two types of motor activities studied will be dealt with, in turn, in the following sections.

Neural mechanisms. The neural mechanisms by which the modulation of the H-reflex is brought about during walking and standing are difficult to determine in human experiments, but some suggestions can be made which are illustrated in the schematic diagram of Fig. 2.7. The H-reflex increases more or less in parallel with the level of EMG activity, curve 1 in Fig. 2.7A.

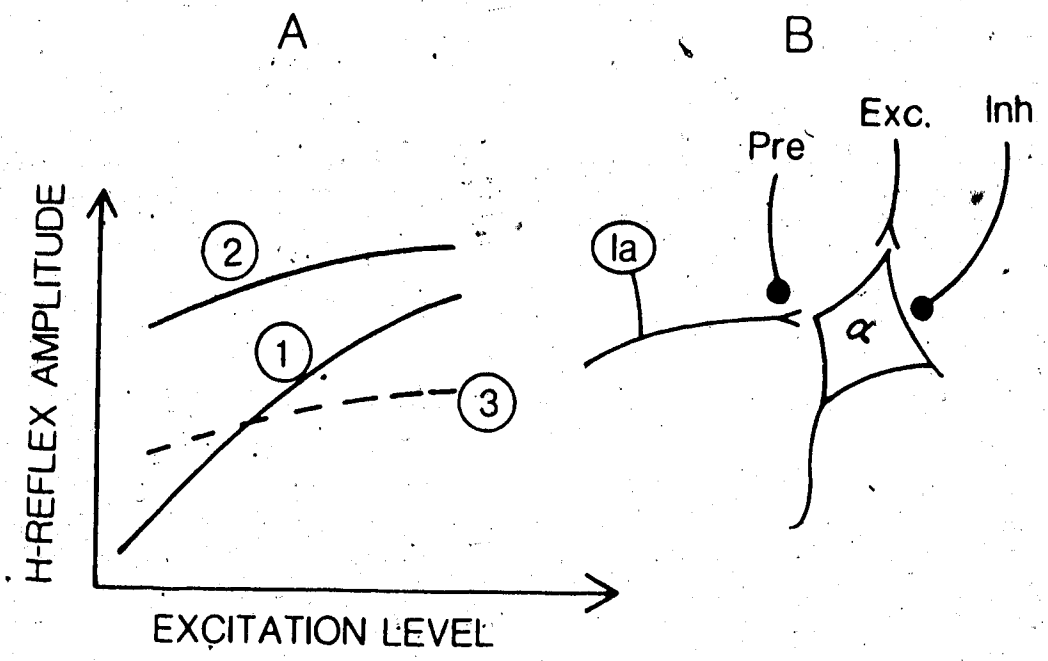

Figure 2.7: (A) Expected relation between the H-reflex amplitude and the level of α-motoneuron excitation for different combinations of excitatory, inhibitory, and presynaptic inputs to the motoneurons (B). Further explanation in Discussion.

If the same mechanisms are used as in the cat, α-motoneurons are depolarized by a combination of added excitation (Exc. in Fig. 2.7B) and decreased post-synaptic inhibition (Inh.), such that the resistance of the cell body is little affected (Shefchyk et al., 1984). The EPSP from primary muscle spindle receptors (Group Ia fibers) is then relatively constant at all phases of the cycle (Shefchyk et al., 1984) and the size of the H-reflex will therefore reflect the percentage of voluntarily activated α-motoneurons.

The much larger H-reflex in quiet standing could arise if weak excitatory inputs are active and inhibitory inputs are inactive, or greatly decreased compared to the levels during walking. Therefore, the size of the EPSP would be large during quiet standing because less shunting would be produced by inhibitory inputs. However, the EPSP would decrease in size with increasing excitation, because of the additional conductance produced by more excitatory inputs (i.e., decreased resistance). Therefore, as the number of active motoneurons increases with increasing excitation, the H-reflex would increase more slowly during standing (curve 2 in Fig. 2.7A) than during walking (curve 1 in Fig. 2.7A).

Morin et al. (1982) suggested that the differences between the two states might arise from presynaptic inhibition (Pre. in Fig. 2.7B). This

mechanism would reduce the Ia EPSP by a constant factor at all levels of excitation, without affecting postsynaptic conductance, and therefore produce a proportional reduction in the H-reflex (compare the dashed curve 3 in Fig. 2.7A with the solid curve 2). Clearly, if walking and standing are compared at only one level of excitation, presynaptic inhibition can appear to be an explanation for the results. Morin et al. (1982) used only one level of excitation and so did not anticipate the change in slope. One could of course postulate that the level of presynaptic inhibition is also tied to the level of EMG in just the right way to produce the observed change in shape between curves 1 and 2, but the post-synaptic mechanisms suggested above are far simpler to envisage. These suggestions should also be directly testable by intracellular recording from α-motoneurons in paralyzed decerebrate cats during fictive walking and tonic states with comparable levels of α-motoneuron excitation. Once data is obtained from these experiments, a mathematical model of how motoneurons are controlled in various types of motor activities may be formulated.

Another possible explanation for the difference between the amplitude of the H-reflex during walking and standing is that the size of the EPSP's during

walking are smaller than during standing because the high frequency discharge of the Ia-afferents during walking results in a depression of transmitter release and hence smaller EPSP's (Curtis and Eccles, 1960). However, if the depression lasted throughout the step cycle, it would be functionally equivalent to presynaptic inhibition, which can not explain our results (see above). If the depression only occurred when the afferents were firing fastest, it would have an analoguous effect to that of refractoriness which was also ruled out as an explanation of the results (see Results). In conclusion, while changes in the amplitude of the EPSP's due to this well known depression phenomenon may have occurred, postsynaptic factors such as those described above must also be considered.

Functional implications. The large difference in the y-intercepts (Fig. 2.6) of the H-reflex vs EMG curves between walking and standing is of functional importance. During standing, most of the body weight is supported by the skeleton, so the activity of the leg and other muscles during quiet standing is minimal (Basmajian, 1967). The large value of the H-reflex during quiet standing implies that even a small body sway will result in a relatively large stretch reflex in the soleus which will tend to counteract the sway. Thus, the large reflexes when the subjects were

standing, are consistent with the control of ankle angle and hence body position in this task. However, a comparably large stretch reflex during the swing phase of walking, where the EMG activity of the soleus is also minimal, would impede ankle dorsiflexion and would therefore be inappropriate. As discussed in the Introduction the stretch reflex of a muscle will be much more influenced by fusimotor effects than will the H-reflex, and possibly, because of the temporal dispersion of the afferent volley (Burke, 1983), also by the state of certain spinal interneurons (e.g., Ib interneurons, and Renshaw cells). However, at least in the mesencephalic walking cat, peripheral fusimotor effects add to and reinforce the modulation produced centrally (Murphy et al., 1984; Taylor et al., 1985), and both the stretch reflex and the H-reflex are modulated in essentially the same way (Akazawa et al., 1983).

Foot contact with the ground (HC) occurred during co-contraction of the ankle flexors and extensors, at a time when the amplitude of the H-reflex was relatively low. Therefore, the reflex was not adjusted to help overcome the loading of the foot at the time of HC. Indeed, it has been suggested that the stretch reflex would occur too late to contribute force to counteract the increased loading at the time

of foot contact (Grillner, 1972; Melvill Jones and Watt 1971; but see Stuart et al., 1973). The sudden impact and loading of the foot at the time of HC is compensated by a stiffening of the ankle resulting from a co-contraction of the ankle flexors and extensors which may be pre-programmed (Engberg and Lundberg, 1969).

The H-reflex increased rapidly to a maximum value during stance and then abruptly decreased to a low value after TO. The highest values of the stretch reflex during walking are therefore timed to resist the stretch of the ankle extensors while the foot is flat on the ground and the body rotates over this fixed support and to assist the "push-off" phase (i.e., the ankle extension which occurs late in the stance phase). This extends the finding of Dietz and his collaborators who showed that the stretch reflex of the triceps surae contributes significantly to the tension required for the "push-off" phase of running (Dietz et al., 1979). Thus, the stretch reflex amplitude appears to be appropriately adjusted in each phase of the step cycle to the requirements of locomotion.

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III. DIFFERENCE IN THE AMPLITUDE OF THE HUMAN SOLEUS H-REFLEX DURING WALKING AND RUNNING.

In a previous publication (Capaday & Stein, 1986) we reported that the H-reflex of the human soleus muscle was strongly modulated in amplitude during the step cycle in a manner appropriate to the requirements of locomotion. The reflex output was largest late in the stance phase when it would assist in lifting the body off the ground. The same reflex was absent during the swing phase when it would oppose ankle dorsiflexion. The size of the H-reflex was also much larger at an equivalent level of e.m.g. during standing than during walking. In particular, during quiet standing the background e.m.g. activity of the soleus is nominally zero as it is also during ankle dorsiflexion in the swing phase of locomotion. However, during quiet standing the amplitude of the reflex is very large which would make it useful in counteracting forward body sway, but during the swing phase of walking the reflex is shut-off when it would oppose ankle doriflexion. We therefore concluded that during walking the modulation of the amplitude of the H-reflex was not simply a passive consequence of the

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α-motoneurone excitation level (measured experimentally as the rectified surface e.m.g.) and that it depended on other central neural mechanisms.

Is the pattern and extent (minimum to maximum) of modulation of the H-reflex similar in running and walking, and is the relation between the size of the H-reflex and the background e.m.g. the same in the two locomotor tasks? A priori, a difference in the pattern of modulation may be expected since, for example, the impact force on the ankle at the time of heel contact (HC) during running is larger than during walking and therefore a larger reflex response may be desirable to further increase the stiffness of the ankle. If the relation between the H-reflex amplitude and the e.m.g. were different in the two tasks, it would be further evidence that the size of the H-reflex depends on central neural mechanisms other than the excitation level of the α-motoneurones. Furthermore, any such change in the relationship between these two variables may provide some clues on how the stretch reflex is adapted to the motor task. The validity of inferring changes in the short latency stretch reflex from changes in the H-reflex is discussed in detail in Capaday & Stein (1986). Briefly, while the extent of potentiation or depression of the H-reflex may not be identical to that of the stretch reflex (Van Boxtel, 1986) the two

never undergo changes in the opposite direction (Akazawa, Aldridge, Steeves & Stein, 1982; Aldridge & Stein, 1982). Furthermore, during locomotion, the effects of the fusimotor system on the muscle spindles tend to reinforce the effects of the modulation of the H-reflex (Taylor, Stein & Murphy , 1985; Loeb & Hoffer, 1985).

The contribution of the stretch reflex to sprinting, which is a digitigrade locomotor [illegible] was investigated by Dietz and colleagues [illegible]z, Shmidtbleicher & Noth, 197[illegible] They showed that, during sprinting, the stretch reflex produces a large increase of (e.m.g.) activity in the triceps surae g[illegible] following contact of the foot with the ground. The reflex also contributes significantly to the muscular tension exerted by this group during the short (150-200 ms) stance phase.

In this study, we have investigated the modulation of the H-reflex in various phases of running, in which the locomotor pattern is plantigrade (heel to toe), and compared it to that during walking in the same subject.

METHODS

The details of the experimental procedures and the data analysis methods were described in detail in a previous publication (Capaday & Stein, 1986). Here, we briefly describe these as well as some of the modifications that were made in the present experiments.

H-reflexes of the soleus muscle were obtained from 8 human subjects during level walking (4 km/hr) and running (8 km/hr) on a treadmill. The average walking cycle time was 1100 ms and that for running was 640 ms. The e.m.g.'s of the soleus and the tibialis anterior muscles were recorded with surface silver disc electrodes. A similar silver disc electrode was used to stimulate the tibial nerve in the popliteal fossa. The stimulus return electrode was placed either above the patella or above the popliteal fossa.

The major problem with electrical stimulation of the tibial nerve during locomotion using surface electrodes is that the distance between the stimulating electrode and the nerve changes because of the large displacements at the knee joint. Therefore, the effective stimulus strength (the current density) is not constant throughout the locomotor cycle. However, by repeating the experiment at several stimulus intensities and using the M-wave

(which is the electrical response of the muscle to electrical stimulation of its nerve) as a measure of the effective stimulus strength, H-reflexes occuring at various phases of the step cycle could be compared at essentially the same stimulus intensity (details in Capaday & Stein, 1986). The M-waves were also closely matched in comparing the walking and running data of each subject. We tried to select values of the M-wave which fell on the relatively flat region of the curve relating H-reflex amplitude and stimulus intensity (Capaday & Stein, 1986). The position of this flat region of the curve did not seem to change between walking and running (i.e., it occurred at about the same range of values of the M-wave as in standing). In some subjects, however, the M-waves could only be matched at high amplitudes (i.e., in the portion of the curve where the H-reflex decreases). In all cases the results were qualitatively similar.

It is important to have a good measure of the average e.m.g. activity in each of the two locomotor tasks so that the reflex responses can be compared at corresponding levels of activity. The average e.m.g. activity of the soleus and the tibialis anterior muscles during the locomotor cycle was measured by triggering the averaging computer from the suitably conditioned output of a switch placed under the heel

inside the subject's shoe. The switch closed and hence triggered the computer at about the time when the foot was flat on the ground. Typically, the e.m.g. activity of each muscle during the locomotor cycles (high pass RC-filtered at 10 Hz, full-wave rectified, and low pass RC-filtered at 100 Hz) was averaged in real time (n=100) and the standard error of the mean was also computed.

This procedure was repeated several times during the course of an experiment to ensure that the pattern of activity remained essentially the same throughout the duration of the experiment. The extent of any possible cross-talk between the ankle extensors (medial gastrocnemius (MG), lateral gastrocnemius(LG), and soleus) was determined by direct trans-cutaneous maximal stimulation of the LG or the MG while recording simultaneously the e.m.g. response of the stimulated muscle and its spread over the soleus. This was done to insure that the e.m.g. activity recorded over the soleus muscle was in fact produced for the most part by soleus and not by some combination of soleus activity and that of the other foot extensors. The extent of the cross-talk measured in this way was less than or equal to 10% (0.1 mV of activity picked up at the soleus electrodes for every 1 mV of gastrocnemius activity).

The method of obtaining the reflex responses of the

soleus muscle in the various phases of the step cycle is described in detail in the paper by Capaday & Stein (1986) and by Akazawa et al. (1982). In this study, however, the step marker was obtained from a switch placed under the heel inside the subject's shoe, instead of passing the tibialis anterior e.m.g. through a schmitt trigger circuit. The computer received the step mark, generated by the heel switch, and a stimulus mark. On the occurrence of the stimulus mark the soleus e.m.g. (unrectified, and RC filtered between 10 Hz and 300 Hz) was sampled for approximately 60 ms. The latency between the step mark and the stimulus mark was used to decide in which of 16 phases of the step cycle the stimulus occurred. Having determined this, the sampled signal from soleus was averaged with other signals which occurred in the same phase. By this method the average H-reflex response (usually, n=10-20) of the soleus in each of 16 different phases of the locomotor cycle was obtained.

The reason for dividing the locomotor cycle into 16 phases is that this gives a good temporal resolution of events in the step cycle. The procedure of "phase-dependent" averaging was done in real time and allowed the experimenter to determine, after averaging a suitable number of responses, the size of the M-wave

(effective stimulus strength) in each of the 16-phases of the step cycle. The experimenter could then adjust the output voltage of the stimulator for the next series of averages in order to obtain M-waves in the desired range. By repeating this procedure several times during the course of an experiment M-waves of approximately the same size could be obtained in all 16-phases of the step cycle.

In a few experiments the WATSMART system (Northern Digital, Waterloo, Canada) for reconstruction of the three dimensional kinematics of points in space was used to determine the ankle displacement as a function of time in each of the two locomotor tasks. Thus, the changes in length of the soleus muscle, which acts only at the ankle joint, were estimated.

RESULTS

The H-reflex of the soleus during the running cycle increased progressively during the stance phase, reaching its peak value usually at about the time of the peak e.m.g. activity. The H-reflex rapidly decreased at the end of the stance phase and was absent during the swing phase (ankle dorsiflexion). An example from one subject of the H-reflex modulation during the running cycle is shown in Fig. 3.1.

In Fig. 3.2 the peak to peak (p-p) amplitude of the H-reflex in each of the 16 phases of the running cycle is plotted, as well as the average soleus e.m.g., the average tibialis anterior e.m.g., and the p-p amplitude of the M-wave in each phase of the cycle. This subject had the largest phase difference between the H-reflex and the e.m.g. (a lag of 2/16 of a cycle). In many subjects little or no phase difference was observed while in others a small phase lead occurred. Overall, no significant phase difference was observed between the peak soleus e.m.g. and the peak H-reflex.

In this subject, heel contact (HC) occurred at about the 14 th phase of the cycle, but the H-reflex was relatively low at this time as it was in other subjects. The e.m.g. level at the time of HC of both the soleus and the tibialis anterior increased on the

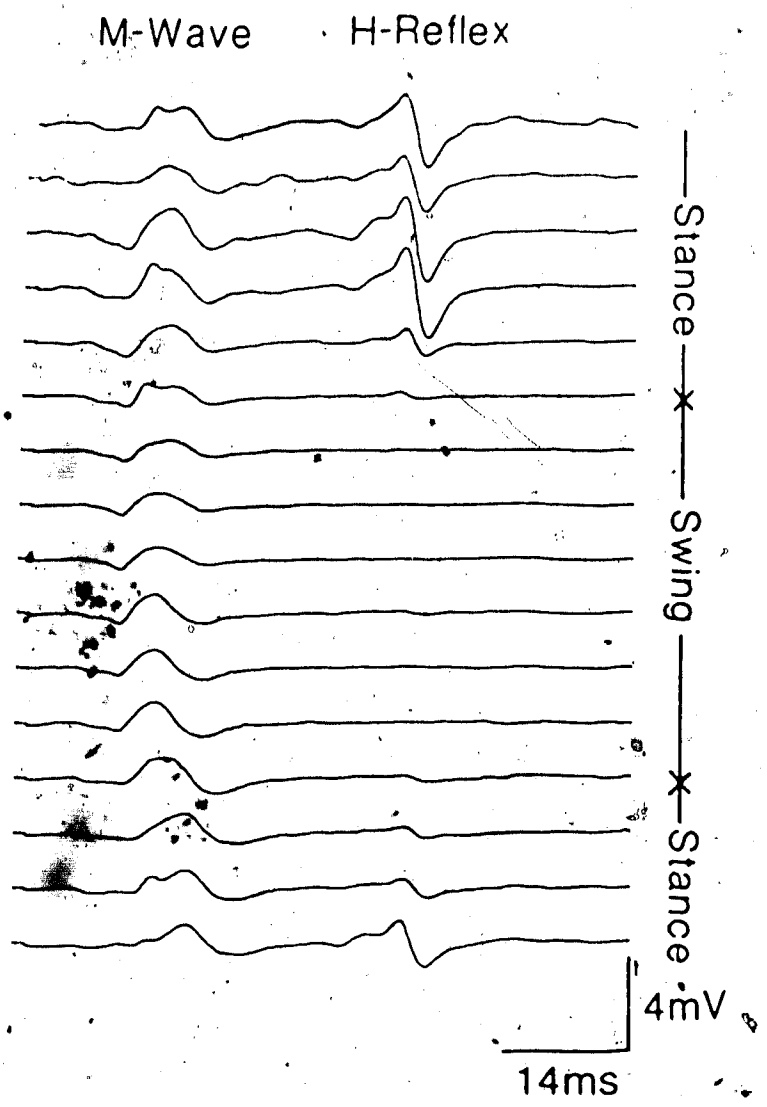

Figure 3.1: Amplitude modulation of the H-reflex during the 16 phases of the running cycle. Each record is the average of about 15 responses of the soleus muscle to stimulation of the tibial nerve. The first record from the top is the response that occurred at about one third of the way through the stance phase. Note how the reflex increases progressively during the stance phase and that it is absent during the swing phase.

average 1.8 times during running compared to walking. The increase of activity in these two muscles at the time of HC serves to stiffen the ankle joint and thus prevent the foot from extending too quickly towards the ground after the HC. Therefore, the adaptation to the higher impact forces on the ankle at the time of HC is at the level of the command signals to the muscles rather than at the reflex level.

In Fig. 3.2 the period in the stance during which the soleus muscle is lengthening is indicated. In running the soleus undergoes a lengthening contraction during most of the stance phase. The same is true during walking (Fig. 3.3), and hence the spindle afferents will be firing at relatively high rates (Loeb, Hoffer & Pratt, 1985; Prochazka, Westerman & Ziccone, 1976). Since the presence of an H-reflex indicates that there is transmission from the Ia-afferents to the α-motoneurones during this phase of locomotion, part of the muscular activity in this phase must be due to the stretch reflex.

The peak value of the H-reflex during running was on the average significantly smaller ($p<0.05$ for a one tailed T-test) than during walking. This finding is especially noteworthy as the peak e.m.g. levels of the soleus attained during running were on the average 2.4 times greater than during walking. An example of the pattern of the H-reflex modulation

during walking, as compared to that during running in the same subject, is shown in Fig. 3.3. The peak value of the H-reflex during running in this subject was 3.8 mV and that during walking was 7.8 mV. The peak e.m.g. level of the soleus was 3.2 times larger during running than during walking.

The relation between the H-reflex p-p amplitude and the mean level of the e.m.g. at the time the reflex was elicited is shown for two subjects in Fig. 3.4. In all eight subjects the slope of the least squares fitted line was always steeper for walking data than for running. There was no significant or systematic differences in the y-intercepts. Therefore, the threshold of e.m.g. activity at which the H-reflex appears is essentially the same during walking and running. This is in marked contrast to the large change in the value of the y-intercept which occurs between standing and walking (i.e., the H-reflex is very large during quiet standing; Capaday & Stein, 1986).

It may be argued that the decreased size of the H-reflex during running is due to a saturation of the motoneurone pool, since the soleus e.m.g. was greater during running than during walking. The more motoneurones are recruited, the fewer are left to recruit, and this may explain why the H-reflex

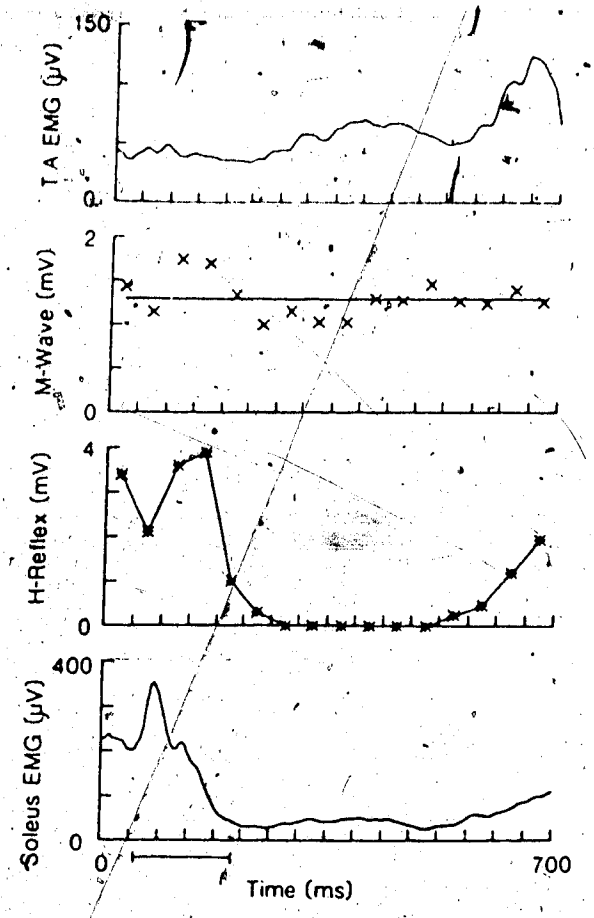

Figure 3.2: Plot of the peak to peak value (p-p) of the soleus H-reflex in each of the 16-phases of the running cycle (same data as in Fig. 3.1), as well as the corresponding average soleus and tibialis anterior e.m.g. activity (n=100 steps). The marker below the solus e.m.g. represents the period in the running cycle when this muscle is undergoing a lengthening contraction. The size of the p-p value of the M-wave in each of the 16 phases of the cycle is shown above the plot of the H-reflex vs phase. The horizontal line through the M-wave values represents the mean value (1.3 mV, SD=0.26 mV).

decreases at high levels of the e.m.g.. However, the H-reflex is reduced in size at all levels of e.m.g. (Fig. 3.4). Thus, a mechanism other than a simple saturation of the motoneurone pool is the cause of the reduction of the H-reflex during running.

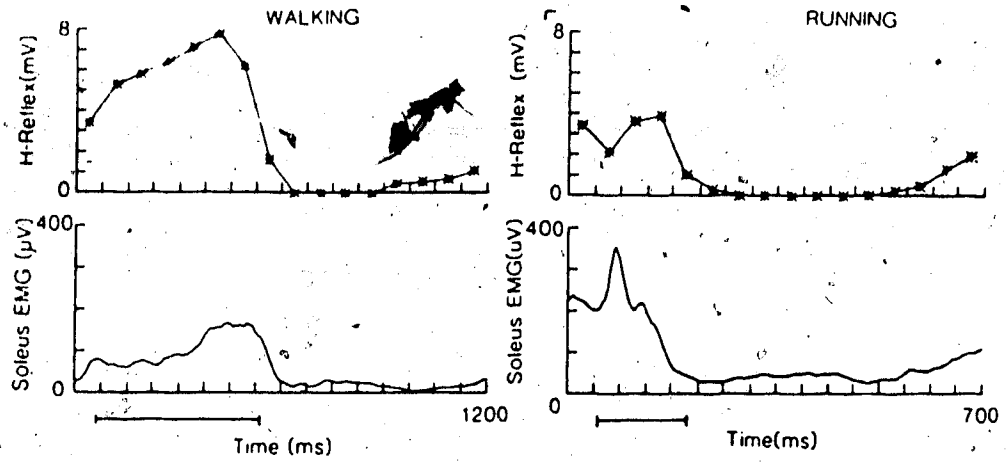

Figure 3.3: Comparison, in the same subject, of the extent (minimum to maximum) of the amplitude modulation of the soleus H-reflex during the walking and running cycles. Note that the extent of the modulation is much less during running than during walking despite the fact that the peak value of the e.m.g. is 3.2 times bigger during running than during walking. The marker below each of the average soleus e.m.g. records indicates the period in the locomotor cycle during which this muscle is lengthening.

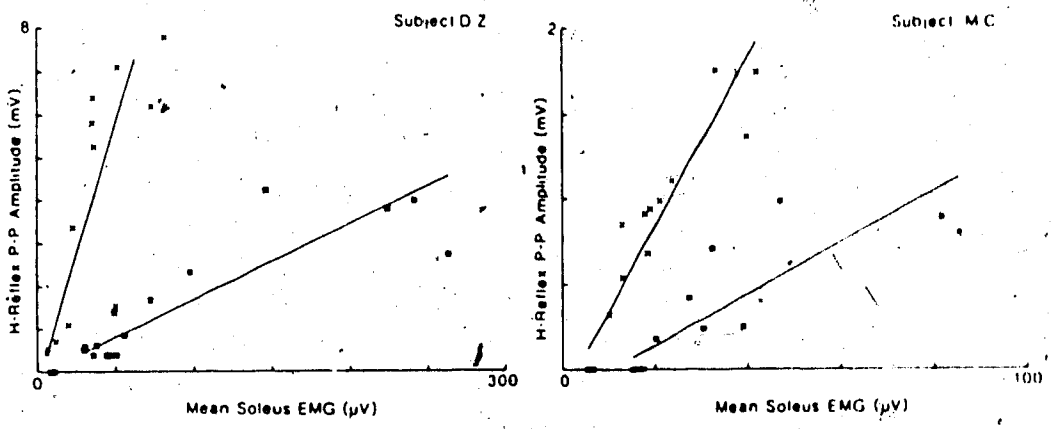

Figure 3.4: Relation between the p-p value of the H-reflex and the mean level of soleus e.m.g. activity at the time the reflex was elicited during walking (x) and running (\). The data from two different subjects are shown; subject D.Z is the one whose data are presented in Fig. 3.1, 3.2, and 3.3. The mean value of the e.m.g. at the appropriate time in the step cycle was determined from the computed average locomotor pattern.

DISCUSSION

The first new finding reported in this paper is that the H-reflex is modulated in amplitude during running. The reflex sensitivity is relatively high during the stance phase of the running cycle, when the soleus muscle is undergoing a lengthening contraction during most of that phase. Since the spindle afferents are also firing at high rates during stance in cats (Loeb et al, 1985; Prochazka et al., 1976) and presumably in man, the stretch reflex would contribute to the muscle tension required to decelerate the downward and forward motions of the body and to lift the body off the ground. The reflex is absent during the swing phase, since a high reflex sensitivity at this time would activate the soleus muscle and thus oppose the active dorsiflexion of the ankle. Thus, the pattern of modulation of this reflex is appropriate to the requirements of running.

The second new finding is that during running the soleus H-reflex was on the average less than that during walking, despite the fact that the peak e.m.g. activity was on the average 2.4 times greater during running than during walking. Moreover, there was a decrease in the slope of the least-squares line fitted to the relation between the H-reflex amplitude and the mean level of background e.m.g..

Neuronal mechanisms

What mechanism(s) can account for these observations? Evidence was presented in the Results section to support the idea that the reduction of the H-reflex size and the reflex slope (H-reflex vs e.m.g.) were not due simply to a saturation of the motoneurone pool. Alternatively, saturation may occur on the afferent side. During unrestrained locomotion in cats, the Ia-spindle afferents never discharge anywhere near their maximum possible rate (500 impulses/s or more). Typically, the peak firing levels attained are about 200 impulses/s (Loeb et al., 1985; Prochazka et al., 1976). Thus, most of these afferents should discharge an additional impulse in response to an electrical stimulus. In addition, several minutes of tonic stimulation of the Ia-fibres (e.g., 20 mins at 200 impulses/s) are required to appreciably increase their electrical threshold (Jack, 1978). Therefore, during the brief stance phase of running (600-700 ms) the electrical threshold of these fibres should not significantly increase.

Another possible mechanism was proposed by Pierrot-Deseilligny (1985), based upon experiments on the depression of H-reflexes in the triceps surae group of relaxed human subjects by paired (conditioning-test) stimuli to the soleus nerve. He proposed that during the stance phase of locomotion the Ib-afferents of the

triceps surae inhibit the stretch reflex output of this group. Such a reduction of the stretch reflex output, he argued, would allow for the ankle dorsiflexion in the stance phase to proceed unopposed by excessive stretch reflex which would otherwise occur in this group when the triceps [illegible] undergoes a lengthening contraction. However, [illegible] subjects were used in his experiments, and it remains an open question whether the state of the Ib-pathway to the motoneurones is the same at rest and during locomotion.

Computer modelling, on the other hand, allows for the systematic investigation of the factors that affect the input/output properties of the stretch reflex. We have recently analyzed by computer simulation the influences of both pre-synaptic and post-synaptic mechanisms on the size of the reflex output of a motoneurone pool (Capaday & Stein, 1987). The model contains a representation of the subthreshold behaviour of the motoneurones (integration of synaptic inputs) and the statistical distribution of the motoneurones in the pool according to their resting conductance. This feature allows for the orderly recruitment of the motoneurones in the order of low resting conductance to high resting conductance. The range and distribution of the

resting conductances fitted data obtained from cat motoneurones (Gustafsson & Pinter, 1985). Values for other motoneurone properties such as the membrane capacitance and the time constant of the after-hyperpolarization were obtained from the literature on cat motoneurones. There were some small quantitative differences depending on the assumptions we made about the distribution of excitation to the motoneurones but the results were, in all cases qualitatively similar.

The main finding from this analysis was that regardless of the post-synaptic mechanisms by which the motoneurones were depolarized, the size of the reflex output remained tied to the level of excitation of the pool. This finding was surprising to us and contrary to our initial qualitative analysis (Capaday & Stein, 1986), but was also verified by mathematical analysis (Capaday & Stein, 1987). An increase in the amount of pre-synaptic inhibition decreased the size of the reflex output at all levels of excitation, as well as the slope and y-intercept of the curve relating these two variables.

In conclusion, more complex explanations are possible involving time varying mixtures of conductances, perhaps through oligosynaptic pathways (Burke, Gandevia and Mc Keon, 1984; Pierrot-Deseilligny, 1985). However, the observed

differences in the H-reflex modulation during running and walking can be most simply accounted for by a tonic increase in the amount of pre-synaptic inhibition of the Ia terminals to the α-motoneurones during running.

Functional implications

In the stance phase of the locomotor cycle the e.m.g. activity of the soleus during running was on the average 2.4 times higher than during walking. The higher level of muscle activity and hence stiffness of the ankle muscles is required to decelerate the faster downward and forward motions of the body in a shorter period of time, as well as to push the body off the ground more rapidly. Concomitantly, there is a decrease of the slope of the H-reflex vs e.m.g. relation (Fig. 3.4). The increase of the stretch reflex, or the H-reflex, with the background activity level has been termed "automatic gain compensation" (Marsden, Merton & Morton, 1972; Matthews, 1986). That is, the gain of the reflex increases as a function of the excitation level of the motoneurone pool. It follows from our data, therefore, that the gain of the H-reflex is reduced during running compared to walking. Why should the H-reflex gain, which is a measure of the central component of the stretch reflex gain, be turned down

during running ?

At this stage no definite answer can be given, but some suggestions can be made. The stretch reflex output depends on both the extent and rate of muscle stretch (Matthews, 1970; Gottlieb & Agarwal, 1981) both of which are increased during running. Moreover, as we have suggested the stretch reflex contributes part of the motor output of the soleus during locomotion. Therefore, a decrease in the central component of the reflex gain during running (as judged from the decrease of the slope of the H-reflex vs e.m.g. curve) may be an adaptation to ensure that the net motor output does not saturate. In addition, since the stretch reflex increases the stiffness of a contracting muscle (Hoffer & Andreassen, 1981; Nichols, 1985), the increased muscle stiffness coupled with a high reflex gain and the reflex delay may lead to instability (i.e., tremor) (Stein & Lee, 1981).

In conclusion, we suggest that the stretch reflex acting as a feedback mechanism, contributes to the tension of the extensor musculature of the leg in both walking and running. However, there are advantages to reducing the central gain of the monosynaptic reflex during running, compared to walking, and a reduction does occur as indicated by the H-reflex measurements we have made.

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IV. A METHOD FOR SIMULATING THE REFLEX OUTPUT OF A MOTONEURON POOL.

Since the first intracellular recordings from spinal motoneurons (Brock et al., 1952), much has been learned about the synaptic circuits impinging on these final common pathways for motor output. Yet, such recordings have only rarely been possible in normal, behaving animals and only then in quiet states such as sleep (Glenn and Dement, 1981). To study reflex function in active animals and in human studies of both normal and pathological states, we must still rely on reflex testing, generally of whole motor pools with electrical or mechanical stimuli.

The results of these studies are often interpreted qualitatively in terms of a "circuit diagram" derived from intracellular recording studies, without much attempt to validate the predictions against some model of the neural network. One reason for this lack of validation is that single motoneurons have a complex mixture of intrinsic and synaptic currents that is far from being fully understood (Burke and Rudomin, 1977). In addition, to model the response of a motor pool,

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Journal of Neuroscience Methods 21, 91-105.

the way in which these currents vary over the entire population of motoneurons must be known, an even more formidable task.

What we would like to propose in this paper is a simple model of a motor pool, but one which catches enough of the flavor of the biological system that it may be useful to a number of individuals engaged in reflex studies in animals or humans. The model can be programmed on a sufficiently powerful microcomputer and even allows for some results of interest to be derived analytically. By way of example, we will give a few computer simulations and analytical results relevant to recent studies on the modulation of the H-reflex during locomotion in normal human subjects (Capaday and Stein, 1986, 1987).

The H-reflex is the electrical analog of the tendon jerk, and is routinely used for reflex testing. The H-reflex often changes with the excitation level of the motor pool, as assessed experimentally from the mean level of the rectified surface EMG. We will concentrate on the mechanisms that may lead to a change in the slope and y-intercept of the H-reflex vs EMG relation. Both these changes occur in going from a standing posture to walking and running (Capaday and Stein, 1986, 1987).

We also show that a change in the slope of the line relating the reflex output to the level of EMG

represents a change in the gain (in the formal sense of the output divided by the input) of the pathway from the Ia afferents to the α-motoneurons (central gain). The change in gain as well as threshold is counter to the suggestion made by several authors that only the threshold of this reflex changes (Feldman and Orlovsky, 1972; Houk, 1976).

Description of the model

The H-reflex represents the synchronous discharge of α-motoneurons to Ia-EPSP's. Only the interaction of the monosynaptic EPSP current with the combination of excitatory and inhibitory currents acting across the motoneuron membrane is considered here. Either the combination of these currents will depolarize the motoneuron to threshold, which means that the motoneuron will contribute to the reflex output, or the membrane potential will remain subthreshold and the neuron will not contribute to the reflex output.

For this purpose therefore, a classical, subthreshold model of a motoneuron is sufficient as shown in figure 4.1. It includes a resting conductance (Gr), excitatory (Ge) and inhibitory (Gi) conductances which represent in effect descending control of the motoneurons, the monosynaptic EPSP conductance (Gepsp), the fast potassium current (Gkf) which repolarizes the motoneuron after a spike (Barrett et al., 1980), and finally the afterhyperpolarization conductance (Gahp) which regulates the rate of motoneuron firing (Granit, 1972). For simplicity, we will ignore subthreshold membrane nonlinearities and the cable properties of the dendritic tree. These simplifications are justified if we consider that, in the end, it is the integration of synaptic currents at the axon hillock

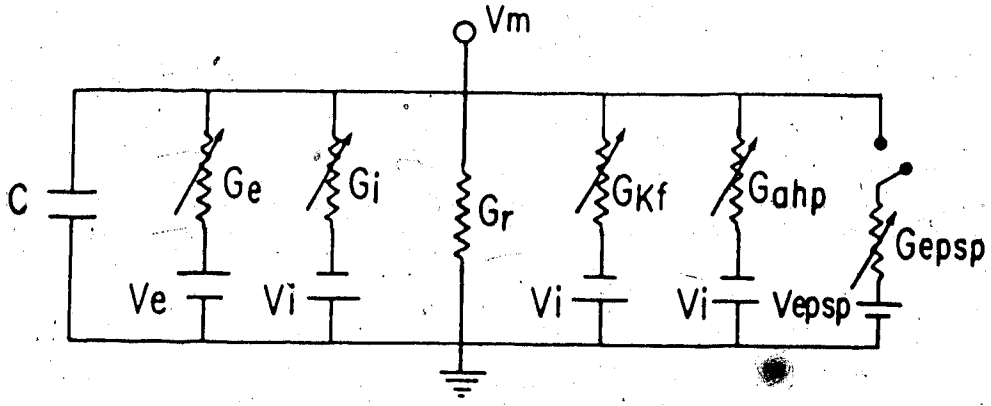

Figure 4.1: An electrical model of the subthreshold behavior of α-motoneurons. The excitatory conductance (Ge) depolarizes the motoneuron toward threshold, the inhibitory conductance (Gi) hyperpolarizes the motoneuron and the resting conductance (Gr) determines the resting membrane potential. The fast potassium current which flows through the conductance (Gkf) serves to repolarize the motoneuron after an action potential and the conductance of the after hyperpolarization (Gahp) limits the firing rate of the motoneuron. Closing the switch produces an EPSP in the motoneuron. More details are given in the text.

that matters.

Increasing the Ge conductance will depolarize the motoneuron to threshold, an increase in the Gi conductance will hyperpolarize the motoneuron, and closing the switch shown in figure 4.1 will produce an EPSP in the motoneuron. The conductance Gkf and Gahp are only activated if the membrane potential (V) reaches threshold (voltage dependence) and are time dependent, with an approximately exponential decay (Barrett et al., 1980). The total current (Itot) flowing across the membrane is given by:

$$Itot = C\,dV/dt + Ge(V-Ve) + Gi(V-Vi) + Gepsp(V-Vepsp) + Gkf(V-Vkf) + Gahp(V-Vahp) + GrV = 0 \qquad (1)$$

where: C dV/dt is the capacitative current, Ve, Vi, Vepsp, Vkf, and Vahp are the reversal potentials of the respective currents. Notice that all changes of membrane potential are referenced with respect to a resting potential of zero. Once activated the conductances Gkf and Gahp decay exponentially with respective time constants obtained from the literature on cat motoneurons (Barrett et al., 1980; Burke and Rudomin, 1977). The size of the EPSP will depend on the EPSP current and the values of all the conductances which are active:

$$EPSP = \frac{Gepsp(Vepsp-V)}{Gr+Ge+Gi+Gkf+Gahp+Gepsp} \qquad (2)$$

The range of values for the EPSP conductance was obtained from Eccles's classic book (Eccles, 1964). The range of values of the various conductances used in the computations as well as those of other parameters are listed in table 1. The membrane potential (Vm) will depend on the sum of all currents flowing across the membrane and the values of all the active conductances. If we take the reversal potential of all the inhibitory currents to be the same, then:

$$Vm = \frac{GeVe + Vi(Gi+Gkf+Gahp)}{Gr+Ge+Gi+Gkf+Gahp} \qquad (3)$$

Because of the membrane capacitance (C) the membrane potential will not change instantaneously to its steady-state value but will be a function of time given by the solution to the differential Eq. 1 which can be rewritten as:

$$\tau \frac{dV}{dt} = (Vm - V) \qquad (4)$$

where: τ=C/Gtot is the membrane time constant (Gtot=Gr+Ge+Gi+Gkf+Gahp+Gepsp) and Vm is given by Eq. 3.

The solution of Eq. 4 is composed of the sum of several exponential processes, but it cannot be obtained analytically because Gtot and hence τ are

TABLE 1

PARAMETER	VALUE
Gkf	1-2 μS
Gahp	1-2 μS
Gepsp	0.015-0.06 μS
Time constant of Gkf	3-5 ms
Time constant of Gahp	50-70 ms
Threshold (Vt)	10-12 mV
Membrane capacitance	4.2 nF
Mean value of Gr	0.69 μS
Minimum value of Gr	0.17 μS
Vi=	-70 mV
Ve=	60 mV

Table 4.1: Values of various parameters used in the computations described in the text. The mean value of the resting conductance (Gr) used was 0.69 μS. The actual statistical distribution of the resting conductances is given by equation 6, where the parameter a in that equation is equal to the minimum value of Gr given above.

changing with time. It can, however, be evaluated numerically for example by a fourth order Runge-Kutta type algorithm (Hornbeck, 1975). Once a motoneuron is active in the model it discharges repetitively as long as the excitatory drive to it is maintained (slow processes of adaptation are ignored). An EPSP induced by electrical stimulation of the muscle nerve can occur at any point along the membrane potential trajectory. If the sum of the EPSP and the value of the membrane potential at the time the EPSP occurs is large enough to reach threshold (Vt) the neuron will discharge an action potential and contribute to the reflex output. Unless the EPSP is very large the motoneuron will not fire an action potential at all times during its membrane potential trajectory.

A novel aspect of the present approach is the development of simple methods for determining the fraction of motoneurons in a pool which respond to each stimulus . To determine this fraction two points along the depolarization trajectory are important (figure 4.2A). First, the time (t1) when the sum of the membrane potential and the EPSP are just large enough to reach threshold. Second, the time (t2) when the depolarization of the membrane reaches the threshold on its own. Therefore, the proportion of the time that the motoneuron can be brought to threshold by the EPSP, or equivalently the firing

probability is given by:

$$P = \frac{t2-t1}{t2} \qquad (5)$$

If the EPSP is large enough to bring the membrane potential to threshold at its most hyperpolarized point (i.e., just after the motoneuron fired) then t1=0 and P=1; the motoneuron will always fire in response to such an EPSP. If there is no EPSP, then t1=t2 and P=0. For intermediate values of the EPSP the probability of firing in response to that EPSP will be between 0 and 1. Thus, among the motoneurons that are active (i.e., firing repetitively) only a proportion of these (Na), given by the product of P and the fraction of active motoneurons, will be discharged.

Not all motoneurons are equally excitable; in fact, Gustafson and Pinter (1985) have reported an approximately eleven fold difference in the intrinsic excitability (defined as the ratio of rheobase current to membrane capacitance) of the triceps surae motoneurons. This can be accounted for by an asymmetric distribution of resting membrane conductances (Gustafsson and Pinter, 1985). The distribution is skewed such that a large proportion of the motoneurons have a low resting conductance (high resistance) and a relatively small proportion have a

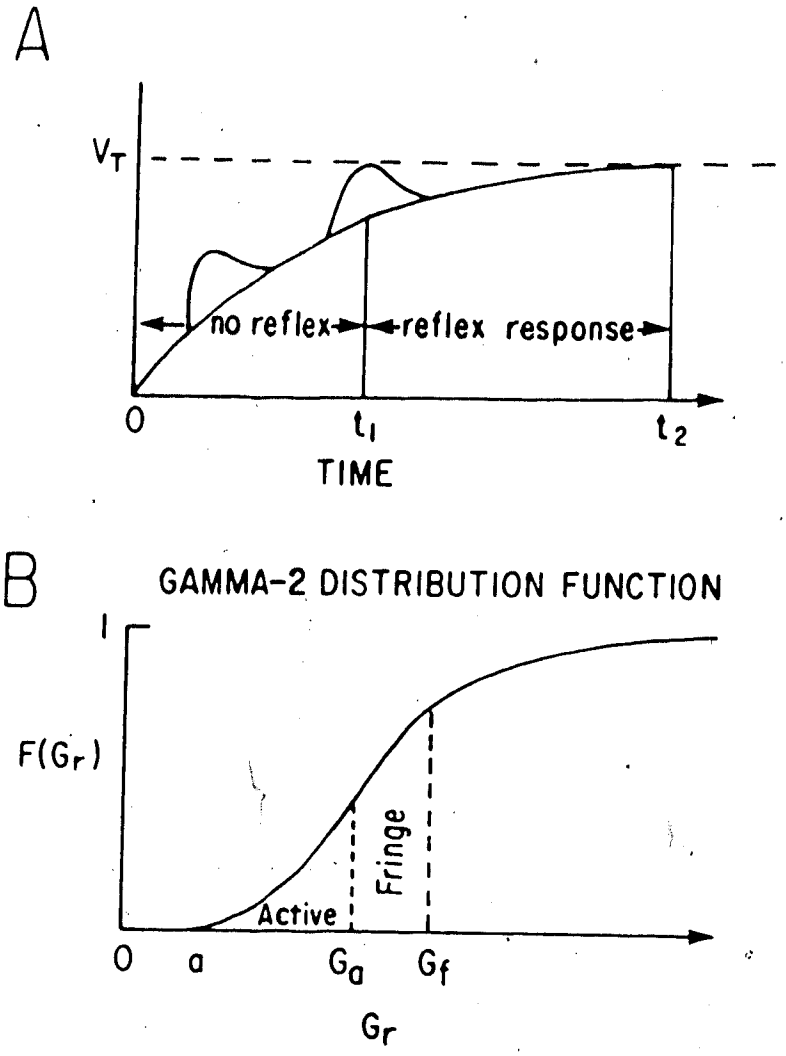

Figure 4.2: A) Schematic illustration of a motoneuron's membrane potential trajectory towards threshold showing how its probability of firing in response to an EPSP is calculated. In the interval between time zero and t1 the EPSP will not bring the membrane potential to threshold, in the interval between t1 and t2 the EPSP will make the motoneuron

fire. The firing probability is equal to the proportion of the time t2 during which the EPSP will make the motoneuron fire. B) An example of the Rayleigh distribution function with a starting value of a. Neurons with a resting conductance Gr $\leq$ Ga are active (i.e., firing repetitively). Those with a resting conductance Ga<Gr$\leq$ Gf are not active but will be reflexly recruited by the Ia-EPSP (i.e, they are in the subliminal fringe).

high resting conductance (low resistance).

Another novel aspect of our approach is inclusion of a simple probability density function consistent with the skewed experimental observations:

$$f2(Gr) = \frac{2}{b}(Gr-a)\exp[-(Gr-a)^2/b] \qquad (6)$$

This function is a Rayliegh probability density function (Peebles 1982). Note that Eq. 6 applies for Gr > a, the minimum resting conductance; the value of b is determined from the mean value of the distribution which is a+2b. This skewed statistical distribution of the motoneurons according to their resting conductance allows for their orderly recruitment in the direction of low resting conductance to high resting conductance.

The next issue to address is the distribution of the excitatory, inhibitory and EPSP conductances across the motoneuron pool. Based on the theoretical analysis of Stein and Bertoldi (1981) the EPSP conductance may be related to the square root of the motoneuron's resting membrane resistance. Very little is known about the distribution of descending excitatory and inhibitory inputs to the motoneurons. One of the few findings on this issue is that the size of the corticomotoneuronal EPSP is correlated to that of the Ia EPSP in the same motoneuron (Clough et al.,

1968). In the absence of exact information on the relations between these variables and the motoneuron's resting conductance, we made the assumption that the parameters Ge, Gi, and Gepsp are independent of the resting conductance (Gr). In other words, in the absence of detailed information, we chose the null hypothesis that all motoneurons in the pool are excited or inhibited to the same extent. These simplifying assumptions also allow for the derivation of some simple analytical relations to be presented below. Several examples where the conductances Ge, Gi, and Gepsp were made functions of Gr were also simulated. For instance, we simulated the situation were Ge is inversely related to the resting conductance Gr, Gi is directly related to Gr, and Gepsp is related to the square root of 1/Gr (i.e., the square root of the resting membrane resistance). These assumptions did not qualitatively affect the results, although small quantitative differences were found. Therefore, for simplicity, the presentation given below is based on the null hypothesis as discussed above.

The motoneurons which are active are those whose steady-state membrane potential is equal to or greater than the threshold (Vt). Using Eq. 3, this requires that the resting conductances Gr be less than or equal

to a value Ga given by:

$$Ga = [Ge(Ve-Vt)+Gi(Vi-Vt)]/Vt \qquad (7)$$

A fraction of the population will not be excited, if their Vm< Vt- EPSP. This requires that the resting conductance be greater than a value Gf where:

$$Gf = [Ge(Ve-Vt)+Gi(Vi-Vt)+Gepsp(Vepsp-Vt)]/Vt \qquad (8)$$

Thus, the motoneuron pool can be divided into three groups (Figure 4.2B): a) a fraction with $Gr \leq Ga$ will have $Vm \geq Vt$, and therefore will fire repetitively and be activated by the EPSP on a proportion of the trials given by Eq. 5, where t1 and t2 are obtained from the solution to Eqs. 2 and 4; b) a fraction with $Ga < Gr \leq Gf$ will have $Vt\text{-}EPSP \leq Vm < Vt$. They will not be firing tonically but are part of the subliminal fringe which will be discharged by the EPSP; c) and finally a fraction with $Gr > Gf$ will be subthreshold for both tonic firing and activation by the EPSP. In terms of the probability distribution function F2(Gr), which is the integral of the density function, the proportion of active motoneurons is 1 - F2(Ga), and the proportion in the fringe is given by F2(Ga) - F2(Gf).

The computations of the equations described above were done on a PDP 11/34 computer by a program written in the DESCTOP system simulation language (Korn,

1985). The simulation package is also available for IBM compatible PC's. The program can be obtained from the authors on request.

Results

Some simulated results using the model descibed above and suitable values obtained from the literature for cat motoneurons are shown in figure 4.3. At rest (no external excitatory or inhibitory inputs) a small reflex response is elicited. As the level of excitatory input is increased, the reflex response is increased even before any overt activity of the motoneurons is observed, reminiscent of the well known Jendrassik manoeuvre. Also shown in figure 4.3 are the effects of adding a constant postsynaptic inhibition and increasing the amount of presynaptic inhibition (decreasing the Gepsp). The postsynaptic inhibition shifts the curve to the right, without much change in its form, so that more excitation is required to obtain the same reflex output, whereas the presynaptic inhibition reduces the reflex at all levels of the excitatory conductance.

Notice also that, as the level of excitatory input increases, the number of reflexly recruited motoneurons increases to a maximum and then begins to decrease. The reason for this is shown in figure 4.4 where the number of reflexly recruited motoneurons is plotted against the number of active motoneurons. The number of active motoneurons is used as the x-axis because in many experimental situations the level of excitatory drive is not known and one can only relate

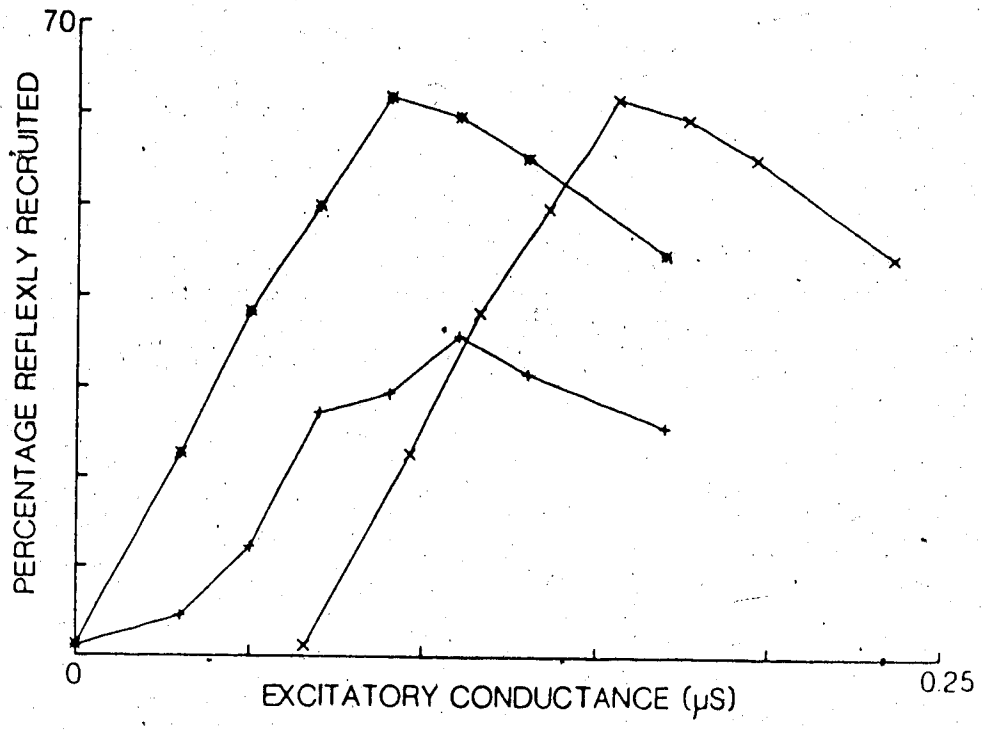

Figure 4.3: Relation between the excitatory conductance Ge and the percentage of reflexly recruited motoneurons. The EPSP conductance was 0.04 μS for the curves marked with the symbols (X) and (*), and 0.02 μS for the curve marked with (+). The rightmost curve represents the reflex response when the inhibitory conductance Gi was increased to 0.2 μS. The most excitable motoneurons begin to discharge when Ge is equal to 0.03 μS in the absence of post-synaptic inhibition and at 0.09 μS in its presence.

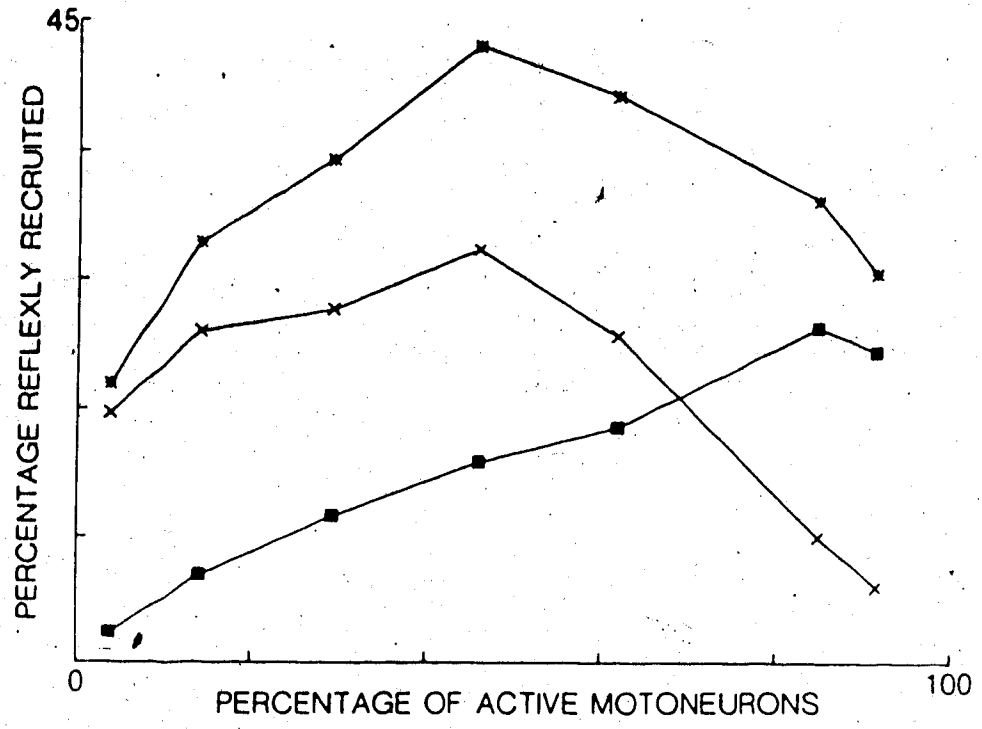

Figure 4.4: Relation between the percentage of active motoneurons (the excitation level of the motoneuron pool) and the percentage of reflexly recruited motoneurons. The topmost curve represents the total proportion of motoneurons reflexly recruited and is the sum of the two curves below it. The curve marked with the symbol (X) represents the contribution of motoneurons in the subliminal fringe, that marked with (*) represents the contribution of the motoneurons that are both active and reflexly recruited by the Ia-EPSP (Gepsp=0.04 μS).

the reflex to the mean level of EMG activity, which is related to the number of active motoneurons. When there is activity in the motoneuron pool the total number of reflexly recruited motoneurons is the sum of the motoneurons which are reflexly recruited and active (Na), as well as those that are in the subliminal fringe (Nf) (i.e., inactive but reflexly recruited). It can be seen in figure 4.4 that the number of motoneurons that are active and reflexly recruited increases over most of the excitation level of the pool, whereas the number in the subliminal fringe increases over the first fifty percent of the excitation level and decreases thereafter. Since the number of motoneurons in the fringe decreases faster than the number that are active and reflexly recruited increases, the total number decreases. Two factors contribute to the decrease of the subliminal fringe. First, as the excitation level increases, fewer motoneurons are available to be recruited and second, the EPSP is increasingly shunted by the excitatory conductance and the large resting conductance of the remaining motoneurons.

When the EPSP is small the reflex output increases over a much greater range of the motoneuron pool excitation level than when it is large (Figure 4.5). This is due to the way the subliminal fringe motoneurons are recruited by the EPSP. As the size of

the EPSP increases, the contribution of the subliminal fringe motoneurons reaches a maximum at a relatively lower excitation level than when the EPSP is smaller (Figure 4.5) and declines rapidly thereafter. Thus, a large EPSP recruits, initially, a very large proportion of motoneurons, and as the excitation level increases fewer motoneurons are left in the subliminal fringe. Note that the contribution of the motoneurons that are active and reflexly recruited increases over essentially the whole range of the excitation level in each case (Figure 4.5).

In plotting the percentage of motoneurons excited by the EPSP all neurons are given equal weight, whereas those with larger resting conductances produce larger amounts of EMG and tension. The simplest weighting is to scale the contribution of a neuron to the reflex according to its resting conductance. This is justified if we assume that a mixed muscle has an approximately ten-fold range of motoneuron resting conductances (Gustafsson and Pinter, 1985; Kernell, 1966) and that the range of motor unit potentials in such a muscle is also ten-fold (Milner-Brown and Stein, 1975).

The effects of various combinations of postsynaptic excitation and inhibition and of presynaptic inhibition on the weighted reflex output are shown in

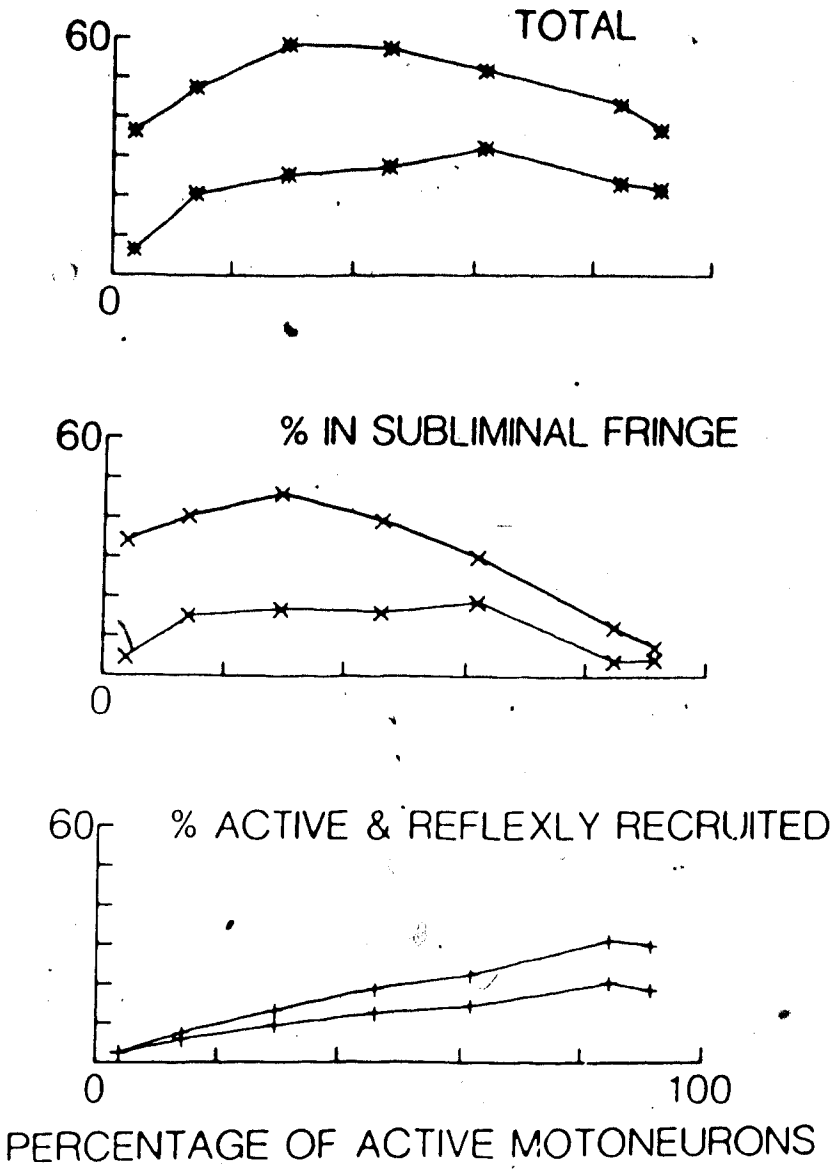

Figure 4.5: Dependence of the percentage of motoneurons reflexly recruited on the size of the EPSP. The total percentage of motoneurons reflexly recruited is plotted in the topmost graph. The contribution of those in the subliminal fringe and those that are active and reflexly recruited are shown

respectively in each of the two lower graphs. The topmost plot of each pair represents the respective response when the Gepsp was 0.06 μS and that of the lower plot when the Gepsp was 0.03 μS. Note that the proportion of the active and reflexly recruited motoneurons (+) increases over essentially the whole range of excitation level, whereas the proportion in the subliminal fringe (X) and hence the total recruited (*) begin to decrease at a much lower level of the excitation level when the EPSP is large.

figure 4.6. In one case the motoneurons were depolarized by increasing the excitatory conductance and setting the inhibitory conductance to zero. In the second case, the motoneurons were depolarized by increasing the excitatory conductance and setting the inhibitory conductance to a constant value. This was done to determine whether the effects of postsynaptic inhibition could be distinguished from those of presynaptic inhibition. Finally, the situation in which motoneurons are depolarized by an increase of the excitatory conductance and a reduction of the inhibitory conductance such that the total membrane conductance remains approximately constant was also simulated. This mechanism of motoneuron depolarization was reported to occur during fictive locomotion in the cat (Shefchyk, et al. 1984). Since the total membrane conductance remains approximately constant, the EPSP is not shunted by the increasing excitatory conductance. Regardless of the particular combination of Ge and Gi used to depolarize the motoneurons, the size of the reflex remains essentially tied to the excitation level (figure 4.6). This is because each of the two subgroups (those active and recruited and those in the subliminal fringe) remain tied to the excitation level. The basis for this result can be shown analytically, and may have been anticipated from figure 4.3. First, the

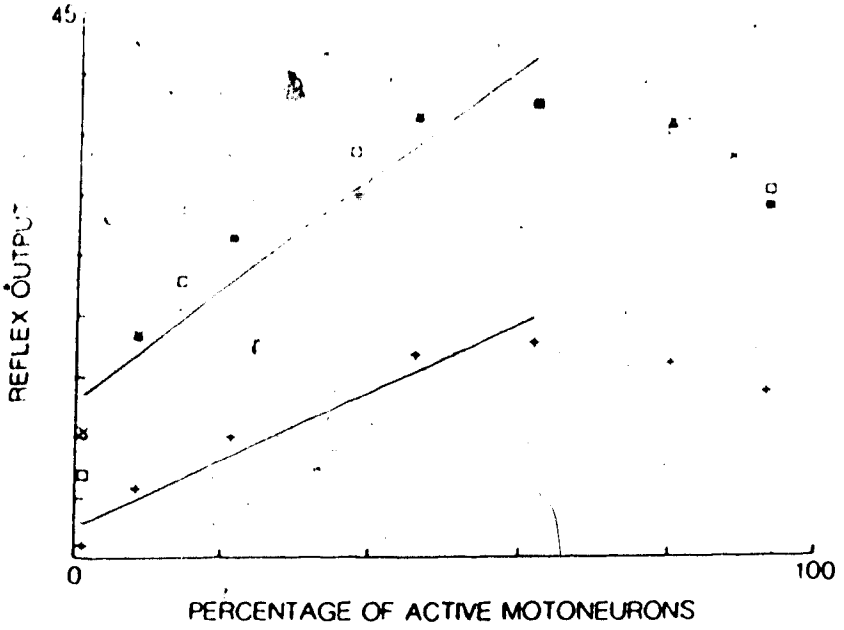

Figure 4.6: Size of the reflex output (in arbitrary units) as a function of the number of active motoneurons in four different conditions. The topmost points represent the response when the motoneurons were depolarized by: 1) an increase of the excitatory conductance (Gi=0) ( ), 2) by an increase in the excitatory conductance with a constant amount of inhibitory conductance (Gi=0.2 μS) acting on the motoneurons (X), and finally 3) by an increase of the excitatory conductance and a removal of an equal amount of inhibitory conductance ( ). The lowermost points represent the reflex response when the Gepsp was reduced from 0.04 μS to 0.02 μS. The straight lines were fitted to the points on the increasing portion of the reflex output.

proportion of motoneurons that are active and reflexly recruited is considered.

Clearly, if the inhibitory current is increased, the excitatory current must also be increased by the same amount if the membrane potential is to reach threshold. At the threshold potential the added inhibitory current will be equal to:

$$\Delta Ii = Gi(Vi-Vt)$$

and the excitatory current must therefore be increased by an amount:

$$\Delta Ie = Ge(Ve-Vt)$$

Because the sum of the two must be zero, it therefore follows that:

$$\frac{\Delta Ge}{\Delta Gi} = \frac{(Vt-Vi)}{(Ve-Vt)} \qquad (9)$$

Since the Vt, Ve, Vi are constants, the amount by which the Ge must be increased is a constant proportion of the increase in Gi and is independent of the motoneurons's resting conductance. The consequence of Eq. 9 is that the added inhibitory current is exactly counteracted by an increase of the excitatory current. This has the effect of keeping the firing probability of a motoneuron the same regardless of the combination of Ge and Gi acting across its membrane. It can also be verified that by increasing the inhibitory conductance by an amount ΔGi

and the excitatory conductance by an amount KΔGi in Eq. 7 (where K is equal to the expression on the right hand side of Eq. 9), the value of Ga and hence the proportion of active motoneurons does not change. Since neither the probabilities of firing of the active motoneurons nor their number changes, the proportion of motoneurons that are active and reflexly recruited must remain the same.

The number of motoneurons in the subliminal fringe is also tied to excitation level for the following reason. The motoneurons in the subliminal fringe are those whose resting conductance is $Ga < Gr \leq Gf$. From Eqs. 7 and 8 it follows that Gf is given by:

$$Gf = Ga + Gepsp(Vepsp-Vt)/Vt \qquad (10)$$

Thus, the extent of the subliminal fringe depends only on the EPSP conductance and the excitation level and is independent of the particular mixture of excitatory and inhibitory conductances used to reach that level. The EPSP conductance also determines the probability of firing of a motoneuron and hence the number of reflexly recruited motoneurons that are active. Therefore, presynaptic inhibition, by decreasing the size of the EPSP, decreases the size of the reflex at all excitation levels as well as the steepness and y-intercept of the relation between reflex output and excitation level, as shown in figure 4.6.

Note that Eq. 10 applies only when the excitation level is above zero (i.e, there are some active motoneurons in the pool). If the excitation level is zero, then the extent of the subliminal fringe is given by Eq. 8. This equation incorporates the intuitive notions that the size of the reflex output of a quiescent motoneuron pool is directly related to how close the motoneurons are to threshold and on the size of the EPSP.

Discussion

The simulations have revealed that the size of the monosynaptic reflex (H-reflex, or short latency stretch-reflex) depends only on the excitation level of the motoneuron pool (i.e., the number of active motoneurons) and is independent of the way the motoneurons are depolarized by post synaptic mechanisms. This result was also demonstrated analytically.

The H-reflex is relatively independent of peripheral effects, such as the level of fusimotor drive to the muscle spindles. It thus reflects the state of the central component of the stretch-reflex, namely the effectiveness of the synaptic transmission from the Ia-afferents to the α-motoneurons. The theoretical importance of the H-reflex vs EMG curves is that a change in the slope of this relation is due to a change in the gain of the pathway from the Ia-afferents to the motoneurons (central gain). Hence, it is important to determine the possible neural mechanisms that can alter the central gain of the monosynaptic reflex.

The H-reflex is a linearly increasing function of the background EMG for a fixed stimulus strength (Gottlieb and Agarwal, 1971, 1979; Capaday and Stein 1986). This has been termed "automatic gain compensation" which means that the gain of the reflex

increases with the excitation level of the motoneuron pool (Marsden et al., 1972; Matthews 1986). The term "automatic gain compensation" was introduced to explain why for a fixed stimulus strength the reflex increases with the excitation level. At each level of motor activity the gain of the monosynaptic reflex is different, hence the size of the reflex changes with the excitation level of the motoneuron pool. We have shown that the basis for this may be a recruitment of progressively larger motor units rather than an increase of the number of motoneurons recruited (Figure 4.4) and this conclusion is consistent with the experimental observations of Harrison and Taylor (1981) on cat triceps surae motoneurons. Suppose that H-reflexes are obtained in two different tasks in the same subject. If these are plotted against the bacground EMG and fall on lines of different slope, it must be due to a change in the gains between the two tasks. Therefore, a change in the slope of the H-reflex vs EMG curve is due to a change in the central gain(s) of the monosynaptic reflex.

It was shown in this paper that presynaptic inhibition can change both the slope and y-intercept of this relation. Presynaptic inhibition is therefore a possible mechanism for changing the central gain of

the monosynaptic reflex. It was also shown that post-synaptic factors do not markedly affect the relation between these two variables (figure 4.6). The curve parameters are essentially independent of the particular mixture of excitatory and inhibitory conductances acting on the motoneurons. This gives a rationale for the existence of presynaptic inhibition in a monosynaptic pathway. In the absence of an interposed interneuron the reflex input-output properties of a motoneuron pool are tied to its excitation level and therefore are not independently controllable.

These observations may also be used to explain, for example, our recent findings of changes in the relationship between the H-reflex and the EMG in going from the standing posture to walking and running (Capaday and Stein, 1986; Capaday and Stein 1987). The very large value of the y-intercept during standing means functionally that forward body sway during quiet standing will be opposed by a relatively large reflex output. This must be due to a large EPSP resulting from a removal of, either, or both, presynaptic and postsynaptic inhibition. Moreover, the very large EPSP would saturate the reflex output at a low level of motoneuron pool activity and thus produce a relatively flat relation between reflex output and EMG activity which is observed

experimentally.

The zero or slightly negative values of the y-intercept observed during walking and running are due to strong hyperpolarization of the motoneurons during their "off" phase (zero activity), possibly in conjunction with increased presynaptic inhibition at zero and low levels of activity. As both of these inhibitory influences are removed during the active phase of motoneuronal activity in walking, a relatively steep relation between reflex output and EMG would result, again as observed experimentally. Finally, the difference between walking and running is largely a difference in the central gain of this reflex (Capaday and Stein, 1987). According to the present analysis, the lower gain during running could only result from an increase in presynaptic inhibition.

These examples illustrate the utility of the present approach in understanding the mechanisms underlying changes in reflex characteristics during functional motor tasks. The method should be applicable to a variety of such studies and can be used to design invasive animal experiments to verify the predicted mechanisms.

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V. RECIPROCAL INHIBITION OF SOLEUS MOTOR OUTPUT IN HUMANS DURING WALKING AND VOLUNTARY TONIC ACTIVITY

In contrast to the many studies of autogenic excitatory reflexes from group Ia afferents in humans, the corresponding inhibitory reflexes from these afferents to antagonist α-motoneurones have been studied far less. The most widely held view, based on H-reflex studies, is that the inhibition mediated by Ia inhibitory interneurones decreases when the motoneurone pool is active and increases when the antagonist motoneurone pool is active (e.g., Shindo, Harayama, Kondo, Yanagisawa & Tanaka, 1984; Cavallari, Fournier, Katz, Pierrot-Deseilligny & Shindo, 1984; Day, Marsden, Obeso & Rothwell, 1984). These alterations in the efficacy of inhibitory action are attributed to a parallel convergence of descending inputs onto Ia inhibitory interneurones and α-motoneurones, as reviewed by Lundberg (1966; 1970). When antagonist motoneurones are activated by higher centres, the inhibitory transmission via Ia inhibitory interneurones may also be potentiated (Tanaka, 1974). When agonist motoneurones are activated (and antagonists are inhibited), transmission from the

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antagonist Ia inhibitory interneurones may be depressed (Shindo et al., 1984, Cavallari et al., 1984; Day et al., 1984).

However, Crone, Hultborn and Jespersen (1985) and Iles (1986), in recent H-reflex studies of the human ankle musculature, failed to confirm an increase in the potency of Ia inhibition acting upon the extensor (soleus) during progressively more forceful flexor (tibialis anterior) contractions. In part, these discrepancies between the various investigations may be due to differences in the details of applying the H-reflex methodology. In particular, small test reflexes are more prone to inhibition than larger test reflexes (Crone et al., 1985; see also Mazières, Morin, & Pierrot-Deseilligny, 1984; Meinck, 1980). Thus, a failure to maintain the same test reflex amplitude throughout the range of muscle activity investigated may lead to erroneous conclusions (Crone et al., 1985).

A more basic difficulty concerns the propriety of the technique itself for quantitative measurements of inhibitory action. The H-reflex represents the synchronous discharge of α-motoneurones in response to a very large e.p.s.p. induced by the electrical stimulation of Ia afferents in the muscle nerve. Summation of small or moderately sized i.p.s.p.s resulting from stimulation of Ia afferents in the

antagonist nerve may be incapable of significantly shunting the very large e.p.s.p.s and so preventing depolarization of the membrane to threshold. Therefore, inhibitory action on motoneurones may go undetected when it is measured by its effect in reducing a large synchronous discharge.

The present investigation attempts to advance current understanding of segmental reciprocal inhibition in the extensor musculature of the human ankle in two main respects. Firstly, we have reappraised the relation between the amount of inhibition and the amount of tonic voluntary motor activity in the inhibited muscle by modifying a technique used by Agarwal & Gottlieb (1972). An inhibitory pulse in the form of an i.p.s.p. may not be capable of shunting a large e.p.s.p. sufficiently to prevent the membrane from depolarizing to threshold, but it will delay the interspike interval of a tonically firing α motoneurone. This can be seen as a depresssion in the peri-stimulus time histograms (PSTH) of single motor units (Kudina, 1980; Ashby & LaBelle, 1977). Similarly, the inhibition will also produce a depression in the mean rectified e.m.g. activity which represents a weighted average PSTH of all discharging motor units. The method, therefore, has the merit of assessing inhibition by its effect in

decreasing naturally occurring, asynchronous motor output.

Secondly, we compared the extent of reciprocal inhibition, measured as described above during voluntary tonic activity, to that during locomotion in the same subject. This was done to determine whether there was a task-dependent modulation of the transmission efficacy of Ia inhibitory interneurones. Such a task-dependent modulation of the autogenic Ia excitatory reflex on soleus motoneurones has recently been shown (Gladay & Stein, 1986, 1987). Specifically, the characteristics of this reflex (threshold and gain) vary systematically in going from standing to walking and running.

METHODS

The experiments reported in this paper were done on 11 normal human subjects ranging in age between 21 and 47 years. All subjects gave their consent after being fully informed of the purpose and procedures of the experiments.

Experimental procedures

Reciprocal inhibition of the ankle extensor muscle, soleus, elicited by electrical stimulation of the common peroneal nerve was investigated at several levels of voluntary tonic contraction and throughout the stance phase of walking. For the tonic contractions subjects stood upright and exerted a maintained plantar flexion torque with their right foot upon a wooden block (3.5 cm high) placed beneath the foot. An analog voltmeter, calibrated so that a full scale deflection of the needle corresponded to the subject's maximum voluntary soleus e.m.g. (high pass filtered 10 Hz, rectified, low pass filtered 20 Hz), provided visual feedback of the level of soleus activity (activation level). During each test the subjects were instructed to maintain a given percentage (up to 80%) of their maximum e.m.g. for a period of about 20 s during which 25 stimuli were applied to the common peroneal nerve in a pseudorandom sequence.

Similarly, inhibition of the soleus muscle during the stance phase of walking (i.e., the phase of the walking cycle during which if is active) was investigated by applying stimuli to the common peroneal nerve in a pseudorandom sequence throughout the locomotor cycle. The subjects walked on a treadmill at a speed of 4 km/h. The average step cycle time was 1100 ms, of which the stance phase comprised about 600 ms. In all cases the locomotor task was studied first followed by the tonic activation task. This allowed the experimenter to determine the range of activation levels of the soleus during the locomotor task. The subject was then asked to approximately reproduce these levels in the tonic activation task. Furthermore, the same effective stimulus strength (see below) could be used during the tonic activation task as during the locomotor task.

E.m.g. recordings

Bipolar e.m.g. recordings were obtained from fine stainless steel wires, each inserted with appropriate aseptic precautions into the soleus muscle by a hypodermic needle. The wires were multistranded, teflon coated, and bared at their tip for about 2-3 mm. Such intramuscular electrodes were used to minimize the pick-up of the very large and broad M-wave of the ankle flexors and foot everters produced

by stimulation of the common peroneal nerve. This method of recording also minimized contamination of on-going soleus e.m.g. activity by that from other nearby ankle extensors such as gastrocnemius. In addition, bipolar recordings were obtained from surface Ag-AgCl disc electrodes (diameter 0.7 cm) placed over the soleus and tibialis anterior (ankle flexor) muscles.

Electrical stimulation

Electrical stimuli were applied to the common peroneal nerve by a surface disc electrode of the same type as that used for surface e.m.g. recordings. The electrode was placed near the head of the fibula, attached to the skin with adhesive tape, and secured by an elastic rubber strap around the leg. The stimulus return electrode, which consisted of a large metal plate covered by gauze and wetted by saline, was attached just below the knee by a rubber strap. Stimulus pulses were 1 ms in duration and delivered in both tasks in an equiprobable pseudorandom sequence with a minimum interstimulus interval of 0.4 s and a maximum of 2 s.

M-waves were recorded over the tibialis anterior (t.a.) and were used as a measure of effective stimulus strength. The M-wave threshold was determined in the quietly standing subject and a value close to

1.5 times motor threshold (m.t.) was used in both the locomotor task and the tonic activation task. In many subjects a stimulus of this strength produced a M-wave of approximately constant amplitude throughout the stance phase of locomotion. This is in marked contrast to stimulation of the tibial nerve in the popliteal fossa during locomotion (see Capaday & Stein, 1986; 1987) where the effective stimulus strength varies widely throughout the locomotor cycle as the distance between the stimulating electrode and the tibial nerve changes with the large angular displacements at the knee.

In those subjects in which there was more than a 20% variation of the M-wave at a fixed stimulus strength the experiment was repeated at several stimulus intensities (up to 2 x m.t.). The records of soleus inhibition at various times during the stance phase could then be compared using trials that produced nearly equal t.a. M-waves.

Data analysis

During the tonic activation task, the effects of the stimuli applied to the common peroneal nerve were determined by averaging (Digital Equipment Co. PDP 11/40 computer) the high-pass (10 Hz) filtered, rectified, and low-pass filtered (100 Hz) intramuscular e.m.g. responses (n = 25) of the soleus.

The total duration of each average was 150 ms including a pre-stimulus period of 50 ms. This pre-stimulus (background) period was used to calculate the average level of e.m.g. activity preceding the inhibitory stimulus. To quantify the effects of the stimulus at each of the tonic activation levels used, the mean level of the depression in the e.m.g. over an interval determined by visual inspection of each record (Fig. 5.1) was computed. The inhibition was measured as the difference between the mean background level and the mean level of the depression (referred to as the mean amount of inhibition). The inhibition was then plotted vs the background activity level. A similar method of measurement was used by Matthews (1986) to study the inhibitory effects of vibrating the triceps on voluntary motor activity in the biceps.

The data was processed on-line for two purposes. Firstly, to determine the t.a. M-wave in various phases of the step cycle, the step cycle was divided into 16 parts, each about 70 ms in duration. The computer used the latency between the step marker and the stimulus marker to determine in which of these 16 phases of the step cycle the stimulus occurred. Responses which occurred in the same phase were averaged together. Secondly, the same method was used to obtain the responses of the soleus to stimulation

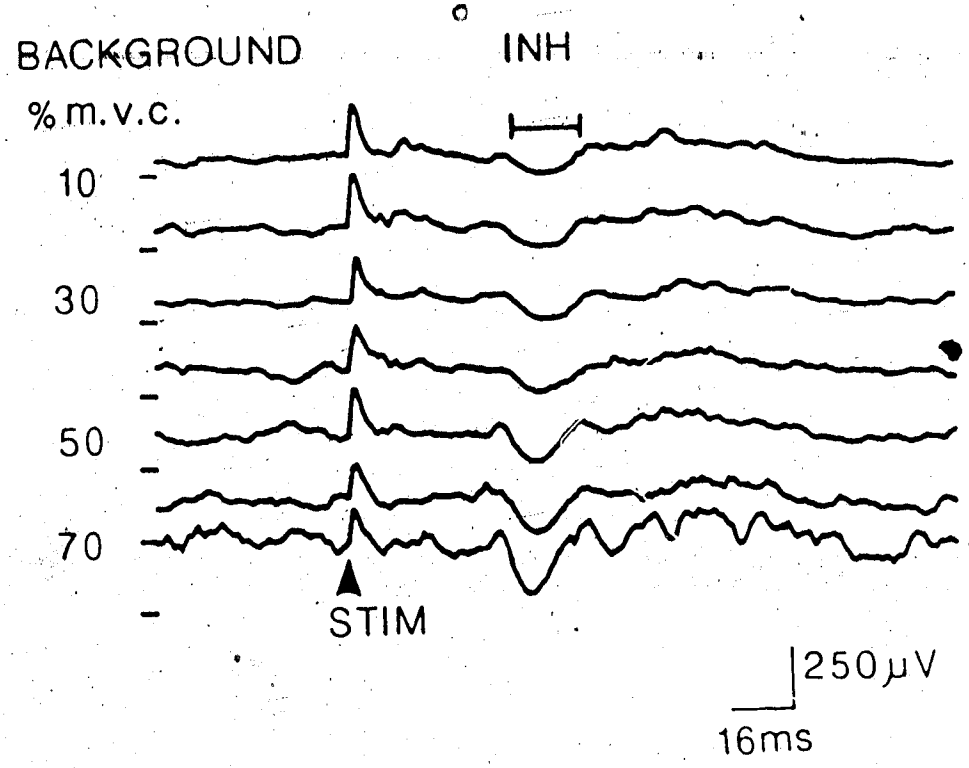

Fig. 5.1. Inhibition of tonic voluntary e.m.g activity in soleus by a stimulus of 1.5 x m.t. to the common peroneal nerve. The e.m.g. activity was rectified, filtered and averaged (n = 25) as described in the Methods. The strength of contractions increases from top to bottom. The contraction strengths, as indicated, varied from appproximately 10 to 70% of the maximum voluntary contraction (m.v.c.). respectively. The short dash at the left of each record represents the zero DC level of the record above it. The mean level of activity in the background period prior to the stimulus artefact was compared to the mean level during the period of inhibition indicated by the bar.

of the common peroneal nerve at various phases of the step cycle. Further details of the method of "phase dependent" averaging can be found in previous publications from this laboratory (Akazawa, Aldridge, Steeves & Stein, 1982; Capaday & Stein, 1986; 1987). The on-line facility allowed the experimenter to determine 1) if the stimulus strength initially chosen was producing comparable M-waves throughout the step cycle, or if adjustments were necessary in certain phases and 2) if the stimulus to the common peroneal nerve was producing inhibition of the soleus during the various phases of the step cycle (i.e., whether the stimulus was sufficiently strong or properly located over the nerve).

The data obtained during walking (soleus and tibialis anterior e.m.g.s as well as the step marker and stimulus marker) were also recorded on FM magnetic tape for off-line analysis. The tape-recorded data was used, when necessary, to check the on-line analysis and to obtain a measure of the average e.m.g. patterns during unperturbed step cycles. The computer selected and averaged step cycles in which no stimulus occurred to provide a representative measure of the patterns during the unperturbed step cycles of an experimental trial which typically lasted about 6 - 7 min.

RESULTS

Inhibition of tonic soleus activity

Stimulation of the common peroneal nerve inhibited soleus e.m.g. activity at all levels of voluntary activation tested (Fig. 5.1). The records are from one subject and are arranged in order of increasing activation level from top to bottom. The amount of inhibition, measured from the mean value of the depression in the rectified and filtered e.m.g., always increased in proportion to the activation level (Fig. 5.2). In the 11 subjects studied the linear product-moment correlation coefficient (r) between the amount of inhibition and the background activation level was at least 0.9. The inhibitory phenomenon always began at nearly the same latency as the H-reflex in the same muscle, which is strong evidence that it is of segmental origin. The simplest interpretation is that it represents the classic reciprocal inhibition (Eccles, Fatt & Landgren, 1956) mediated by Ia inhibitory interneurones, although later parts of the inhibition may be mediated by other inhibitory pathways containing more synaptic relays.

The inhibition in Fig. 5.2 decreased the e.m.g. activity by about 35% on average. The peak value of the inhibition is also plotted in Fig. 5.2 (X's) against the background e.m.g. level. The slope of the

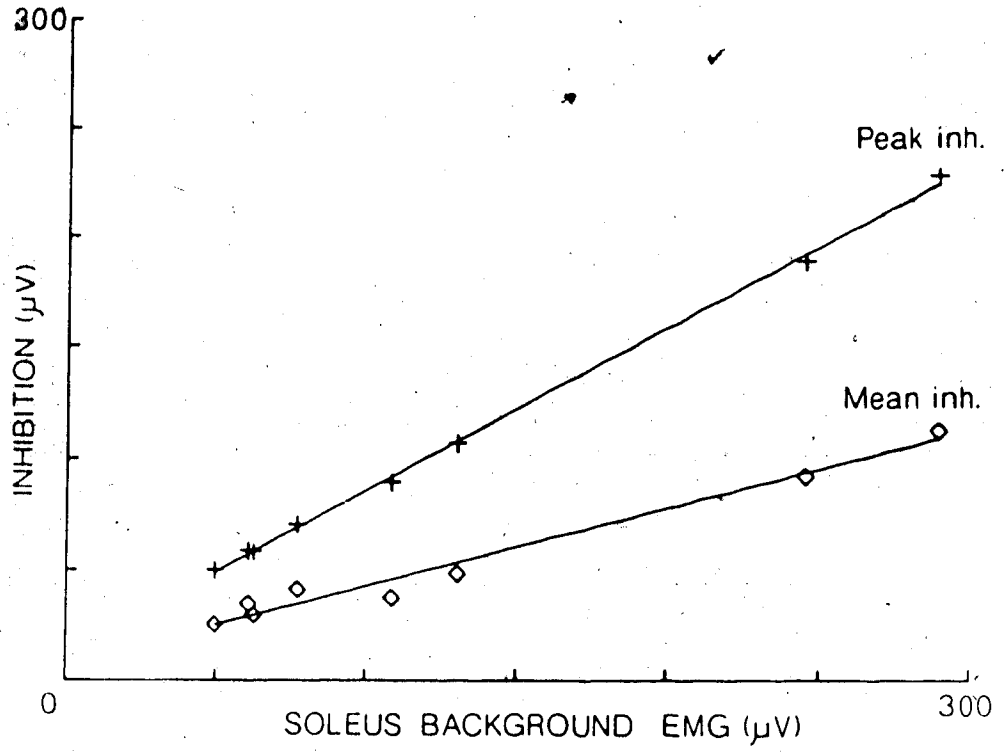

Fig. 5.2. Relation between the amount of inhibition and the background activation level, as measured by the mean value of the rectified and filtered e.m.g. Both the mean decrease in the e.m.g. (diamonds) during the inhibitory' period (see Fig. 1) and the peak decrease (X) are plotted against the background e.m.g. level. The slopes of the lines were 0.35 and 0.73 and the linear regression coefficients were r= 0.99. Thus, transiently nearly 3/4 of the on-going activity ceased and was delayed for approximately 20 ms.

least-squares fitted line is nearly 0.75. These results clearly show that the large majority (up to 75%) of the discharging motor units can be momentarily inhibited (i.e., their firing time is delayed) at all levels of motor activity. Thus, the inhibitory pathway to the soleus α-motoneurone pool is not turned off as the activity in the pool increases.

Inhibition of soleus activity during walking

Stimulation of the common peroneal nerve produced inhibition of the soleus muscle at all times in the stance phase of the walking cycle (Fig. 5.3). The e.m.g. pattern of the soleus during walking (Fig. 5.4A) consists of a ramp-like increase of activity following heel contact (h.c. in Fig. 5.4E), reaching a maximum just before the heel comes off the ground (h.o.), and then ceasing abruptly just before the toe leaves the ground (t.o.). Therefore, the e.m.g. activity of the soleus increases throughout most of the stance phase of walking.

Moreover, as can be seen in Fig. 5.4B, the amount of inhibition increases from the beginning to the end of stance, even though the M-wave is quite constant (Fig. 5.4C). As in the tonic activation task, a strong linear correlation is observed between the amount of inhibition and the mean value of the e.m.g. at the time in the step cycle when the inhibitory stimulus

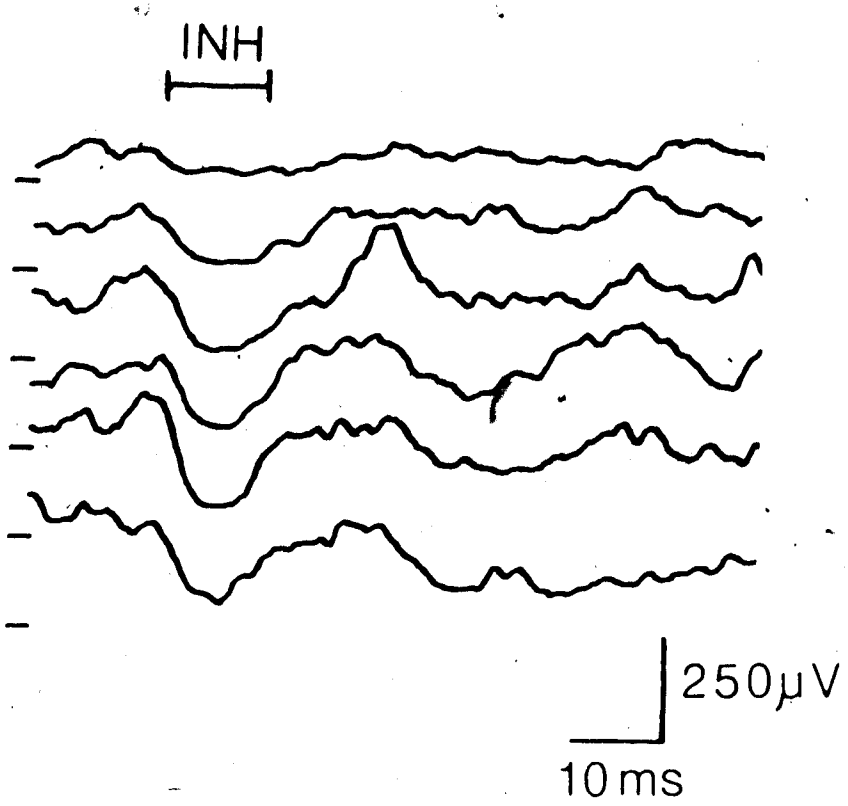

Fig. 5.3. Inhibition of soleus motor output at various times in the stance phase of walking. The top record was obtained from stimuli applied between 157 and 235 ms following heel contact and the ones below it at progressively later times in the stance phase. In this subject the M-wave of the ankle flexors and everters produced an artefact in the soleus record, so the sampling was delayed to eliminate the artefact. After correcting for the delay the inhibition occurred from 38 - 50 ms following the stimulus, as indicated by the bar.

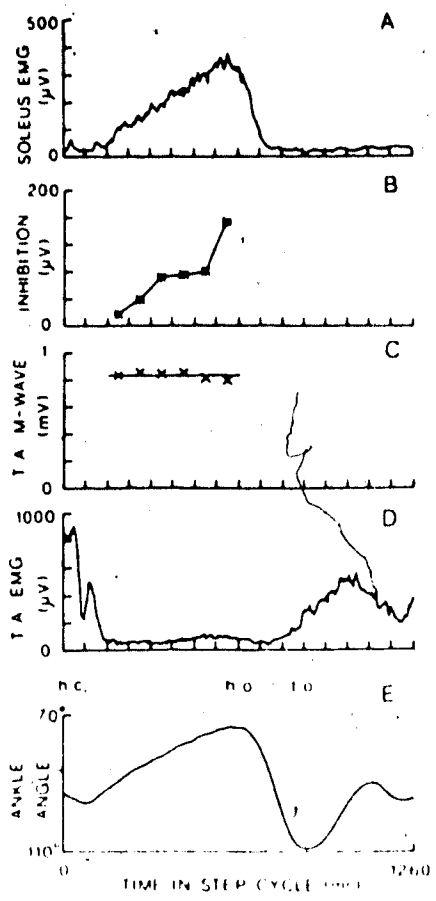

Fig. 5.4. As the soleus e.m.g. activity increases during the step cycle (A), so too does the inhibition (B) from stimulating the common peroneal nerve, even though the M-wave (C) elicited by the stimulus in the tibialis anterior (t.a.) does not change. From the e.m.g. pattern in (D) the inhibition of soleus clearly occurs when the t.a. muscle is essentially inactive. Finally, the changes in angle ankle (E) are shown together with an indication of when the heel contacts the ground (h.c.), when it comes off the ground (h.o.) and when the toe comes off the ground (t.o.) to end the stance phase.

occurred (Fig. 5.5). One can also directly compare the amount of inhibition during walking (*) and during tonic activity (X) in the same subject. The slopes of the two regression lines were not significantly different, indicating that the transmission efficacy of Ia inhibitory interneurones mediating the inhibition was essentially the same in the two tasks.

Two other points are evident from Fig. 5.4. Firstly, the e.m.g. pattern of tibialis anterior (t.a.) consists of two bursts of activity: one burst occcurs at the time of h.c. and serves to stiffen the ankle, while the other burst occurs just after t.o. and dorsiflexes the ankle. In between the t.a. is essentially silent, so clearly the active muscle, soleus, can be inhibited by a volley from Ia afferents of its inactive antagonist during locomotion.

Secondly, the measurement of ankle angle (Fig. 5.4E) reveals that the soleus, which acts only at the ankle, is stretched during most of the stance phase. Equivalently, its antagonist t.a. must shorten during most of the stance phase. On the assumption that the spindles in a shortening locomotor muscle are unloaded in man as in the cat (Prochazka, Westerman & Ziccone, 1976) the t.a. muscle spindle afferents contribute little inhibition to soleus α-motoneurones during most of the stance phase, unless a perturbation

unexpectedly stretches the muscle. However, late in the stance phase, the soleus shortens for a period of about 200 ms (Fig. 5.4E) as it lifts the body off the ground and consequently stretches the quiescent t.a. In this part of stance the t.a. may inhibit the soleus motor output via the increased discharge of its spindle afferents acting through the reciprocal inhibitory pathway, as will be discussed later.

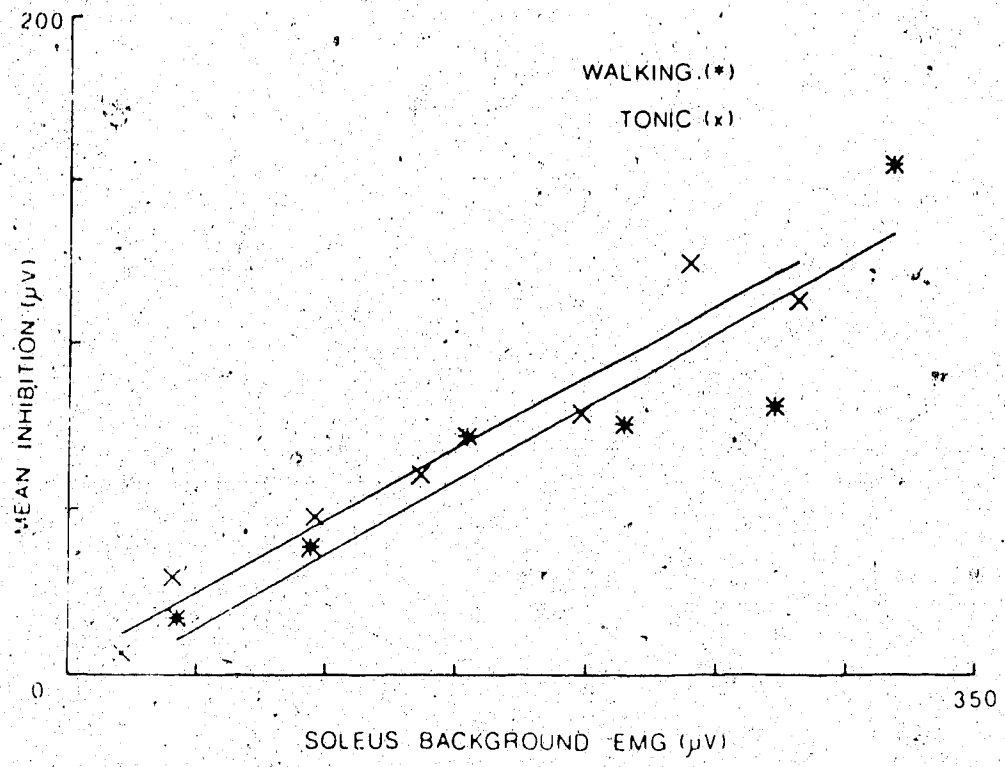

Fig. 5.5. Comparison of the mean amount of inhibition in the same subject as a function of the background e.m.g. level for the walking data (*) of Fig. 5.4 and for the tonic activation task (X). The slopes of the lines were 0.40 ± 0.09 (mean ± S.E.) for walking and 0.47 ± 0.05 for the tonic activation task. Neither the slopes nor the intercepts were significantly different between the two tasks.

DISCUSSION

Four questions warrant careful discussion. 1) What methodological considerations limit the interpretation of these experiments done on human subjects? 2) What are the functional implications of the inhibition described here? 3) What are the neuronal mechanisms that account for our results? 4) Finally, what accounts for the differences in the results obtained by the present technique and those obtained by the H-reflex technique?

Methodological issues

One criticism that may be levelled against the present method of investigating reciprocal inhibition is that the stimulus strength used (typically, 1.5 x m.t.) was too large. A strong stimulus might saturate Ia inhibitory interneurones and produce such a powerful inhibition of antagonist motoneurones that no changes in the transmission efficacy of Ia inhibitory interneurones would be revealed. However, qualitatively similar results were obtained in the tonic activation task when the stimulus to the common peroneal nerve was kept at 1 x m.t., which is the stimulus strength generally used in the reciprocal inhibition studies with conditioned H-reflexes (e.g., Shindo et al., 1984).

Moreover, a strong stimulus in the range used might antidromically activate Renshaw cells via motor axon collaterals (Baldissera, Cavallari, Fournier, Pierrot-Deseilligny & Shindo, 1987) and be less effective than a weaker one, since Renshaw cells of agonist motoneurones are known to inhibit Ia inhibitory interneurones projecting to antagonist motoneurones (Hultborn, Jankowska & Lindström, 1971). If the conduction velocities of a significant number of human Ia fibres overlap those of α-motor axons, strong stimuli would tend to depress transmission of Ia impulses via Ia inhibitory interneurones and hence decrease the inhibition of antagonist motoneurones. Furthermore, Ia inhibitory interneurones of antagonistic muscles mutually inhibit one another, as has been shown in the cat hindlimb (Baldissera, Hultborn & Illert, 1981), and evidence for this mechanism in humans has been recently published (Baldissera et al., 1987). Activation of soleus Ia inhibitory interneurones by either descending inputs or Ia afferent feedback would inhibit Ia inhibitory interneurones of the t.a. muscle.

Finally, one may argue that the stimuli used would also activate cutaneous afferents and produce inhibition by a flexor reflex mechanism not mediated by Ia inhibitory interneurones. The presence of the inhibition at a low threshold (1 x m.t.) and at short

latency (about equal to that of the H-reflex in this muscle) are contrary to this explanation. Furthermore, we never observed a flexor reflex in the t.a. (an ankle flexor). It is, therefore, unlikely that this reflex was elicited in our experiment.

Five conclusions may be drawn from the above discussion. Firstly, the same quantitative relation between the amount of inhibition and the amount of activity may be seen at several stimulus strengths. Secondly, excitation of Renshaw cells by collaterals of motor axons in the common peroneal nerve was not sufficient or appropriately timed to inactivate Ia inhibitory interneurones projecting to soleus α-motoneurones. Thirdly, if the latter Ia inhibitory interneurones were inhibited by extensor Ia inhibitory interneurones, this inhibition was incapable of suppressing inhibition of active soleus motoneurones. Fourthly, if an increase in pre-synaptic inhibition of Ia terminals occurred when the dorsiflexors were inactive (Crone et al., 1985), it was insufficient to prevent transmission of the Ia afferent volley to the Ia inhibitory interneurones. Finally, although some cutaneous afferents were probably stimulated, the flexor reflex did not appear to contaminate our results.

These findings in the intact human are fully consistent with recent direct recordings of i.p.s.p.s from Ia inhibitory interneurones to active motoneurones during fictive locomotion in the cat (Pratt & Jordan, 1987). These workers found that i.p.s.p.s could be evoked in knee flexor motoneurones during their active phase and that the i.p.s.p.s increased with membrane depolarization as would be expected on the basis of the increasing electrical gradient for the chloride ions.

Matthews (1986) recently investigated the effects of mechanical vibration of the triceps brachii on the activity of the biceps brachii. He found that the biceps could be inhibited by the application of a few cycles of the vibratory stimulus to the triceps at each of the contraction strengths investigated (not exceeding 50% of maximum). His method of measuring the amount of inhibition was similar to ours and the relation between amount of inhibition and backround activation level (measured in Matthews' study as force) was also linear. Therefore, inhibitory pathways of the arm muscles appear to behave similarly to those of the ankle.

It should also be pointed out that no direct descending inhibitory pathways to Ia inhibitory interneurones are known, so direct inhibition of Ia inhibitory interneurones from higher centres may not

be possible. Moreover, as discussed above, the possible inhibition from Renshaw cells and antagonistic Ia inhibitory interneurones may be insufficient to turn them off. This point was emphasized by Pratt and Jordan (1987) since Ia inhibitory interneurones in their experiments could induce i.p.s.p.s in active α-motoneurones at all times during the fictive locomotor cycle.

Functional Significance

Two functional roles for inhibition of an active motoneurone pool may be suggested. First, an open inhibitory pathway to an active motoneurone pool allows for the quick cessation of activity whenever this may be required. For example, if the body is thrown backwards while walking over uneven ground, thereby stretching the ankle flexors, a quick halt of ankle extensor activity would be needed to prevent a fall. The disynaptic Ia inhibitory pathway is the shortest latency inhibitory reflex known that is capable of providing this coordinative function. Furthermore, because Ia inhibitory interneurones receive convergent inputs from many supraspinal and peripheral fibre systems (Jankowska, 1984) they can mediate α-motoneurone inhibition from a variety of sources.

This same pathway may also be an integral part of the neuronal system of walking, contributing to the rapid cessation of activity in the ankle extensors at the end of the stance phase (Fig. 5.4). As the ankle flexors are stretched from h.o. until the end of the stance phase (Fig. 5.4E), their Ia spindle afferents would inhibit the activity in ankle extensors via Ia inhibitory interneurones. In conjunction with a decrease of the central excitatory drive to motoneurones of the ankle extensors, this reflex would contribute to the rapid cessation of their activity (Fig. 5.4A). A peripheral reflex input that depends on the exact kinematic events at the ankle would be useful. For example, if raising the body off the ground is somewhat delayed, the inhibition from the ankle flexors would also be delayed, thus allowing for a small prolongation of extensor activity.

We have previously hypothesized, based on the modulation of the H-reflex and measurements of muscle length (Capaday & Stein, 1986; 1987), that part of the motor output of soleus during locomotion (walking, running) is due to the autogenic Ia afferent feedback. We propose here that Ia afferents from their antagonists, the ankle flexors, may also contribute to the rapid and timely cessation of this activity via the Ia inhibitory pathway.

Neural Mechanisms

Our finding that the amount of inhibition mediated by Ia inhibitory interneurones is proportional to the amount of motor activity stands in contrast to the reports by several other groups (Cavallari et al., 1984; Shindo et al., 1984; Day et al., 1984). These groups all reported a decrease of inhibition with increasing motor activity, as determined from the ratio of conditioned to test H-reflex amplitude. In these studies, however, the size of the test reflex was allowed to vary with the amount of motor activity. Recently, the test reflex amplitude was kept constant at all levels of motor activity investigated (Iles, 1986) and the decrease in inhibition was smaller and did not reach statistical levels of significance in one study (Crone et al., 1987).

Other methodological issues applicable to these H-reflex studies can be raised. Classically, the conditioning/test method was developed and used to test the interaction between two variables (excitation and inhibition) on a quiescent motoneurone pool (Lloyd, 1941; Renshaw, 1941) in which the membrane potential of motoneurones was assumed constant. Extending the approach to an active pool introduces a third variable, namely the increased depolarization of motoneurones as the recruitment level increases, which may change the interaction between the other two

variables in complex ways. Finally, as pointed out in the Introduction, the response to the synchronous volley that produces an H-reflex may not be the same as the response to more natural activation of the motoneurones by voluntary means.

Our results, using natural activation of motoneurones, demonstrate that transmission from Ia inhibitory interneurones to α- motoneurones is not completely inhibited, if it is inhibited at all, when the pool is active. Thus, these interneurones remain able to inhibit tonically firing motoneurones in the pool. As activity in the pool increases, there are more active motoneurones to inhibit and the amount of inhibition increases approximately in proportion to the amount of motor activity.

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VI. GENERAL DISCUSSION

In the first section of the discussion preliminary experiments done to test the hypothesis based on the modelling studies in chapter 4 are briefly described, and the major result presented.

Following this, several issues that have not been fully discussed in the previous chapters are addressed. First, the main results of the simulation studies are discussed in more qualitative and intuitive terms. Some additional justifications of certain assumptions made in the model are also given. Second, a rationale for using the surface EMG as a measure of the level of activity in the α-motoneuron pool and thus net motor output is provided. Third, a discussion of the independence of the monosynaptic reflex amplitude from the level of motor activity is presented with a historical and critical perspective. Finally, neural mechanisms, other than presynaptic inhibition, that may contribute to the observed modulation of the monosynaptic reflex are evaluated.

The effects of postsynaptic inhibition on reflex amplitude

In chapter 4 the simulation study of the factors that can affect the monosynaptic reflex output of a motoneuron pool led to the hypothesis that

postsynaptic inhibition could not provide for the independent control of monosynaptic reflex output from the level of motor output. Presynaptic inhibition, on the other hand, could change the size of the reflex output independently of the level of motor activity.

Experiments were done in decerebrate cats to test the first and more controversial part of the hypothesis. Variations in the level of Soleus motor output were produced by stimulation of the contralateral common peroneal nerve at a strength 2-5 times motor threshold and at a stimulation frequency between 50-100 Hz. This produces the classic flexor and crossed-extensor reflexes, with flexion of the ipsilateral leg and extension of the contralateral one. Monosynaptic reflexes were obtained by stimulation of the cut L7-S1 dorsal roots at twice the threshold for obtaining a monosynaptic response. The reflex responses were recorded electromyographically from the Soleus muscle. Reflexes occurring at the same level of motor activity, measured from the Soleus isometric tension record, were averaged together. Thus, a plot of reflex amplitude versus the level of motor activity (tension) was obtained under control conditions. Each point in such a plot was the average of some 8-10 individual responses.

In order to introduce a tonic level of postsynaptic inhibition uncontaminated by any possible presynaptic

inhibition, the nerves to the lateral and medial Gastrocnemius muscles (LG, MG) were stimulated repetitively at physiological rates between 20-40 HZ. The strength of the stimulus to the LG-MG nerves was adjusted to produce at least a.50-60% reduction of the monosynaptic reflex by using the conditioning/test paradigm. This method of stimulation excites the Renshaw cells of the LG and MG motoneurons, which also project to the Soleus motoneurons. The Soleus motoneurons thus receive a tonic level of postsynaptic inhibition and they alone are tested in response to the dorsal root stimulus. Since the dorsal roots are cut, activation of the afferent fibres in the LG-MG nerve cannot influence the Soleus motoneurons. The experiment, activation of the crossed extensor reflex, is then repeated in the presence of repetitive stimulation of the LG-MG nerve, and thus with a tonic level of postsynaptic inhibition in the Soleus motoneurons.

The basic result can be summarized in one figure (Figure 6.1). The peak-peak amplitude of the Soleus reflexes are plotted against the isometric muscle tension. It can be seen that the reflex amplitude increases with the level of motor activity (points labelled with + sign). The plot is well fitted by a straight line having a slope of 0.31 mV/N (SE= 0.043

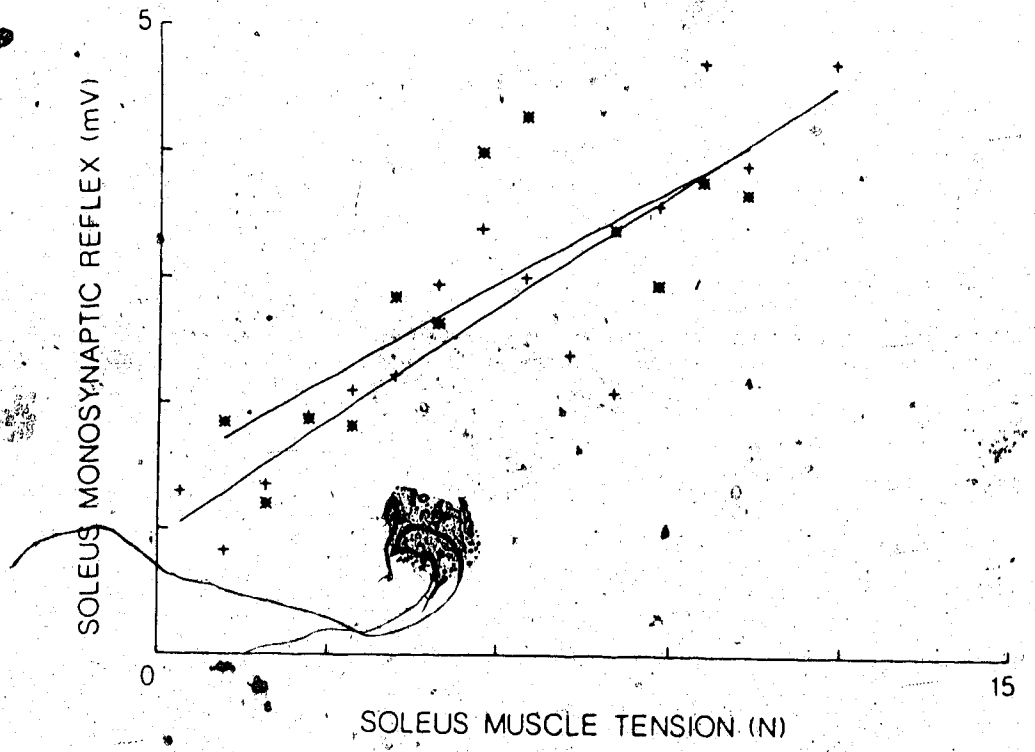

Figure 6.1: PLot of monosynaptic reflex amplitude, obtained during crossed extensor reflexes, vs the Soleus muscle tension. The points obtained in control conditions are designated by the (+) symbol, those obtained during repetitive stimulation of the LG-MG nerves at 37 Hz are plotted using the (*) symbol. The slope of the line fitted to the control points is 0.31 mV/N (SE= 0.043 mV/N) that of the line fitted to the experimental points is 0.26 mV/N (SE= 0.06 mV/N).

mV/N) and a correlation coefficient (r) of 0.89. The reflexes obtained during stimulation of the LG-MG nerve are plotted on the same graph (points labelled with * sign) and it can be seen that they fall on essentially the same line as the control responses. The slope of the line is 0.26 mV/N (SE= 0.06 mV/N) and is clearly not different from the control value. It should also be noted that the highest value of muscle tension attained during stimulation of the LG-MG nerve always less than that attained in the control situation (see figure 6.1) indicating that indeed there was a tonic postsynaptic inhibition acting on the Soleus motoneurons.

It should be recalled, as discussed in chapter 4, that when the motoneuron pool is quiescent, either an increase of presynaptic inhibition or postsynaptic inhibition can decrease the amplitude of the monosynaptic reflex. However, when the motoneurons are active, it appears that postsynaptic inhibition evenly distributed across the motoneuron pool is not a mechanism that allows for the control of the monosynaptic reflex amplitude independently of the level of motor activity. The main prediction from the modelling studies thus appears to be supported by experiment.

Further discussion on the modelling results

One of the simplifying assumptions that was made in the model presented in chapter 4 was to leave out the cable properties of motoneurons. Introducing this factor would greatly increase the computational complexity of the model and make it less accessible to neurophysiologists. Redman has shown that the decrement in the amplitude of [illegible] synaptic potentials (psps) produced by the cable [illegible] may be compensated for by a mechanism intrinsic to the motoneurons (Redman, 1[illegible]). He proposes that the post synaptic currents ge[illegible] at the dendrites may be greater than those in the soma. One mechanism to account for this, is a greater density of postsynaptic receptors in the dendrites, coupled with the liberation of sufficient transmitter substance to activate the receptors (Redman, 1986). The postsynaptic potentials of dendritic origin recorded in the soma would thus be of similar amplitude to those of somatic origin. The former would, however, have a slower time course. This provides further support for concentrating on the integration of synaptic currents at the axon hillock as was done in the present model. It is difficult to predict qualitatively what effects the shunting produced by introducing tonic postsynaptic inhibition will have on synaptic potentials of dendritic origin. It is

possible that it will shunt them to a greater extent than epsps of somatic origin. This effect will reduce the probability of a motoneuron to fire in response to an epsp. However, as will be discussed below, the time course of the membrane depolarization is also affected by the added conductances and this may counteract the effects of a smaller epsp. The point is that the model is sufficient for the present purposes, since the main prediction derived from it is supported by the experiments.

When the motoneuron pool is active, the amplitude of the monosynaptic reflex output is not altered by tonic postsynaptic inhibition. It was shown that this is because each of the subgroups contributing to the reflex output is little affected by the added inhibition. The mathematical arguments explaining these observations were given in chapter 4. Here these observations are explained in qualitative terms. The motoneurons that belong to the subliminal fringe are in fact slightly more depolarized when additional excitatory conductance is introduced to offset the added inhibitory conductance. The slightly greater depolarization results from the fact that the value of the added excitatory conductance is calculated to just offset the inhibitory conductance for the active motoneurons (see, equation 9). The motoneurons in the

subliminal fringe, in fact, require less added excitatory conductance to just offset the inhibitory conductance than the active motoneurons. This follows from the fact that they are hyperpolarized in relation to the threshold and therefore the electrical gradient for the excitatory current is greater in these motoneurons. Because the membrane potential is slightly depolarized, the epsp, although it is shunted by the added conductances, depolarizes approximately the same number of motoneurons to threshold.

Postsynaptic inhibition has little effect on the probability of firing of the active motoneurons for the following reasons. The epsp, although it is shunted by the added conductances, depolarizes the motoneurons to threshold at about the same time (t1 in equation 5) as when postsynaptic inhibition is absent. The added conductances, excitatory and inhibitory, decrease the time constant of the membrane (see, equation 4), this results in an initial fast depolarization towards threshold. Therefore, the shunted epsp sums with a slightly more depolarized membrane potential at time t1. The time that the motoneurons take to reach threshold due to the depolarizing drive alone (t2 in equation 5) is not affected by the added conductances, probably because it is dominated by the AHP conductance. In other words, the firing rate of motoneurons is primarily

determined by the AHP conductance.

The last point to discuss are the conclusions derived from the model concerning the differences in the H-reflex in the various tasks investigated. The H-reflex was larger at the same level of EMG during the standing task than during walking. In some subjects it was higher at all levels of EMG up to the highest levels that the subject could maintain. In others, the H-reflex was about the same size in the two tasks only at the very highest levels of EMG that the subject could produce (see, figure 2.6). The general conclusion from the modelling studies is that there is, on average, less presynaptic inhibition of the Ia terminals during the standing task than during the walking task. This would give rise to larger reflexes in the standing task, as observed experimentally. It is possible, however, that the level of presynaptic inhibition changes as a function of the level of motor output. For example the relatively flat slope seen in figure 2.6 may be due to an increase in presynaptic inhibition as the level of motor output increases. The average value of the presynaptic inhibition would be, nevertheless, smaller in the standing task than in the walking task. The observations of Shefchyk, Stein, and Jordan (1984) suggest that during fictive locomotion in the cat, the

level of presynaptic inhibition does not change during the locomotor cycle. This may be true in the human, but can only be resolved by experiments of the type suggested in the conclusion section. The H-reflex was greater in the walking task than in the running task at the same level of EMG. The most likely explanation for this is that the level of presynaptic inhibition is, on average, less during walking than during running. Time varying levels of postsynaptic inhibition cannot be excluded, but the average value would still be less during walking than during running.

The EMG as a measure of motor output

The amplitude of the H-reflex was different, on an absolute basis, in each of the motor tasks investigated. For example, it was very large during quiet standing and much smaller in early stance, despite the fact there is much more EMG activity in the Soleus in early stance compared to quiet standing. The maximum amplitude of the reflex during running was smaller than that during walking, although running involves a much greater activation of the Soleus. However, aside from the absolute difference in reflex amplitude between tasks, it was hypothesized that the monosynaptic reflex output could be controlled by a central factor independently of the level of motor

activity. This proposal stemmed from the observation that the plot of reflex amplitude vs the mean level of the rectified EMG activity, at the time the reflex was elicited, was different in each of the three tasks investigated. Since, the plots do not superimpose, the size of the reflex appears to be independent of the level of motor output.

For this conclusion to be valid, the mean value of the rectified EMG signal must be related to the number and rate of discharge of the active motoneurons, to the same extent in each of the tasks investigated. There is no doubt on both experimental and theoretical grounds that the gross EMG signal depends on the number and rate of discharge of the active motoneurons (Milner-Brown and Stein, 1975; De Luca, 1979). However, is there a unique relation between the mean value of the gross EMG and the level of activity of the α-motoneurons in the pool? It may be possible that a given mean level of EMG activity may be produced by different combinations of motoneuron discharges. For this to occur the two factors, number and discharge rate, contributing to the mean value of the EMG would have to be dissociated from each other. This implies that a given mean value could be produced by either many motoneurons discharging slowly, or a relatively smaller number discharging rapidly.

However, during increasing contractions lasting about one second, the firing rate of single motor units increases monotonically (e.g., Desmedt & Godaux, 1978). This is of the same order of magnitude as the duration of the Soleus EMG during walking in humans at 4 km/h. It was also shown in the cat that, the firing rate of single motor units increases monotonically with the whole muscle EMG, over an approximately two fold range of walking speeds ranging from 0.5 to 1.2 m/s (Hoffer, et al., 1987a). Such a two fold range of locomotor speeds in the cat, corresponding to walking and trotting, is comparable to that between walking and running in the present study on humans. Similarly, the firing rate of individual motor units increases monotonically, up to their saturation level, with contraction strength during tonic contractions (Milner-Brown, Stein, & Yemm, 1973) It may be concluded from the above findings that the firing rate of individual motor units in the three tasks investigated in this study, standing, walking, running, increased monotonically with the level of EMG activity. Furthermore, it is well known that in most natural motor tasks motor units are recruited in an orderly fashion (Milner-Brown, Stein and Yemm, 1973; Desmedt and Godaux, 1978; Grimby, 1984; Thomas, Ross, and Stein, 1986; Hoffer et al., 1987b). Orderly recruitment in the direction of small slow twitch

motor units to large fast twitch motor units was shown to occur in tonic contractions of increasing strength (Milner-Brown et al., 1973) and during slowly increasing contractions reaching a maximum in about 5-7 sec (Desmedt and Godaux, 1978). The recruitment order was exactly the same for the motor units recorded in the slowly increasing contraction and when the contraction was done in about 200 ms but reached the same maximum force level (Desmedt and Godaux, 1978). Recently, orderly motor unit recruitment was shown in man during walking and running (Grimby, 1984) and in the cat during walking and trotting (Hoffer et al., 1987b).

In summary, in the tasks investigated in this study, motor units most likely increased their firing rate in parallel with the EMG and were recruited in an orderly fashion. In this situation the mean value of the rectified EMG will be a fair measure of the motor output. The EMG will probably reflect the firing rate and number of recruited motor units to a similar extent in each of the tasks. In other words, firing rate and number of active units should each be weighted by similar amounts in each of the tasks. There may be situations, however, such as during ballistic contractions where only a few motor units are active at very high initial rates of firing rates

(e.g., Desmedt & Godaux, 1978). In this case, the firing rate would contribute relatively more to the EMG than the number of active motor units. This is a case where the contribution of firing rate is relatively more weighted than that of the number of firing units. The mean value of the EMG obtained in this case could not be compared to that obtained in a situation where the relative weighting of these two factors is different.

An experiment, consisting of recording the surface EMG and simultaneously the activity of single motor units in the various tasks investigated, could resolve the issue. If at the same mean level of EMG the firing rate of motor units is essentially similar in each of the tasks, then it is clear that the two factors contributing to the EMG are weighted equally in these tasks.

Independence between monosynaptic reflex output and motor output

In 1969 Kots published a series of papers (reviewed by Kots, 1977) dealing with changes in H-reflex amplitude during the latent period of a voluntary plantarflexion of the ankle signaled by either an auditory, somesthetic, or visual cue. He reported a progressive increase in the H-reflex amplitude beginning about 60 ms prior to motor activity. This

reflex potentiation was restricted to the motor pool of the ankle extensors and was thus a specific phenomenon associated with voluntary activation of a muscle group. He called this reflex potentiation preceding voluntary movement the "tuning" phase and ascribed it to the action of descending commands on the segmental interneuronal systems. Most of these experiments were done starting from rest (i.e., no motor activity in the ankle extensors) so that the reflex potentiation may have been simply a reflection of a slow depolarization of the motoneurons to threshold. However, the same time course of reflex potentiation was also observed when the subject maintained a tonic level of motor activity prior to presentation of the movement cue. Although the mean level of EMG activity was not measured prior to the reflex responses, visual inspection of figure 12 (in Kots, 1977) reveals that the EMG levels were approximately constant during the reaction time.

Therefore, it appears that during the latent period there was a potentiation of the H-reflex, due to a central factor, despite a constant level of motor activity. Kots did not discuss this finding as showing independence of reflex output from motor output, but rather suggested that it demonstrated the general nature of the "tuning" process (Kots, 1977). Kots' observation of reflex "tuning" demonstrates that

preceding motor activity there may be a descending influence on the segmental interneuronal system. Part of this "tuning" process may indeed be directed onto the interneurons mediating presynaptic inhibition, although Kots did not present any specific neural mechanism to account for the "tuning" phase. However, it does not follow from these observations that the efficacy of synaptic transmission from the Ia-afferents to the motoneurons is specifically altered in order to adapt the stretch reflex output to the requirements of the task, as discussed in various parts of the thesis.

In other words the observation reported in this thesis, that during movement the CNS sets the level of monosynaptic reflex output independently from the motor output does not follow from Kots' observations or similar observations by other authors (Sheirs & Brunia, 1985; Requin, Bonnet and Semjen, 1977). For example, the "tuning" phase may have represented a gradual change in the level of presynaptic inhibition from a "resting" level to a fixed "movement" level. It this case there would be no task dependent modulation of the monosynaptic reflex, reflexes obtained in different tasks would fall on the same curve relating reflex amplitude to the level of motor activity. It remains an important task, however, to

understand in neural terms the "tuning" events that precede voluntary movements and Kots' work is an important beginning.

There was, however, a paper published in 1970 (Gottlieb, Agarwal and Stark, 1970) that pointed to the possibility of the independence of monosynaptic reflex output from the level of motor output, as well as suggesting presynaptic inhibition as a possible neural mechanism for producing this effect. This paper was in many respects ahead of its time, or at least foreshadowed things to come. The authors used methods of data acquisition by computer, quantitative methods of data reduction and analysis, and discussions of neurophysiological results in terms of concepts from control theory. The H-reflex potentiation they observed during isometric contractions, going from tonic ankle dorsiflexion to tonic ankle plantarflexion, could however be explained simply as resulting from the large burst of Soleus EMG activity necessary for the rapid reversal of foot torque. In fact, the temporal profile of the H-reflex potentiation during the isometric contraction is roughly proportional to the first derivative of the Soleus EMG burst.

More recently, Soechting, Dufresne, and Lacquaniti (1981) studied the reflex responses of the biceps or triceps brachii muscles to torque pulse perturbations

in three simple motor tasks. In one task, the subject was instructed not to resist the perturbation and in the other to do so. Finally, the subject was asked to track a visual target moving at constant velocity. They found that the amplitude of the computed impulse response of the biceps or triceps brachii muscles to the torque pulse perturbations was dependent on the particular motor task the subject was instructed to perform. They argued that a "central factor" must be involved in the reflex modulation, because the rate of increase of the amplitude of the impulse response was different from that of the EMG in each of the tasks they investigated. They attributed the observed modulations to changes in the sensitivity of the muscle spindles produced by the fusimotor system. Although, the sensitivity of the muscle spindles is set centrally, via the gamma motoneurons, the same muscle stretch would produce a different pattern of afferent activity. Therefore, the resulting reflex response will be different and this without any change in the transmission properties of the central pathway producing the response. Clearly, any study using muscle stretch as an input cannot establish that a particular pattern of reflex modulation is due either uniquely, or partly, to a change in the central pathway producing the response. If such a change

occurs, the same afferent input will produce a different reflex output. It was also suggested, as an alternative to changes in fusimotor activity, that the selective activation of different reflex pathways, each having its own dynamic characteristics, could account for their results.

The first demonstration that there is a task dependent change in the amplitude of the H-reflex and apparently independent of the level of EMG activity was published in 1982 by Morin, Katz, Mazieres and Pierrot-Deseilligny. They demonstrated that the H-reflex was larger during a steadily maintained voluntary contraction of the ankle extensors compared to its amplitude during the early part of stance. In their study, therefore, only one level of contraction was studied so it remained to be observed whether this could occur over a wide range of activation levels and in different tasks. We published in 1985 (Capaday and Stein, 1985) an abstract summarizing the contents of chapter 2 without knowledge, at the time, of the work of Morin and his colleagues.

Our observations on the modulation of the H-reflex during walking have been independently confirmed by Crenna and Frigo (1987). Llewellyn, Prochazka, and Vincent (1986) have shown that T-reflexes are also strongly modulated during walking and have confirmed, also using T-reflexes, our observations on the

difference in monosynaptic reflex amplitude between walking and standing. The reported independence of monosynaptic reflex output from the level of motor output has been confirmed by Romano and Schieppati (1987) in a different experimental paradigm.

Other possible mechanisms of H-reflex modulation

Presynaptic inhibition was presented as the major neural mechanism to account for the differences in the amplitude of the monosynaptic reflex in the different motor tasks investigated. However, because of overlap of conduction velocities between the Ia-fibres and the Ib-fibres, and because of the nature of the experiment (recruitment of alpha motor fibres by the stimulus), the changes in the amplitude of the H-reflex may reflect changes in the state of the Ib and Renshaw interneurons. The influence of large cutaneous afferents is probably far less important than the potential contribution of the above two factors because several synapses are intercalated between the cutaneous afferents and the motoneurons.

Let us consider the possible contribution of the Renshaw cells first. These neurons are inevitably activated when the stimulus elicits an M-wave and hence activates alpha motor fibres both orthodromically and antidromically. The antidromic invasion of motoneurons within the spinal cord will

activate Renshaw cells via the motor axon collaterals. The volley from the fastest alpha fibres will arrive in the spinal cord before that of the slowest Ia-fibres. Activation of the Renshaw cells by the fast alpha volley will inhibit the response of motoneurons to the volley of the slow Ia-fibres. However, by keeping the size of the M-wave constant and thus activation of the same number of alpha fibres, the same number of Renshaw cells will be activated for a given state of excitability of these neurons. Therefore, as long as the state of excitability of the Renshaw cells stays the same changes in the amplitude of the H-reflex must be due to other factors.

For the Renshaw cells to contribute to the observed difference between walking and standing their excitability would need to be greater in walking than in standing. This would result in the smaller reflex amplitudes observed in walking. Similarly, the excitability of the Renshaw cells needs to be greater in running compared to walking in order to explain the difference in reflexes between these two tasks. What then is known about the changes in Renshaw cell excitability as a function of the level of motor output?

In general, Renshaw cells are inhibited as the level of motor output increases (Hultborn and Pierrot-

Deseilligny, 1979). Therefore, Renshaw cell excitability decreases as the strength of contraction increases. It follows from this that if Renshaw inhibition were the only factor, H-reflexes should be larger in running than in walking, which they are not. The decrease of Renshaw cell excitability with increasing levels of motor output is thought to allow for the higher discharge frequencies and recruitment of motor units necessary to produce higher contraction strengths (Hultborn, Lindstrom, and Wigstrom, 1979; see also Noga, Shefchyk, Jamal, and Jordan, 1987). It may also have a second functional role in increasing the potency of Ia-interneuron inhibition of the antagonist motoneurons (Hultborn and Pierrot-Deseilligny, 1979). This follows from the fact that Renshaw cells directly inhibit Ia-interneurons projecting to the antagonist motoneurons (Hultborn, Jankowska, and Lindstrom, 1971).

The difference between the amplitudes of the H-reflexes in the standing task and those in the walking task are also not explainable by a change in Renshaw cell excitability. Hultborn and Pierrot-Deseilligny (1979) reported that the Renshaw cells produce more inhibition during tonic contractions (e.g., standing) than in increasing contractions (e.g., walking) of the same strength. Therefore, the excitability of Renshaw cells is greater during tonic contractions than during

progressively increasing contractions. Again, if Renshaw inhibition were the only factor affecting reflex output, reflexes would have to be larger in the locomotor tasks than in standing, which they are not.

The functional role of the Ib-afferents is not known, but it is generally accepted that they are involved in force regulation (Houk and Rymer, 1981). The Ib-interneurons inhibit homonymous and synergistic motoneurons (Eccles, 1964). Little, if anything, is known about any change in the state of Ib-interneurons as a function of motor output level or in different motor tasks. It is therefore conceivable that if their excitability increases in going from standing, to walking, to running, this may contribute to the decrease in the amplitude of the H-reflex. However, the method of measurement adopted in the present studies, measuring the peak to peak amplitude of the reflex, may minimize oligosynaptic contributions such as those of the Ib-interneurons. The peak to peak value of the compound action potential (H-reflex) is probably due in large part to the response of the motoneurons to the fastest Ia-fibres, which at least in the cat are a little faster than the fastest Ib-fibres. Therefore, the peak to peak measurement will be less affected by oligosynaptic contributions than a measurement such as the area under the rectified

waveform of the compound action potential. The latter would also reflect the relatively more delayed discharge of motoneurons to the slower Ia-fibres, and hence may possibly be more affected by oligosynaptic influences.

In the introduction it was pointed out that there may be a polysynaptic excitatory pathway between the Ia afferents and the motoneurons, in addition to the monosynaptic connection. If the H-reflex is due in part to the polysynaptic pathway, then changes in the excitability of the interneurons in this pathway may account for the observed differences in the amplitude of the H-reflex in the different tasks. For such an interneuronal pathway to have an influence on the H-reflex output, the rise time of the monosynaptic epsp in the motoneurons must be sufficiently slow to allow a contribution from the polysynaptic pathway. This is what has been argued by Burke et al. (1984) on the basis of their estimate of monosynaptic epsp rise time in motoneurons of humans. They estimated this rise time, using the post stimulus time histogram method (PSTH) (Ashby and Labelle, 1977), to be about 2.4 ms with a standard error of about 1 ms. This they argue would allow for at least an oligosynaptic contribution to the H-reflex. A rise time which exceeds 1 ms, the minimum time to traverse an additional synapse (Eccles, 1964), is not the only condition necessary to

allow for an oligosynaptic contribution. Motoneurons are much larger than interneurons and would thus tend to have faster time constants. This would allow for a faster rise time of the epsp produced by the Ia afferents in the motoneurons compared to that in the interneurons. Therefore, the interneurons may not reach threshold in time to affect the motoneurons. It is possible that the interneurons have special membrane properties that allow for fast rise times of post synaptic potentials, or lower thresholds for spike initiation. In summary, it is by no means certain that the H-reflex can be significantly affected by oligosynaptic contributions as this requires several factors to work in concert. It would be interesting to look at this question more carefully in animal experiments, as well as to evaluate the PSTH method in such experiments. Finally, the conclusion that during activity of the motoneuron pool, only presynaptic inhibition can affect the monosynaptic component of the H-reflex, is not invalidated by any possible oligosynaptic contributions.

Conclusions

It was shown in this study that the monosynaptic reflex of normal human subjects is task dependent and that its pattern of modulation in a motor task is likely to be of functional value. For example it was

suggested, based on measurements of ankle angle, Soleus EMG, and H-reflex measurements, that part of the Soleus motor output during locomotion may be due to the stretch reflex. Experiments by my colleagues in the laboratory are currently under way to estimate the contribution of the stretch reflex to the net motor output of the Soleus during walking.

Evidence was also given that the efficacy of synaptic transmission between the Ia-afferents and the motoneurons can be controlled by the CNS independently from the level of motor activity. A computer model was developed to analyze the central neural mechanisms that may influence the input/output characteristics of this pathway. It was found that presynaptic inhibition was the only central mechanism that could allow for control of the monosynaptic reflex amplitude independently of the level of motor activity. The results obtained from preliminary experiments done in the cat support this conclusion. Techniques may be developed to record from single motor units in the soleus during at least standing and walking and the PSTH method used to estimate the size of the epsp in each of these tasks. This would allow for a comparison of the relative size of the epsp in these two tasks. If the predictions made in this thesis are correct, then the epsp should be on average larger in

the standing task than in the walking task. It remains to be established, in natural motor activities such as walking, whether the source of the postulated presynaptic control is central or peripheral, and if central which structures are involved. The effects of presynaptic inhibition on the reflex muscle stiffness should also prove to be interesting experiments, especially if done in a context requiring adaptive control of the stretch reflex.

An investigation of the relation between motor unit firing rate and EMG activity, as suggested in a preceding section of this chapter, would be a useful study towards understanding the use and limitations of the gross EMG as a measure of activity in the motoneuron pool.

Finally, it seems logical to extend the study of reflex modulation during posture and locomotion described in this thesis to pathological cases. Most prominently in patients with strokes in cortical areas, Parkinsons patients, and in patients with cerebellar dysfunction. Many of these patients have an inability to walk, although the reasons are likely to be quite different for each pathology.

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