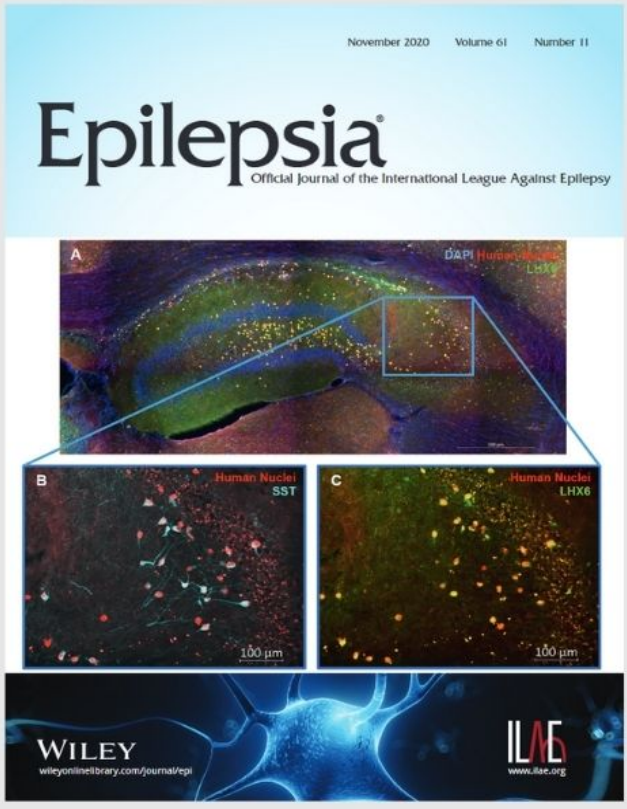
Cardiovascular safety of fenfluramine in the treatment of Dravet syndrome: Analysis of an ongoing long-term open-label safety extension study



Discover this research article in full today.

View enhanced article features, including:

- **full article audio recording**
- **video abstract**
- **author discussion**
- **infographic**

INVITED REVIEW

ABSTRACT: The Hoffmann reflex (H-reflex) is extensively used as both a research and clinical tool. The ease with which this reflex can be elicited in several muscles throughout the body makes it an attractive tool. This review discusses some of the important limitations in using the H-reflex. In particular, the inaccurate but widely held assumptions that the H-reflex (1) represents the monosynaptic reflex of the Ia afferent onto homonymous motoneurons, and (2) can be used to measure motoneuronal excitability are addressed. The second part of this review explores the utility of the H-reflex as a neural probe in neurophysiology and motor control research. Applications ranging from the investigation of the functional organization of neural circuitry to the study of adaptive plasticity in spinal structures in health and disease suggest that the H-reflex will continue to be an extensively used tool in motor control neurophysiology.

Muscle Nerve **28:** 144–160, 2003

THE H-REFLEX AS A TOOL IN NEUROPHYSIOLOGY: ITS LIMITATIONS AND USES IN UNDERSTANDING NERVOUS SYSTEM FUNCTION

JOHN E. MISIASZEK, PhD

Department of Occupational Therapy and Centre for Neuroscience, University of Alberta, 2-64 Corbett Hall, Edmonton, Alberta T6G 2G4, Canada

Accepted 29 January 2003

The Hoffmann reflex (H-reflex) is perhaps the most extensively studied reflex in the literature on human and mammalian neurophysiology. This is due largely to the ease with which the reflex can be elicited in a variety of muscles. The H-reflex can be elicited in most muscles whose nerve can be accessed by percutaneous electrical stimulation at some point along its path. Indeed, H-reflexes have been recorded in over 20 muscles throughout the body including muscles of the hand, arm, leg, foot, and jaw. The relative ease with which the H-reflex can be elicited in muscles throughout the body, involving both spinal and cranial nerves, has also made the H-reflex an attractive clinical tool. However, there are limitations to the interpretation of H-reflex data, both as a clinical and research tool, that have often been overlooked. The purposes of this review article are to (1) define the limitations in the interpretations of the H-reflex in neurophysiology and motor control research (and by extension as a clinical tool), and (2) highlight the insights into the function of the nervous system that can be achieved with the use of the H-reflex as a neural probe.

The neural circuitry responsible for the H-reflex is predominantly characterized by the monosynaptic projection of the group Ia afferents onto the homonymous motoneurons. This basic neural circuit is schematically represented in Figure 1. In general, percutaneous electrical stimulation of the mixed nerve will activate the large-diameter group Ia afferents. (The methods for eliciting the H-reflex have recently been comprehensively reviewed, along with detailed technical considerations.[90] Thus, the details of the techniques will not be addressed in the present review.) The afferent volley then proceeds to the spinal cord leading to a monosynaptic excitation of the target motoneurons and the subsequent activation of the muscle fibers. As the neural circuitry of the H-reflex is largely the same as the monosynaptic stretch reflex (tendon-tap reflex), the H-reflex has often been described as the electrical analog of the stretch reflex. However, since the H-reflex is evoked by the direct activation of the afferents, the sensory endings of the muscle spindle sense organs are bypassed along with the influences of γ-motoneuron activity on spindle sensitivity. Thus, the H-reflex

Abbreviations: EMG, electromyography/electromyogram; EPSP, excitatory postsynaptic potential; 5-HT, 5-hydroxytryptamine (serotonin); H-reflex, Hoffmann reflex

Key words: H-reflex; human; motor control; neural circuitry; presynaptic inhibition

Correspondence to: J. E. Misiaszek; e-mail: john.misiaszek@ualberta.ca

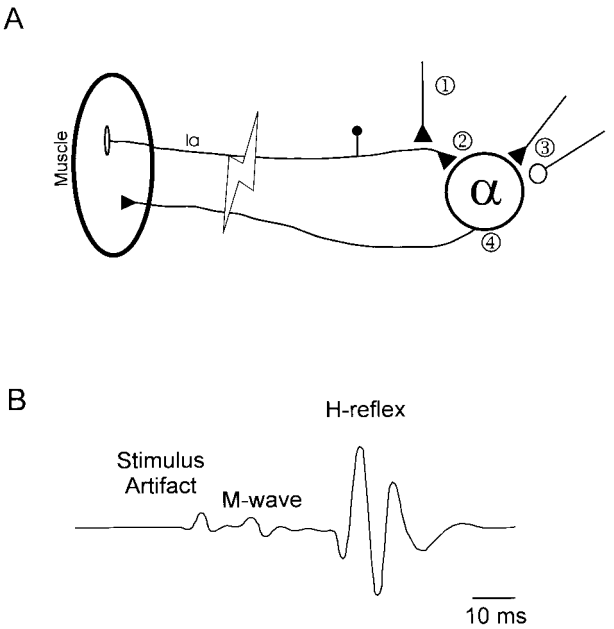


FIGURE 1. (A) Schematic depiction of the neuronal components of the H-reflex arc. Shown are a Ia afferent with a monosynaptic projection to an homonymous α-motoneuron, a presynaptic connection onto the Ia afferent terminal, an excitatory postsynaptic connection, and an inhibitory postsynaptic connection. Each of the factors which can contribute to modulation of the amplitude of the H-reflex are indicated by numbers: 1, presynaptic inhibition; 2, homosynaptic depression; 3, fluctuations in motoneuronal excitability due to excitatory and inhibitory postsynaptic influences; and 4, changes in motoneuron membrane properties. **(B)** Sample trace of the electromyographic record of an H-reflex recorded in soleus depicting the H-reflex, M-wave (from direct activation of the α-motoneurons by the electrical stimulus), and stimulus artifact. In other muscles, for which the conduction distance is shorter, the H-reflex may overlap with the M-wave making dissociation of the two waveforms difficult.

can be used as a tool to measure the excitability of the neural components of the arc, irrespective of sense organ sensitivity.

The largely monosynaptic nature of the reflex circuitry makes the H-reflex an attractive tool for research and in clinical neurophysiology. Indeed, the simplicity of this reflex circuit has led to the misunderstanding that the H-reflex can be used as an unambiguous measure of the excitability of the motoneuron pool. This misunderstanding may lead to erroneous interpretations of the data both in research and clinical studies. Changes in the amplitude of the reflex (assuming the methods are technically sound, see Zehr[90]) can be explained by at least three possibilities: (1) alteration in the excitability of the motoneurons; (2) variation in the amount of neurotransmitter released by the afferent terminals; or (3) variation in the intrinsic properties of the motoneurons.[13] Moreover, the H-reflex is not purely a monosynaptic reflex originating from only group Ia afferents, but is confounded by oligosynaptic contributions from the Ia and other large-diameter afferents. Thus, the use of the H-reflex as a research or clinical tool becomes limited. These limitations shall be explored in the subsequent sections of this review. Nevertheless, the H-reflex remains a potentially powerful tool in the research and clinical settings, provided it is used in adequately designed and controlled studies. Some of the potential uses of the H-reflex in the research setting will be explored later in this review.

LIMITATIONS TO THE INTERPRETATION OF H-REFLEX DATA

At first glance, the H-reflex technique seems simple and straightforward. However, if the methodology used is not sound, the data become confounded by multiple factors and interpretation becomes impossible. One must consider aspects beyond the direct, technical issues surrounding the procedures for stimulating and recording, and consider the idea that the H-reflex is highly modifiable and is influenced by a multitude of factors. Furthermore, even if H-reflexes are sampled with meticulous care for all confounding factors, the interpretation of the data is often marred by one of two overarching assumptions. The first assumption is that the H-reflex is derived purely from group Ia afferents, projecting monosynaptically onto the target motoneurons. The second, and perhaps most widely abused assumption, is that the H-reflex reflects the excitability of the motoneuron pool being tested. Neither of these assumptions is valid and each places limitations on the interpretations of the results from H-reflex studies.

The H-Reflex Is More than Just a Ia Monosynaptic Reflex. In 1951, Magladery et al.[64] asserted that the H-reflex elicited in the soleus muscle was monosynaptic, based upon the sufficiently brief latency from time of stimulus to onset of the waveform. Subsequently, Burke et al.[10] suggested that the composite excitatory postsynaptic potential (EPSP) of the H-reflex in the motoneurons of soleus had a sufficiently long rising phase to permit oligosynaptic inputs to reach the motoneuron before the EPSP began to fade. This indicates that the oligosynaptic inputs have ample time to contribute to the H-reflex. There is also considerable evidence from cats[36,54,55] and mounting evidence in humans[10,11,39] for the existence of oligosynaptic pathways from group Ia afferents onto homonymous muscles. Thus, the earliest component of the H-reflex (~0.5 ms) is still

predominantly comprised of the monosynaptic Ia effects, but the later portions of the reflex probably include contributions from oligosynaptic Ia pathways.

Moreover, it must be considered that electrical stimulation of the mixed nerve to evoke the H-reflex is unlikely to reflect isolated recruitment of the group Ia afferents. A convenient practice in H-reflex testing is to evoke reflexes with stimulus intensities sufficient to elicit a small direct motor response (M-wave).[90] The M-wave represents the direct activation of the muscle fibers with the recruitment of the α-motoneurons by the electrical stimulation (Fig. 1B). Since the axons of the α-motoneurons are smaller in diameter than the axons of the group Ia afferents, the presence of the M-wave indicates that smaller-diameter afferents will also be recruited, including group Ib afferents serving Golgi tendon organs, some larger-diameter cutaneous afferents, and possibly some group II muscle spindle afferents. None of these afferent sources can be conclusively excluded from contributing to or confounding the H-reflex recorded in the muscle following the stimulus.

Factors Affecting Transmitter Release from the Terminals of the Ia Afferents. Perhaps the most troubling assumption that is often made in using the H-reflex as a research or clinical tool is the belief that the H-reflex is a measure of the excitability of the motoneuron pool. However, this assumption is not valid as the amplitude of the H-reflex will be affected by variations in the amount of neurotransmitter that is released from the Ia afferent terminals. There are two factors that can affect neurotransmitter release: (1) presynaptic inhibition of the Ia afferent terminals, and (2) postactivation depression. The evidence that these mechanisms contribute to the regulation of the amplitude of the H-reflex has been succinctly reviewed elsewhere[90] (see Rudomin and Schmidt[78] for an extensive review on presynaptic inhibition, and Stein[84] for an extensive review of the evidence for presynaptic inhibition in humans) and will not be discussed here. Rather, the following sections will review the evidence in the literature that describes sources for each of these presynaptic modifications in reflex excitability and the implications for using the H-reflex as a research tool.

Events that Lead to Presynaptic Inhibition of the H-Reflex Arc. Presynaptic inhibition of the monosynaptic reflex arc was initially described in the late 1950s and early 1960s in the cat.[31,37] The initial studies identified suppression of the monosynaptic Ia EPSP following conditioning stimulation of other, heteronymous group I afferents. From these early studies, the mechanisms and characteristics of presynaptic inhibition in the mammalian spinal cord have been extensively detailed.[78] Throughout the 1960s, Eccles and his colleagues systematically mapped the presynaptic inhibition in Ia afferents of various muscles throughout the hindleg of the cat generated by stimulation of heteronymous afferent sources. The Ia afferents from most muscles appear to be presynaptically inhibited by stimulation of predominantly hindleg flexor group I afferents.[31] However, conditioning stimulation of some hindleg extensor group I afferents also produced primary afferent depolarization (which results in presynaptic inhibition) in Ia afferents of the hindleg.[31] Moreover, selective stimulation of heteronymous Ia or Ib afferents led to primary afferent depolarization of hindleg Ia afferents. The important consideration here is that activation of remote muscle afferents leads to presynaptic inhibition of the Ia afferent, and presynaptic suppression of the H-reflex.

In humans, presynaptic inhibition of the H-reflex can also be initiated by heteronymous afferent activation. For example, conditioning stimulation of the common peroneal nerve at group I strength results in presynaptic inhibition of the soleus H-reflex with an interstimulus delay of between 80 and 120 ms.[51,93] This example is technically the easiest available to elicit presynaptic inhibition of an H-reflex in humans, in the case the H-reflex of the soleus muscle. However, it may be assumed that the extensive heteronymous projections leading to presynaptic inhibition described in the cat[31] are also candidates for initiating presynaptic inhibition of the H-reflex in humans. Indeed, Iles and Roberts[53] demonstrated that vibration of heteronymous muscles throughout the leg resulted in a mapping of presynaptic inhibitory connectivity very similar to that described in the cat. The implication is that activation of distant afferent sources can lead to presynaptic inhibition of H-reflexes. Thus, during testing, changes in the posture of the subject or motion about one or more joints will lead to changes in the activity of afferents, which in turn could lead to alterations in the level of presynaptic inhibition. Brooke and his colleagues demonstrated that passive motions of the leg (but with the ankle joint immobilized) led to suppression of the ipsilateral soleus H-reflex.[65] It is important to note that the suppression of the H-reflex occurred even if the subjects maintained a mild tonic contraction of the soleus muscle[6,67] (Fig. 2), indicating that the excitability of the soleus motoneuron pool was relatively constant. The conclusion was that passive movements of the limb causes afferent activation

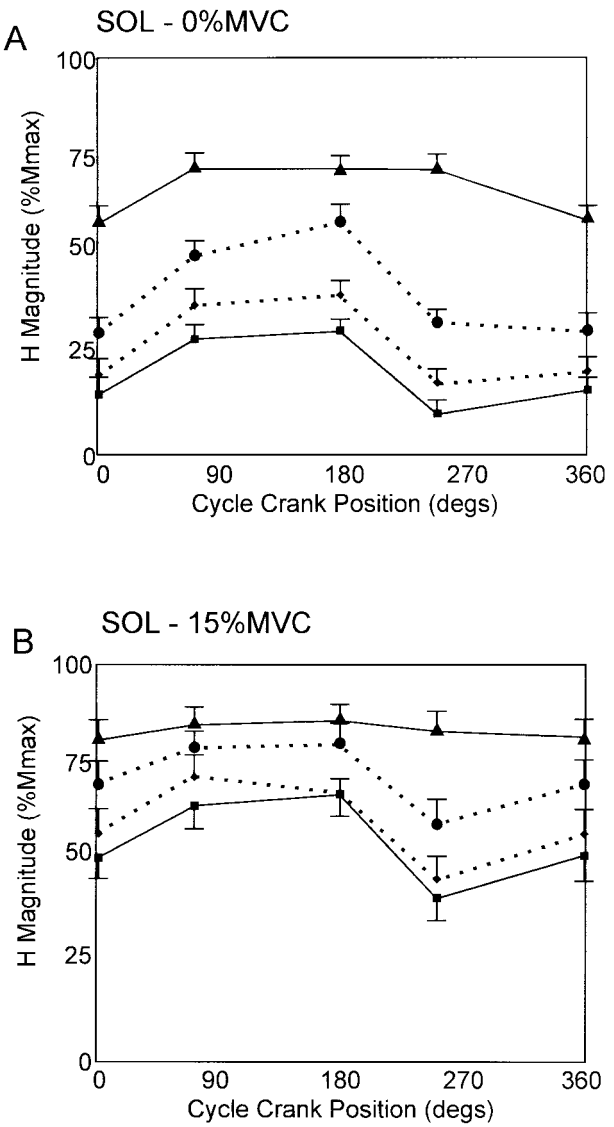


FIGURE 2. Phase modulation of the soleus (SOL) H-reflex during passive pedaling of the test leg with and without tonic contraction of the target muscle. The ankle was securely braced at 90° to prevent movement of the ankle joint during pedaling. In each panel, the four lines represent the average H-reflex amplitude from four subjects during passive pedaling at different rates: solid line with filled triangles, stationary; dotted line with filled circles, 10 rpm; dotted line with filled diamonds, 30 rpm; and solid line with filled squares, 60 rpm. In **(A),** the soleus muscle was quiescent and, in **(B),** the subjects maintained a tonic contraction of soleus of 15% maximum voluntary contraction (MVC). Note that the pattern of modulation and the rate-dependent decrease in H-reflex amplitude are retained when the soleus muscle was tonically contracted, suggesting the effects are due to presynaptic inhibition of the Ia afferent. (Modified from Misiaszek et al.,[67] with permission).

that then leads to presynaptic inhibition of heteronymous Ia afferents. Moreover, placing the leg statically at various points in the movement cycle also attenuated the soleus H-reflex, with maintained tonic contraction of soleus. Therefore, motion is not a prerequisite of the afferent-induced presynaptic inhibition, as a simple change in leg posture is sufficient to alter the level of presynaptic inhibition.

The afferent drive that leads to the presynaptic inhibition of the H-reflex need not be derived from intralimb sources. Cheng et al.[18] demonstrated a similar decrease in amplitude of the soleus H-reflex with passive motion of only the contralateral leg. Other interlimb sources of H-reflex modulation have been reported. For example, rhythmical arm swing leads to phasic modulation of the ipsilateral soleus H-reflex.[45] Unfortunately, in this study, the H-reflexes were sampled from quiescent muscles, thus not permitting speculation as to whether this interlimb modulation was the result of pre- or postsynaptic influences. More recently, Collins et al.[22] reported that bilateral active arm cycling attenuated the soleus H-reflex while subjects maintained a tonic contraction in soleus. This suggests presynaptic inhibition of the soleus H-reflex with active cycling of the arms. However, from this study, it is not possible to determine whether the inhibition of the soleus H-reflex is related to descending motor commands associated with the arm cycling task or afferent feedback arising from the movement.

Presynaptic inhibition of the H-reflex can also arise from descending supraspinal sources. In early animal studies, it was shown that stimulation of brainstem vestibular nuclei resulted in primary afferent depolarization of Ia afferents in the legs.[78] More recently, Gosgnach et al.[41] demonstrated that monosynaptic reflexes recorded in the paralyzed cat were presynaptically inhibited when brainstem regions important for the initiation of locomotion (the mesencephalic locomotor region) were electrically stimulated. This is in contrast to the work of Misiaszek et al.[69] who showed no difference in the soleus H-reflex amplitude in the decerebrate cat spontaneously walking on a treadmill, compared to H-reflexes obtained during periods of tonic soleus activity in the same preparation. The results of Misiaszek et al.[69] suggest that the spinal networks involved in rhythm generation for locomotion do not generate presynaptic inhibition of the monosynaptic reflex per se. The implication is that the result of Gosgnach et al.[41] probably represents presynaptic inhibition derived from the brainstem structures that were electrically stimulated.

Presynaptic inhibition derived from supraspinal sources has also been shown to contribute to modulation of H-reflexes in humans. For example, soleus H-reflexes are smaller following sudden whole body

tilts, compared with quiet standing, but with matched background electromyogram (EMG) activity in soleus.[73] This modulation of the H-reflex may involve activation of the vestibular apparatus,[56] consistent with the evidence from animal work that vestibular stimulation leads to presynaptic inhibition in Ia afferent pathways.[78]

In another example, mental rehearsal of a movement leads to modulation of H-reflex amplitudes in leg muscles[4] or arm muscles.[40] The modulation in amplitude could not be explained by changes in background EMG activity, suggesting changes in presynaptic inhibition of the Ia afferent pathway. Simple observation of a movement also leads to modulation of the H-reflex in a hand muscle. The pattern of modulation was characterized as the "inverted mirror" of the pattern of corticospinal excitability, suggesting that the H-reflex arc is modulated at a site prior to the motoneuron pool[3] (Fig. 3). In addition, Hasbroucq et al.[44] demonstrated that H-reflexes decrease in amplitude during the foreperiod of a choice reaction-time task in a forearm muscle, despite tonic activation of the target muscle. Taken together, these observations indicate that activation in cortical structures may also lead to modulation of H-reflexes through presynaptic mechanisms.

It should also be noted that there are factors that may not directly generate presynaptic inhibition of Ia afferents, but that modulate the presynaptic inhibition derived from other sources. For example, in animal studies, it has been shown that stimulation of cutaneous afferents, pyramidal tract fibers, and other descending tracts[78] did not produce primary afferent depolarization (and thus presynaptic inhibition) of Ia afferents, but did inhibit the primary afferent depolarization generated from other sources. Galvanic stimulation of the vestibular apparatus,[52] magnetic stimulation of the motor cortex,[51] and stimulation of cutaneous afferents[51] may lead to a similar interaction on Ia–Ia presynaptic inhibition in humans. Thus, the level of presynaptic inhibition that is present at the Ia afferent terminals is affected by direct and indirect factors, each of which would contribute to the variations in the amplitude of the H-reflex tested.

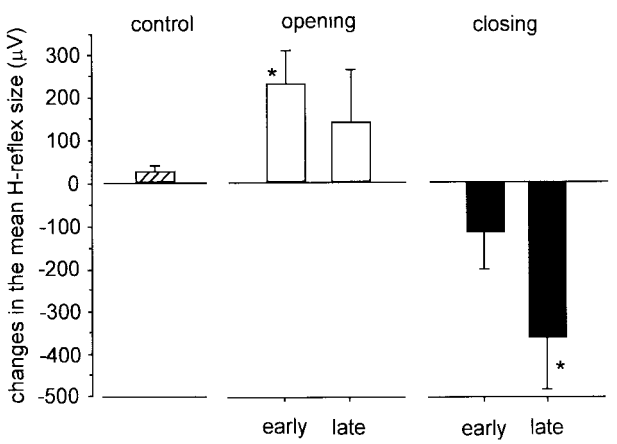


FIGURE 3. Changes in excitability of the H-reflex in flexor digitorum superficialis while subjects observed a video showing a human hand opening to extend a rubber band (white columns) or closing onto a sphere (black columns). The reflex elicited either 250 ms (early) or 750 ms (late) after the onset of the observed movement. The target muscle was quiescent throughout the experiment. The asterisks indicate significant differences ($P < 0.05$) in amplitude, with respect to the control condition (observing a stationary hand). The data are the average from six subjects. (Modified from Baldissera et al.,[3] with permission).

Postactivation Depression and the H-Reflex. As the term postactivation depression implies, the history of activity at the Ia afferent to α-motoneuron synapse is an important factor affecting transmission in the H-reflex arc. It has been suggested that postactivation depression results from reduced release of neurotransmitter from synaptic terminals that have recently been activated.[49,60,85] If this is the case, then any prior activation of the Ia afferent can be expected to lead to a reduction in the available neurotransmitter stores in the Ia afferent terminals. If this depletion becomes pronounced, there will be insufficient stores to allow a full quantum of transmitter to be released with subsequent activations. This mechanism is believed to be responsible for the well-characterized pattern of postactivation depression observed with H-reflex testing.[49,60,75] In fact, postactivation depression (in which subsequent H-reflexes are smaller in amplitude than preceding reflexes) persists for about 8 s.[63] This has important implications for the techniques used in H-reflex testing.[27,90] That is, postactivation depression may be an important factor leading to changes in H-reflex amplitude for any study that attempts to use H-reflex testing during movements. This would particularly be the case during movements that will change the length of the target muscle. Changing the length of the target muscle will activate the muscle spindle stretch receptors. This, in turn, will result in activation of the very Ia afferents which will then be accessed when eliciting the H-reflex. This prior activity in the Ia afferents could lead to suppression of the H-reflex due to postactivation depression.[9,49,89] It should also be remembered that the prior activity in the Ia afferents may render some of these afferents refractory at the time the electrical stimulation to the nerve is delivered, thereby reducing transmission through the H-reflex arc due to reduced Ia afferent recruitment.[9]

One of the techniques that has been used to minimize the effects of postactivation depression is to brace securely the joints that a muscle crosses so as to reduce the stretch imposed on the test muscle.[5] However, this technique is not completely adequate to eliminate the possibility of postactivation depression from contributing to changes observed in the H-reflex between tasks. Changes in fusimotor drive may occur, which would then alter Ia afferent discharge, fluctuations in isometric contraction levels can lead to variations in muscle spindle discharge by unloading the muscle spindle, and bracing does not completely eliminate potential muscle length changes. For these reasons, it is recommended that all conditions be tested with bracing of the necessary joints plus maintaining a tonic level of background activity in the test muscle. Although this contraction may itself affect the amount of postactivation depression generated, presumably the effect of postactivation depression will be consistent between conditions.

Fluctuations in Motoneuron Excitability. It is without question that the excitability of the motoneuron pool plays a substantial role in determining the amplitude of the H-reflex. The point of the preceding arguments was not to dispute this fact, but to highlight the importance of premotoneuronal events in determining the amplitude of the H-reflex as well. The relation between background EMG levels and H-reflex amplitude is well established.[79] The changes in amplitude of the H-reflex that occur during movement can often be largely related to the level of ongoing EMG activity in the test muscle. Moreover, in the quiescent muscle, the level of excitability of the motoneuron pool is not necessarily stable. With converging excitatory and inhibitory postsynaptic events, the level of depolarization of motoneurons may rise and fall below the threshold for activation, leading to changes in H-reflex amplitude with no overt EMG activity. As an example, the soleus H-reflex is largely abolished during the swing phase of locomotion when the soleus muscle is electromyographically quiescent.[14,15,32,35,80,81] In contrast, an H-reflex is readily elicited from the quiescent soleus muscle when a subject is seated. Reciprocal inhibition related to the contraction of the antagonist muscle, via postsynaptic inhibition, is strongly implicated in the abolition of the soleus H-reflex during the swing phase of walking.[80]

Intrinsic Properties of Motoneurons. Variations in the amplitude of the H-reflex may also arise from variations in the intrinsic properties of motoneurons. For example, Wolpaw's group have described long-term adaptations in the magnitude of the H-reflex in animal models induced by training.[87,88] A portion of these adaptations was due to changes at the motoneuron itself. This is of importance if comparisons are to be made between groups of individuals (such as patient populations vs. non-patients) whose motor systems may have undergone extensive plastic changes, or within individuals if recordings are made over long periods of time (for example, before and after a training regimen). More short-term and immediate changes in motoneuron properties may also affect the amplitude of the H-reflex. For example, the neuromodulator 5-hydroxytryptamine [(5-HT) serotonin] is capable of changing the firing properties of motoneurons.[57] There is evidence from animal studies that this substance contributes to the generation of plateau potentials in motoneurons, which alters the firing characteristics of the motoneuron.[48] There is mounting evidence that similar changes in the firing properties of human motoneurons occur.[21,23] The implication is that with a change in task or state, there may be a concomitant change in motoneuronal properties that affects the recruitment gain of the H-reflex.

H-Reflex Amplitude Is the Product of Complex Interactions. As can be seen, despite the relative simplicity of the neural circuitry that mediates the H-reflex, the regulation of the amplitude of the H-reflex remains very complex. From the preceding discussion, it seems obvious that the amplitude of the H-reflex can be affected by many factors related to the physical or mental state of the individual. This makes usage of the H-reflex as an experimental tool problematic if care is not taken to control, or at least minimize, the effects of extraneous variables. For example, simple changes in posture can have a profound influence on the magnitude of the H-reflex. These changes in H-reflex amplitude can be derived from changes in homonymous afferent firing (postactivation depression), from heteronymous intralimb afferent signals resulting in both postsynaptic changes in motoneuron excitability or presynaptic inhibition, interlimb afferent influences (presumably including contralateral, ipsilateral, and diagonally related limbs), vestibular-induced changes in reflex excitability, potential changes in postural set,[76] descending motor commands, or attention.[47] The amplitude of the H-reflex will reflect the net influence of these inputs to the reflex arc. It remains to be determined how each of these individual signals is integrated and to what extent they may affect the amplitude of the H-reflex.

It is also probable that, with a simple change in posture, some of these influences will interact in rather complex ways. For example, as described above, stimulation of cutaneous afferents in the cat does not lead to direct presynaptic inhibition of Ia afferents, but rather suppresses the presynaptic inhibition that is induced by heteronymous Ia afferents.[78] This sort of complex interaction between regulatory inputs is also evident in humans.[53] As described more fully later in this review, Knikou and Rymer[59] demonstrated that changing the static position of the hip results in a switching of the influence of foot sole stimulation on the amplitude of the soleus H-reflex. Such an interaction between conditioning stimuli has important implications, not only in the understanding of the regulation of simple spinal reflexes in motor control research, but also in the technical considerations for using the H-reflex.

The multiple factors that influence the amplitude of the H-reflex make it difficult to use the H-reflex in research or clinical settings. Careful consideration must be given to the extraneous variables. For example, if one wishes to compare the H-reflex between condition A and condition B, then only those factors that change specifically due to condition can be allowed to change. Did the subject look to one side during condition A and the other during condition B? How will this impact the H-reflex amplitude? For the most part, using sufficiently large numbers of subjects and adequately randomizing the experimental protocol can account for these factors. However, attention needs to be paid to ensure that no systematic changes occur that are not intended by the change in condition. If this occurs and cannot be remedied, these additional variables must be measured and accounted for in the statistical analysis. Even then, the potential for confounding factors influencing the data, and thus the conclusions drawn, makes the use of the H-reflex challenging. These factors are paramount in the clinical setting, where the measures from an individual are used either diagnostically or as a means of assessing change over time. Can one be certain that all extraneous factors are adequately controlled in the individual to gain meaningful measures of H-reflex amplitude?

USING THE H-REFLEX AS A NEURAL PROBE

Despite the limitations described in the preceding section, the H-reflex remains a useful probe to study the neural control of movement. This is particularly true in human motor control research, where the techniques available to gain detailed understanding of the workings of the nervous system are limited. The relative ease with which the H-reflex can be recorded, using surface stimulation and recording techniques, from various muscles throughout the body creates opportunity to study many aspects of neural control in motor systems. In the following sections, some of the potential uses of the H-reflex as a probe into the neural mechanisms of motor control will be explored.

Probe for Investigating the Functional Organization of Neural Circuitry. Electrical stimulation of a nerve, so as to generate an H-reflex, results in a synchronous activation of the recruited Ia afferents, with a subsequent relatively synchronous activation of a portion of the pool of target motoneurons. As a result, relatively subtle changes in the excitability of the reflex arc are readily detected. This means, for example, that changes in motoneuron excitability are more readily detected with an H-reflex than from the ongoing EMG trace. The implication is that the amplitude of the H-reflex is a more sensitive measure of neuronal interactions than is simple electromyography. As such, using the H-reflex is more likely to detect functional neuronal interactions, which affect a particular motoneuron pool. Of course, the caveat is that it may not be possible to distinguish between changes due to motoneuron excitability rather than presynaptic inhibition. Nevertheless, a conditioning stimulation applied elsewhere in the body (for example), which then leads to suppression or facilitation of the H-reflex, clearly indicates some form of connectivity.

The use of the H-reflex in this role has been invaluable in describing the neural connections that exist in humans, which may contribute in regulating movements. For example, Iles and Roberts[53] used conditioning stimulation (either electrical or vibratory) of afferent pathways onto the H-reflex in various muscles of the leg. In doing so, many of the heteronymous presynaptic interconnections that were identified earlier in the cat were also described in the human. In other instances, the effects of mechanical or electrical conditioning stimuli have described changes in excitability of H-reflex pathways due to activation of afferents for muscles of the leg (for example, Cheng et al.[17]) and arm (for example, Cavallari and Lalli[16]). More natural activation of afferents can also be used to identify the presence of certain neuronal connections. For example, passively rotating the legs in a cycling motion leads to suppression of soleus H-reflexes in humans, attributed to presynaptic inhibition initiated by afferent sources (see Brooke et al.[5] for review). By isolating

the motion to that of individual limbs[18,24,65] or even individual joints,[8,68] greater detail of the neuronal connectivity that must exist between the limbs and limb segments was described. Similar movement-related suppression of H-reflexes has recently been reported for arm muscles.[38,91] In addition, Hiraoka and Nagata[46] described suppression of the soleus H-reflex with passive motion of the ipsilateral arm, identifying a neuronal interconnection between afferent feedback from the arm and spinal reflexes in the leg.

Although the specific neuronal connections may not always be readily identified using this approach, the identification of an alteration in H-reflex amplitude by a conditioning stimulus elsewhere indicates interaction. Further experiments can then be performed to begin to identify the involved neural structures. For example, McIlroy et al.[65] described suppression of the soleus H-reflex with passive cycling motion of the legs. Later, Brooke et al.[7] demonstrated that the inhibition of the H-reflex occurred at a short-latency following the onset of movement, suggesting that spinal circuitry mediated the effect (Fig. 4A). Brooke et al.[7] also demonstrated that the movement-induced suppression of the soleus H-reflex was present in individuals with a clinically complete cervical spinal cord injury, further suggesting the spinal nature of the circuitry involved (Fig. 4B).

Changes in the excitability of the H-reflex can also indicate the existence of more complex interactions, which may provide insight into the integrative processes of some neuronal circuitries. Knikou and Conway[58] showed that application of pressure to the sole of the foot significantly depressed the soleus H-reflex. It was later demonstrated that electrical stimulation of the plantar skin also produced inhibition of the soleus H-reflex if the hip was in a flexed position.[59] However, changing the position of the hip to extension resulted in the same electrical stimulation of the plantar skin to produce facilitation of the H-reflex. This study indicates that stimulation of the foot sole accesses an inhibitory and facilitatory pathway onto the soleus H-reflex pathway, and that the afferent feedback associated with hip joint angle is used as a switch between them. When studied in conjunction with other reflexes or pathways, the modulation or lack of modulation of the H-reflex can provide even further insight into the organization of neuronal circuitry. Zehr et al.[92] showed a differential task-dependent modulation between a cutaneous reflex recorded in soleus and the soleus H-reflex during leg cycling, suggesting the two reflex systems are regulated by independent mechanisms.

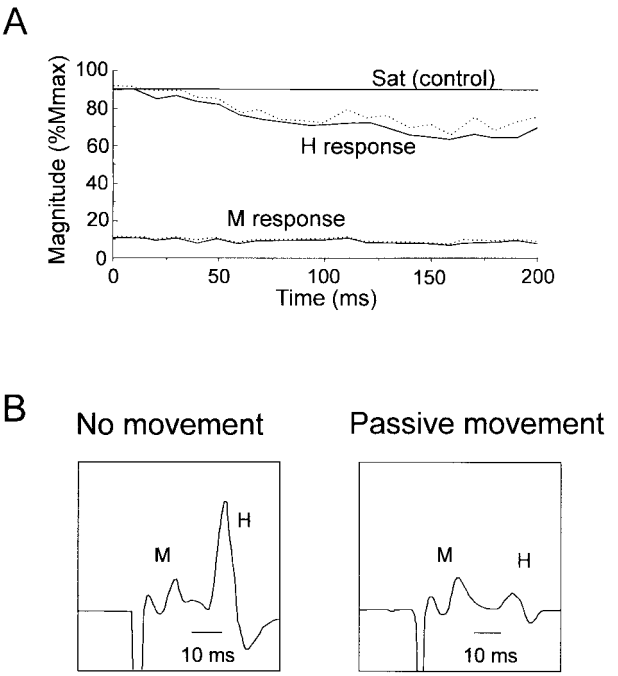


FIGURE 4. (A) Changes in soleus H-reflex amplitude following the onset of passive pedaling. The data are the average data from one subject. The amplitude of the H-reflex, along with one standard error (broken line) are depicted for 200 ms after the onset of the movement. The control reflex amplitude is represented by the horizontal line (Sat). The average M-wave amplitude is also shown for comparison. Note that the depression of the H-reflex occurs at a short latency after movement onset, suggesting spinal circuitry mediates the effect. **(B)** Movement-induced depression of the soleus H-reflex in a clinically complete quadriplegic subject. The left panel shows average H-reflexes (n = 20) for the control (no movement) condition. The right panel shows average H-reflexes (n = 12) when the leg was moved at a pedaling rate of 20 rpm. (Adapted from Brooke et al.,[7] with permission).

The direct identification of neuronal circuitry in the human is limited by the obvious restrictions placed upon human experimentation. The H-reflex allows an indirect look into the organization and connectivity within the sensory-motor systems of the human. Though indirect, the changes in H-reflex excitability that follow various conditioning stimuli allow for conclusions to be drawn about circuitry that must exist to allow the modulation to occur. In some instances, this indirect evidence extends to humans circuitry previously described in an animal model with more direct measures (for example, Iles and Roberts[53]). In other instances, the indirect evidence from humans is later corroborated by more direct evidence from an animal model.[66,70] Regardless, with careful design and creative approaches, the H-reflex provides the possibility to describe aspects of neuronal organization and function in the human.

Probe for a Change in State of Spinal Excitability. In the preceding section, the idea was discussed that neuronal organization could be explored using the H-reflex as a probe, where discrete stimulation of one neural structure (or a group of closely related structures) leads to changes in the excitability of the H-reflex arc. The main point was that by using such a technique, relatively specific connections could be explored. In this section, more generalized conditioning will be explored, involving multiple neural structures and less readily defined circuitry. Ultimately, generalized changes in excitability will also lead to discussions about possible neural circuitry that mediate those changes. Consequently, the previous section and this section are closely related. Indeed, the description of a change in H-reflex excitability can then lead to specific experimental approaches to elucidate the circuitry and mechanisms involved.

Prior to a voluntary movement, the H-reflex is facilitated about 100 ms before the onset of the EMG activity in the agonist muscle.[25] This facilitation is evident with similar timing during a choice reaction test, where the subject must first select the appropriate movement following a go signal.[33,34] Riedo and Rüegg[77] demonstrated that neither the reaction time associated with such a task, nor the premovement increase in soleus H-reflex excitability were affected when subjects performed similar choice reaction tasks while maintaining a steady background level of EMG activity in the target muscle (Fig. 5). The implication is that with the onset of a voluntary movement there is a change in the excitability of the H-reflex arc, largely by altering presynaptic inhibition, which may reflect a state-dependent change in the general excitability of spinal systems in preparation for movement. Collins et al.[20] later showed that changing the kinesthetic requirements of a movement performed in a simple reaction-time task did not result in changes to the premovement modulation of the soleus H-reflex. This suggests that the alteration in soleus H-reflex excitability was associated with preparation of movement and not related to changing sensory requirements of the task, indicating that descending commands prior to movement alter spinal reflex excitability. Similar changes in soleus H-reflex excitability in the foreperiod of a reaction sit-to-stand movement have been described,[42] suggesting that premotor changes in soleus H-reflex excitability and presumably other spinal reflexes, reflect a change in state of the spinal neural circuitry that occurs with a change in task. The results of Hasbroucq et al.[43] suggest that these changes are associated with a change in motor state of spinal neural circuitries. It was shown that increasing the complexity of a choice reaction task, thereby increasing the reaction time, did not alter the timing of the changes in H-reflex excitability with respect to the onset of the EMG burst in the target muscle, in this case the flexor pollicis brevis. That is, the changes in flexor pollicis brevis H-reflex excitability were observed at the same time prior to EMG onset, regardless of the time required to select the appropriate reaction, indicating that the reflex modulation is a component of the motor command associated with movement and not part of the planning or selection processes.

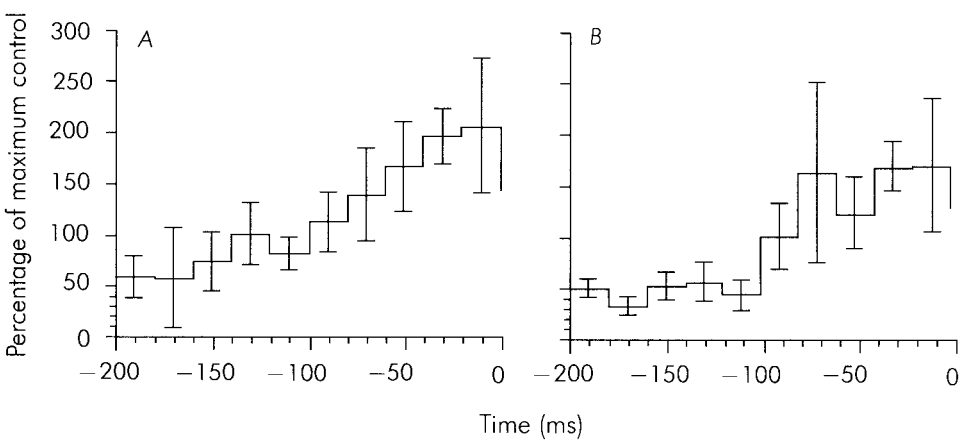


FIGURE 5. Facilitation of the soleus H-reflex prior to the onset of a voluntary reaction movement. In each panel, reflexes were evoked with stimuli that evoked responses of 60% of their maximum value. Panel **(A)** represents data obtained with the soleus muscle initially quiescent, whereas panel **(B)** represents data obtained with the soleus muscle tonically activated. Time, along the abscissa, represents the time prior to the mechanical response associated with the movement. The data are the averages from one subject, and the bars represent the 95% confidence limits. (Modified from Riedo and Rüegg,[77] with permission).

Task-dependent modulation of the soleus H-reflex during locomotion has received considerable attention over the past 20 years.[26] Capaday and Stein[14] described a decrease in the amplitude of the soleus H-reflex during walking, compared to standing, and later, a further decrease in H-reflex amplitude when subjects were running.[15] In contrast, Simonsen and Dyhre-Poulsen[81] concluded that there was no task-dependent difference in the amplitude of the soleus H-reflex between walking and running. There are two reasons for the apparent discrepancy in results. First, Simonsen et al.[82] demonstrated that the maximal M-wave in soleus varies systematically across the step cycle, presumably due to the systematic changes in muscle geometry beneath the recording electrodes. Consequently, Simonsen and Dyhre-Poulsen[81] normalized the amplitude of the H-reflex to the amplitude of the maximal M-wave for the same point in the step cycle. (This contrasts to the more common technique, as utilized by Capaday and Stein,[14,15] of normalizing the amplitude to a single measure of the maximal M-wave, usually obtained during standing or sitting.) Simonsen and Dyhre-Poulsen[81] demonstrated that normalizing the amplitude of the H-reflex to the corrected maximal M-wave reduced some of the variation in the amplitude of the H-reflex described by Capaday and Stein.[14,15] Second, Simonsen and Dyhre-Poulsen[81] based their conclusions on the measure of the peak H-reflex amplitude during the step cycle. The conclusions drawn by Capaday and Stein[14,15] were based on the discrepancy in the amplitudes of H-reflexes between tasks for any given level of background EMG in soleus. Simonsen and Dyhre-Poulsen[81] did not make this comparison. However, examination of the data presented by Simonsen and Dyhre-Poulsen[81] suggests that, for a given level of background EMG, there is a similar discrepancy in H-reflex amplitudes between walking and running. More recently, Ferris et al.[35] demonstrated both of these results. That is, the peak amplitude of the H-reflex is comparable between walking and running, but the amplitude of the H-reflex is larger during walking, compared to running, for any given level of background EMG. Therefore, it would appear that the controversy regarding the task-dependent modulation of the soleus H-reflex during locomotion was largely the result of differences in approach to the analysis of the data.

Despite this recent debate regarding the task-dependent modulation of the H-reflex during locomotion, there is substantial evidence demonstrating a gait-dependent suppression of the soleus H-reflex. The amplitude of the soleus H-reflex is smaller during running, compared with walking, for any given level of background EMG.[15,35] This suggests that there is a task-dependent modulation in the level of presynaptic inhibition of the H-reflex. It has been suggested that the change in presynaptic inhibition between tasks can be attributed to both changes in the afferent feedback associated with the change in behavior[5] as well as changes in central commands.[15,80] Task-dependent modulation of H-reflexes in arm muscles with cycling movements of the arms show similar characteristics,[38,91] indicating a degree of generalizability in the regulation of H-reflexes.

As described above, Gosgnach et al.[41] recently showed that electrical stimulation of the mesencephalic locomotor region to induce fictive locomotion in the decerebrate cat resulted in a tonic level of presynaptic inhibition of Ia afferents prior to the onset of locomotion, which remained throughout the time the cat walked fictively. The implication is that the activation of the mesencephalic locomotor region brings the spinal cord circuitry into a locomotor state, which is reflected in part by the change in excitability of spinal reflexes. This mechanism is probably implicated in the presynaptic inhibition of the soleus H-reflex observed between locomotor tasks[14,15,26] and the modulation of H-reflexes that has been observed prior to the onset of stepping[61] or walking,[32,86] reflecting a change in the spinal circuitry from a resting state to a locomotor state.

Changes in excitability of the H-reflex can also occur in the absence of any movement, whether ongoing or impending. Mental rehearsal or simulation of a motor task has been shown to produce an increase in the amplitude of the H-reflex in the muscles (studied in both arm and leg muscles) that would be the prime movers for the task, independent of changes in the background level of EMG activity.[4,40] The implication of these studies is that imagining movement, which has been shown to involve activation of supplementary motor area, premotor cortex, cerebellum, and basal ganglia, results in a change in the excitability of spinal neural structures, even if no movement is ever intended. As described above, Baldissera et al.[3] demonstrated that simply observing the video image of a hand opening and closing resulted in modulation of H-reflex amplitude in the flexor digitorum brevis. The authors argue that this modulation of the spinal neural systems may be important to prevent the execution of the motor task being watched by the subject. Again, the implication is that the state of neural structures at the spinal level is modified to ensure that the appropriate behaviors are expressed.

Attention may also lead to changes in state of spinal neural structures. Honore et al.[47] observed differential regulation of the facilitation of soleus H-reflexes produced by a mild electrical conditioning stimulus applied to the sural nerve depending upon whether the subjects attention was focused on the cutaneous field of the ipsilateral leg or contralateral leg. This demonstrates that attention can also selectively alter the excitability of spinal circuitry.

In each of the examples described above, changes in the excitability of the H-reflex were documented and suggested changes in the state of spinal neural circuitry. In some instances, the changes in H-reflex excitability were directly related to a change in functional requirements of the reflex arc with a change in task. In other instances, it is unclear whether the changes in reflex excitability reflected a functional change in the reflex pathway or were epiphenomena of a generalized change in spinal excitability. Nevertheless, the above examples demonstrate that the H-reflex is one tool available to determine whether a change in the state of spinal neural circuitry has occurred. One caveat is that the H-reflex cannot be assumed to be able to detect all changes in state in spinal excitability. Staines et al.[83] showed that attending to the position of a passively moving foot resulted in facilitation of tibial nerve somatosensory evoked potentials, but no change in soleus H-reflex amplitude, compared to unattended movements. Presumably, the change in attention resulted in a change in excitability of spinal neural systems, as suggested by the results of Honore et al.[47] However, for this particular task, the circuitry of the simple H-reflex (that is, not conditioned by other sources, such as sural nerve stimulation) was not affected and therefore was incapable of indicating any change.

Probe for Modulation of Presynaptic Inhibition of Ia Afferents. As indicated earlier, the amplitude of the H-reflex is subject to presynaptic inhibition. If the assumption is accepted that the H-reflex is largely reflective of the Ia monosynaptic reflex arc, then the H-reflex can be used to monitor changes to the level of presynaptic inhibition affecting the Ia afferent terminals with monosynaptic connection to motoneurons. Several techniques utilizing the H-reflex have been proposed to investigate the level of presynaptic inhibition that is present at human Ia afferent terminals. These include (1) monitoring H-reflex amplitude in muscles with a maintained tonic activation level,[13] (2) assessing the amplitude of heteronymous Ia monosynaptic facilitation while maintaining a constant amplitude test H-reflex,[50] or (3) measuring the extent of H-reflex suppression produced by vibration of the antagonist muscle at a set latency[50] or a conditioning electrical stimulation of the antagonist motor nerve.[51]

Assessment of Presynapic Inhibition with Tonic Contraction. The most common method of determining whether the H-reflex is modulated by presynaptic inhibition is to record the reflexes while the subject maintains tonic contraction of the target muscle (see Zehr[90]). This method assumes that maintaining a tonic level of activity indicates a tonic level of membrane depolarization, when averaged over the whole of the motoneuron pool. Thus, any changes in H-reflex amplitude in this situation must occur prior to the motoneuron. However, this technique has limitations that are often overlooked. First, steady tonic activity in a muscle is a rather artificial condition not normally seen during natural movements. Consequently, this technique is less than optimal if phase-dependent modulations of presynaptic inhibition are of interest. Some authors have attempted to use H-reflexes recorded when background EMG levels are matched during a movement, or between different movements. However, the geometry of the muscle and the location of the stimulating and recording electrodes may not be the same, and these factors also affect H-reflex amplitude (see Simonsen and Dyhre-Poulsen[81]). One way to overcome this is to minimize changes in length of the target muscle by bracing the necessary joints, and then instructing the subjects to maintain a tonic contraction of the target muscle. The shortcoming of this compensatory method is that the movement being studied will no longer be completely natural, and unknown changes to the control of presynaptic inhibition may be brought about by this novel and artificial motor task.

Second, increasing the excitability of the motoneuron pool with a tonic level of contraction will potentially bring all motoneurons not currently firing ("subliminal fringe") closer to threshold. Thus, the excitatory input necessary to bring these motoneurons to threshold is reduced. Consequently, in H-reflex testing, less transmission from the Ia afferents to the motoneurons is needed to activate the motoneurons and generate a reflex in the EMG. The implication is that by raising the excitability of the motoneuron pool, the smallest amount of excitation onto the motoneurons will bring them to threshold and generate an H-reflex that is close to maximal amplitude. Larger excitatory inputs would not be distinguishable as the motoneurons are already maximally recruited by the smallest inputs. The result would be that presynaptic inhibition of the Ia affer-

ents could be present, but that the modulation in transmitter release results in excitatory inputs that are always sufficient to generate near-maximal H-reflexes. Misiaszek and Pearson[70] noted such an effect when comparing H-reflexes in the decerebrate cat during sinusoidal stretching of the quadriceps muscle (Fig. 6). In that study, the solution was to lower the stimulus intensity to below threshold for the M-wave. This was possible in the cat as the amplitude of the afferent volley could be recorded directly and used as an indicator of stimulus intensity. In human studies, the M-wave is often the only biological marker of stimulus intensity available and it is highly recommended that this marker be used to ensure constancy of stimulus intensity (see Zehr[90]). Thus, the absence of modulation of the H-reflex when the target muscle is tonically active does not necessarily indicate that presynaptic inhibition is not present. However, modulation of the H-reflex in the presence of a tonically active muscle strongly suggests that presynaptic factors are involved.

Third, this technique cannot be used to assess the level of presynaptic inhibition that is present when there is no contraction of the target muscle. Therefore, this technique cannot be used to assess presynaptic inhibition in activities where the target muscle is the antagonist in the movement. To overcome this limitation, the modulation in amplitude of other pathways, such as other reflexes[50] or descending inputs,[13] onto the target motoneuron pool can be used to determine whether these pathways are similarly modulated. The limitation here is that if these other pathways are also modulated by the task being performed, then interpretation becomes limited, particularly if the pathway and the H-reflex are differentially modulated.

H-Reflex Techniques for Assessing Presynaptic Inhibition. Electrical stimulation of the femoral nerve at group I strength results in a monosynaptic excitation of the ipsilateral soleus motoneuron pool. This facilitation of the soleus motoneuron pool results in facilitation of the soleus H-reflex. Hultborn et al.[50] used this

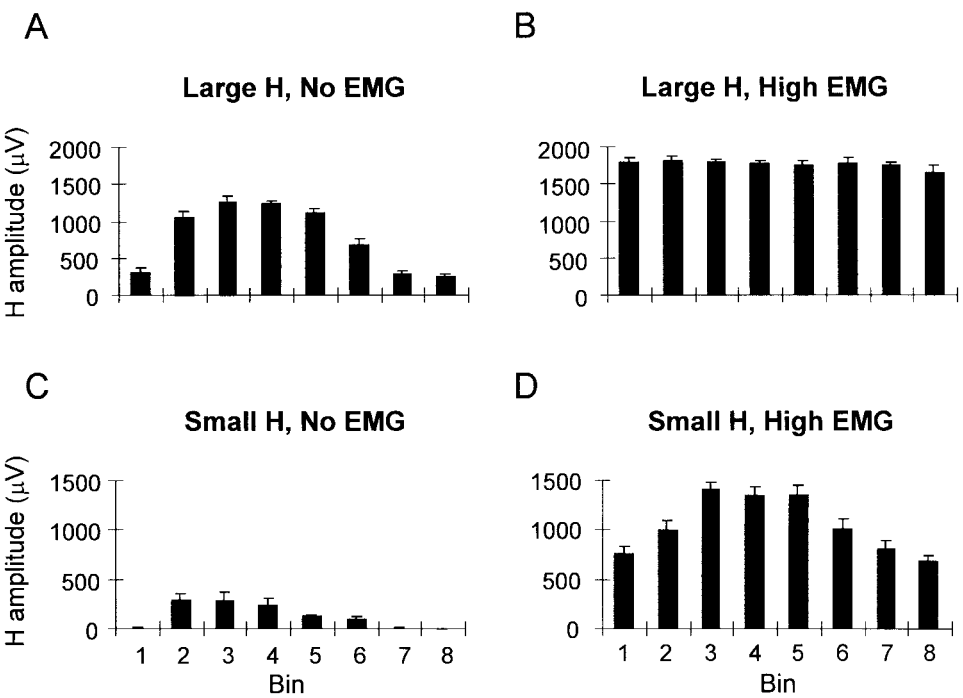


FIGURE 6. Large-amplitude H-reflexes do not modulate with high levels of background activity in the soleus muscle of the cat. Modulation of the soleus H-reflex was induced by applying a sinusoidal stretch of the ipsilateral quadriceps muscle in a decerebrate cat. The ipsilateral leg was extensively denervated and the joints securely fixed to prevent movement. **(A, B)** The average data for reflexes elicited with stimulus strength sufficient to evoke a small M-wave. In **(A),** the soleus muscle was quiescent, whereas in **(B),** the soleus muscle was tonically active, at a level of activity similar to that recorded during spontaneous locomotion on a treadmill. Under these conditions, stretching of the quadriceps failed to induce modulation of the soleus H-reflex. However, if a smaller H-reflex was used, such that no M-wave was evoked by the stimulus, then modulation of the H-reflex with stretching of the quadriceps was observed with the higher levels of background activity in soleus. This is shown in **(C)** and **(D).** The implication is that the Ia afferent excitation derived from the large H-reflex in **(B)** is probably modulated, similar to the other panels. However, it is probably modulated above the level minimally required to bring the motoneurons in the subliminal fringe to threshold. The data were derived from one cat. The cycle of the sinusoidal stretch of the quadriceps was divided into eight equispaced bins for averaging the data. EMG, electromyogram. (Modified from Misiaszek and Pearson,[70] with permission).

facilitation from quadriceps onto soleus as a way of assessing presynaptic inhibition induced by short vibration of tibialis anterior (Fig. 7). In order to quantify the level of presynaptic inhibition, these authors compared the amount of facilitation of the soleus H-reflex that was produced by the femoral nerve stimulation when the test soleus H-reflex was matched between conditions. That is, they raised the stimulus intensity for the soleus H-reflex so that the amplitude of reflex with vibration of tibialis anterior (but without femoral nerve stimulation) matched the amplitude of the H-reflex previously observed with no prior conditioning (vibration or femoral nerve stimulation). In effect, they ensured that the excitability of the soleus motoneuron pool was matched when the vibration was present and when it was absent. Thus, any change in the amplitude of the heteronymous facilitation was attributed to presynaptic mechanisms. With this technique, the H-reflex

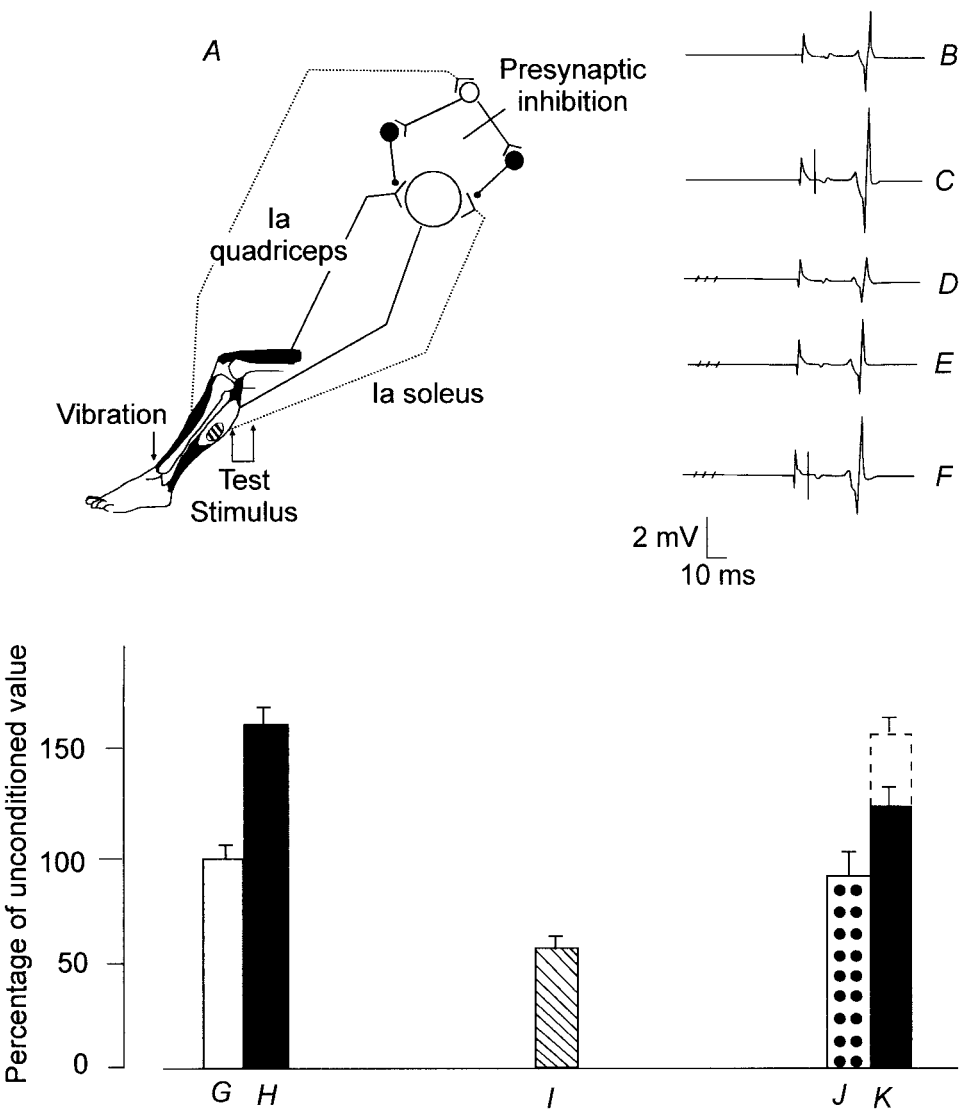


FIGURE 7. Variations in the facilitation of the soleus H-reflex by stimulation of Ia afferents from quadriceps can be used to estimate the level of presynaptic inhibition of the heteronymous projections. The soleus H-reflex in this case is used to assess the amount of facilitation that is induced by stimulation of the Ia afferents from quadriceps [compare **(B),** unconditioned soleus H-reflex, with **(C),** H-reflex with facilitation from quadriceps Ia afferents]. Actual records of the H-reflex are shown in **(B–F)** and the corresponding peak-to-peak magnitudes of the reflexes are shown as histograms **(G–K).** Vibration of the tibialis anterior muscle is used to induce presynaptic inhibition onto the afferents from both the soleus and quadriceps muscles **(A).** This results in suppression of the soleus H-reflex **(I).** If the amplitude of the soleus H-reflex during tibialis anterior vibration is then increased so as to match the unconditioned reflex **(G)** by increasing stimulus intensity **(J),** then the excitability of the soleus motoneuron pool can be assumed to be matched. Consequently, any difference in the amplitude of the heteronymous facilitation [compare **(K)** with **(H)**] reflects the amount of presynaptic inhibition onto the quadriceps Ia afferents induced by the vibration. (Modified from Hultborn et al.,[50] with permission).

assists in determining the amount of presynaptic inhibition that is affecting the heteronymous Ia monosynaptic projection from quadriceps onto soleus motoneurons.

Vibration of the tibialis anterior or electrical stimulation of the common peroneal nerve induces presynaptic inhibition of the soleus H-reflex pathways.[50,74,90] In this situation, the H-reflex is used (with maintained contraction of the soleus muscle) to identify changes to the level of presynaptic inhibition that is generated by the conditioning stimulus. Thus, the H-reflex is used to monitor the extent of presynaptic inhibition generated by this technique. Therefore, changes in the amplitude of the H-reflex reflect a change in the level of presynaptic inhibition generated by stimulation of the group I afferents from tibialis anterior. One of the limitations of this technique is that it is difficult to determine constancy of stimulation of Ia afferents using vibration. Therefore, electrical stimulation of the common peroneal nerve and monitoring the amplitude of the direct motor response in tibialis anterior are preferred.

For the two techniques described above, which use some combination of conditioning stimulation of the H-reflex to assess the level of presynaptic inhibition, there are some common limitations that need to be raised. First, any interpretation of the results is limited to discussion of the specific pathways being tested. That is, the presence or absence of presynaptic inhibition of the heteronymous monosynaptic projection from quadriceps to soleus (the Hultborn technique[50]) indicates presynaptic inhibition of only that pathway. Extension to other pathways, even the quadriceps H-reflex, which utilizes the same Ia afferents, cannot be made. It is argued that one of the functions of presynaptic inhibition is to selectively gate sensory inputs.[78] Therefore, it must be assumed that influences of presynaptic inhibition at one afferent terminal branch are specific for that terminus. Indeed, it has been shown that presynaptic inhibition in one terminal does not affect transmission in other terminals of the same afferent in cats.[19] Second, Capaday[13] states, "these techniques depend upon using a peripheral nerve as a conditioning input with the tacit assumption that the conditioning is itself not modulated in some way (e.g., presynaptically) by the motor task(s)." This is an important point and one that cannot be easily overcome technically. Third, these techniques were developed utilizing specific pathways and largely isolated to the leg in humans. It is not yet clear whether similar techniques can be extended to other pathways or to the arm, which may limit the utility of these approaches.

Probe for Motoneuron Pool Excitability. The common argument that the H-reflex is a measure of the excitability of the target motoneuron pool is no longer valid (see above). Nevertheless it is possible to use the H-reflex in a limited way to monitor motoneuron pool excitability. For example, the technique of Hultborn et al.[50] is a means by which the H-reflex is utilized to ensure that the Ia monosynaptic facilitation from heteronymous sources is tested against a stable level of motoneuron excitability. By ensuring that the unfacilitated (test) H-reflex is of constant amplitude between conditions, Hultborn et al.[50] were able to assess whether the heteronymous Ia projections onto the same motoneurons were presynaptically inhibited. Similarly, Devanne et al.[28] showed that H-reflexes in extensor carpi radialis remained constant in amplitude, while the motor evoked potentials in this muscle, arising from transcranial magnetic stimulation, were facilitated during various "pointing" tasks. This helped to rule out the possibility that the enhanced motor evoked potentials were due to task-dependent differences in the recruitment gain of the target muscle, as such a change would result in parallel results for the H-reflex amplitude. Thus, the H-reflex can be used to indicate that the excitability of the motoneuron pool is constant if the H-reflex amplitude remains constant between conditions.

Probe for Adaptation in Spinal Structures in Health and Disease. Perhaps one of the more promising uses of the H-reflex in motor control research is as a probe for adaptations in the function of spinal structures (1) with training, (2) following injury or disease, or (3) with therapeutic interventions. In this usage, identifying that the manner in which the H-reflex is regulated differs between populations may be of importance in itself, the specific mechanism being of secondary importance. Subsequently, the mechanism of the adaptation can be elucidated. The best example of using the H-reflex in this manner is the work from Wolpaw's group on operant conditioning of the H-reflex. Initially, animals were trained to either upregulate or downregulate the amplitude of the H-reflex.[87] Over time, the amplitude of the H-reflex changed in the desired direction. Subsequently, the mechanisms for the adaptation in reflex size were investigated and thought to include changes: (1) in motoneuron membrane properties, (2) at interneuronal terminals onto the motoneurons, (3) at Ia afferent terminals, and (4) in corticospinal tract terminals onto interneurons. Similar "training" of the H-reflex has been described in

humans, and presumably involves similar mechanisms for mediating the changes.[88,90]

In a more functional context, the operant conditioning paradigm of Wolpaw and the subsequent description of the neural adaptations that account for the effect can, in part, account for the significantly smaller-amplitude soleus H-reflexes observed in the members of the Royal Danish Ballet, compared with other elite athletes.[72] More recently, Aagaard et al.[1] demonstrated that H-reflexes recorded during maximal voluntary contraction increased in amplitude following 14 weeks of resistance training, whereas the amplitude of the H-reflex when the muscle was at rest was not altered by the training. These authors argue that the adaptation in H-reflex amplitude reflects training-induced modifications in the excitability of the reflex arc, which may include increased central motor drive, elevated motoneuron excitability, or reduced presynaptic inhibition. The implication from both of these studies is that adaptation in the amplitude of the H-reflex can be induced by training that does not include specific training (operant conditioning) of the H-reflex.

One of the limitations in using the H-reflex as an indicator of adaptations in spinal neural systems with training is that it requires that the training modify the components of the H-reflex arc. Whereas observing a change in H-reflex amplitude with some training program indicates adaptation in the function of a spinal reflex, no noticeable changes simply indicate that no change to the excitability of this specific arc were induced by the training. Nevertheless, this result in itself can often be of interest, particularly if adaptations in other pathways are noted.

There have been many studies testing the H-reflex in various populations with neural injury and disease. As the H-reflex can be trained, so too it can be detrained. As a result, what is often described are the ways in which the H-reflex in these patient populations differs from the normal population. For example, numerous studies report on the differential regulation of the H-reflex in comparing elderly subjects to young adults. Changes in the level of presynaptic inhibition,[30,71] differential effects of postural constraints,[2,29] and delays in premovement modulation[12,62] have been cited and the implications with regards to deterioration in motor control discussed. The outcome of such studies is a greater insight into possible mechanisms involved in motor dysfunction in these populations, with then the potential for better attempts at therapeutic strategies. However, much can also be gained from the ways in which the regulation of the H-reflex remains unaffected by injury or disease. For example, the modulation of the soleus H-reflex that occurs during passive pedaling in normal subjects is also present in clinically complete spinal cord–injured subjects[7] (Fig. 4B). The implication is that the neural substrates involved in producing the movement-induced modulation of the H-reflex are probably below the level of the lesion and thus within spinal circuitry. However, from a slightly different perspective, the implication is that there are, contained within the spinal circuitry below the level of the lesion, intact and "normally" functioning circuitries that may be involved in the control and regulation of locomotor activities.

CONCLUSIONS

The H-reflex is a valuable tool in the pursuit of understanding the means by which movements are produced and controlled in humans. There remain limited options for probing neural functioning during human movements. The H-reflex, although restricted in many respects as to the information that can be obtained with its use, is capable of providing much insight into the neural control of human movements. Care in the use of the H-reflex is required to ensure that the results obtained are meaningful and the conclusions drawn are valid. In many cases, the information gained from H-reflex studies in humans have been corroborated by evidence in animal experiments, indicating that the H-reflex is valid in its role. Given the strong publication record of the H-reflex, and the creative uses of this relatively simple test that have been developed in recent years, it is reasonable to speculate that the H-reflex will continue to be an extensively used tool in the field of motor control neurophysiology for the foreseeable future.

I thank Dr. E.P. Zehr for his invaluable comments on an earlier draft of this manuscript. My research is supported by the Alberta Heritage Foundation for Medical Research and the Natural Sciences and Engineering Research Council (Canada).

REFERENCES

1. Aagaard P, Simonsen EB, Andersen JL, Magnusson P, Dyhre-Poulsen P. Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses. J Appl Physiol 2002; 92:2309–2318.
2. Angulo-Kinzler RM, Mynark RG, Koceja DM. Soleus H-reflex gain in elderly and young adults: modulation due to body position. J Gerontol A Biol Sci Med Sci 1998;53:M120–M125.
3. Baldissera F, Cavallari P, Craighero L, Fadiga L. Modulation of spinal excitability during observation of hand actions in humans. Eur J Neurosci 2001;13:190–194.
4. Bonnet M, Decety J, Jeannerod M, Requin J. Mental simulation of an action modulates the excitability of spinal reflex pathways in man. Brain Res Cogn Brain Res 1997;5:221–228.

5. Brooke JD, Cheng J, Collins DF, McIlroy WE, Misiaszek JE, Staines WR. Sensori-sensory afferent conditioning with leg movement: gain control in spinal reflex and ascending paths. Prog Neurobiol 1997;51:393–421.
6. Brooke JD, Cheng J, Misiaszek JE, Lafferty K. Amplitude modulation of the soleus H reflex in the human during active and passive stepping movements. J Neurophysiol 1995;73: 102–111.
7. Brooke JD, McIlroy WE, Collins DF, Misiaszek JE. Mechanisms within the human spinal cord suppress fast reflexes to control the movement of the legs. Brain Res 1995;679:255–260.
8. Brooke JD, Misiaszek JE, Cheng J. Locomotor-like rotation of either hip or knee inhibits soleus H reflexes in humans. Somatosens Mot Res 1993;10:357–364.
9. Burke D. Effects of activity on axonal excitability: implications for motor control studies. Adv Exp Med Biol 2002;508:33–37.
10. Burke D, Gandevia SC, McKeon B. The afferent volleys responsible for spinal proprioceptive reflexes in man. J Physiol (Lond) 1983;339:535–552.
11. Burke D, Gandevia SC, McKeon B. Monosynaptic and oligosynaptic contributions to human ankle jerk and H-reflex. J Neurophysiol 1984;52:435–448.
12. Burke JR, Kamen G. Changes in spinal reflexes preceding a voluntary movement in young and old adults. J Gerontol A Biol Sci Med Sci 1996;51:M17–M22.
13. Capaday C. Neurophysiological methods for studies of the motor system in freely moving human subjects. J Neurosci Methods 1997;74:201–218.
14. Capaday C, Stein RB. Amplitude modulation of the soleus H-reflex in the human during walking and standing. J Neurosci 1986;6:1308–1313.
15. Capaday C, Stein RB. Difference in the amplitude of the human soleus H-reflex during walking and running. J Physiol (Lond) 1987;392:513–522.
16. Cavallari P, Lalli S. Changes in excitability of the flexor carpi redialis H-reflex following tactile stimulation of the index fingertip. Exp Brain Res 1998;120:345–351.
17. Cheng J, Brooke JD, Misiaszek JE, Staines WR. The relationship between the kinematics of passive movement, the stretch of extensor muscles of the leg and the change induced in the gain of the soleus H reflex in humans. Brain Res 1995;672: 89–96.
18. Cheng J, Brooke JD, Misiaszek JE, Staines WR. Crossed inhibition of the soleus H reflex during passive pedalling movement. Brain Res 1998;779:280–284.
19. Clements JD, Forsythe ID, Redman SJ. Presynaptic inhibition of synaptic potentials evoked in cat spinal motoneurones by impulses in single group Ia axons. J Physiol (Lond) 1987;383: 153–169.
20. Collins DF, Brooke JD, McIlroy WE. The independence of premovement H reflex gain and kinesthic requirements for task perfomance. Electroencephalogr Clin Neurophysiol 1993;89:35–40.
21. Collins DF, Burke D, Gandevia SC. Sustained contractions produced by plateau-like behaviour in human motoneurones. J Physiol (Lond) 2002;538:289–301.
22. Collins DF, Frigon A, Hoogenboom N, Zehr EP. Modulation of the soleus H-reflex during upper limb cycling movement. Soc Neurosci Abstr 2002.
23. Collins DF, Gorassini M, Bennett D, Burke D, Gandevia SC. Recent evidence for plateau potentials in human motoneurones. Adv Exp Med Biol 2002;508:227–235.
24. Collins DF, McIlroy WE, Brooke JD. Contralateral inhibition of soleus H-reflexes with different velocities of passive movement of the opposite leg. Brain Res 1993;603:96–101.
25. Coquery JM, Coulmance M. Variations d'amplitude des réflexes monosynaptiques avant un mouvement volontaire. Physiol Behav 1971;6:65–69.
26. Crenna P, Frigo C. Excitability of the soleus H-reflex arc during walking and stepping in man. Exp Brain Res 1987;66: 49–60.
27. Crone C, Nielsen J. Spinal mechanisms in man contributing to reciprocal inhibition during voluntary dorsiflexion of the foot. J Physiol 1989;416:255–272.
28. Devanne H, Cohen LG, Kouchtir-Devanne N, Capaday C. Integrated motor cortical control of task-related muscles during pointing in humans. J Neurophysiol 2002;87:3006–3017.
29. Earles DR, Koceja DM, Shively CW. Environmental changes in soleus H-reflex excitability in young and elderly subjects. Int J Neurosci 2000;105:1–13.
30. Earles D, Vardaxis V, Koceja D. Regulation of motor output between young and elderly subjects. Clin Neurophysiol 2001; 112:1273–1279.
31. Eccles JC, Schmidt RF, Willis WD. Presynaptic inhibition of the spinal monosynaptic reflex pathway. J Physiol (Lond) 1962;161:282–297.
32. Edamura M, Yang JF, Stein RB. Factors that determine the magnitude and time course of human H-reflexes in locomotion. J Neurosci 1991;11:420–427.
33. Eichenberger A, Rüegg DG. Facilitation of the H reflex in a simple and choice reaction time situation. Exp Brain Res 1983;7:130–134.
34. Eichenberger A, Rüegg DG. Relation between the specific H reflex facilitation preceding a voluntary movement and movement parameters in man. J Physiol (Lond) 1984;347:545–559.
35. Ferris DP, Aagaard P, Simonsen EB, Farley CT, Dyhre-Poulsen P. Soleus H-reflex gain in humans walking and running under simulated reduced gravity. J Physiol (Lond) 2001;530:167–180.
36. Fetz EE, Jankowska E, Johannisson T, Lipski J. Autogenetic inhibition of motoneurones by impulses in group Ia muscle spindle afferents. J Physiol 1979;293:171–195.
37. Frank K, Fourtes MGF. Presynaptic and postsynaptic inhibition of monosynaptic reflexes. Fed Proc 1957;16:39–40.
38. Frigon A, Collins DF, Zehr EP. H-reflexes in human forearm muscles are attenuated during rhythmic arm movement. Proceedings of the Fourth World Congress of Biomechanics, Calgary, 2002.
39. Fukushima Y, Yamashita N, Shimada Y. Facilitation of H-reflex by homonymous Ia afferent fibers in man. J Neurophysiol 1982;48:1079–1088.
40. Gandevia SC, Wilson LR, Inglis JT, Burke D. Mental rehearsal of motor tasks recruits alpha-motoneurones but fails to recruit human fusimotor neurones selectively. J Physiol (Lond) 1997;505:259–266.
41. Gosgnach S, Quevedo J, Fedirchuk B, McCrea DA. Depression of group Ia monosynaptic EPSPs in cat hindlimb motoneurones during fictive locomotion. J Physiol (Lond) 2000;526: 639–652.
42. Goulart F, Valls-Sole J. Reciprocal changes of excitability between tibialis anterior and soleus during the sit-to-stand movement. Exp Brain Res 2001;139:391–397.
43. Hasbroucq T, Akamatsu M, Burle B, Bonnet M, Possamai C. Changes in spinal excitability during choice reaction time: the H-reflex as a probe of information transmission. Psychophysiology 2000;37:385–393.
44. Hasbroucq T, Kaneko H, Akamatsu M, Possamai C. The time-course of preparatory spinal and cortico-spinal inhibition: an H-reflex and transcranial magnetic stimulation study in man. Exp Brain Res 1999;124:33–41.
45. Hiraoka K. Phase-dependent modulation of the soleus H-reflex during rhythmical arm swing in humans. Electromyogr Clin Neurophysiol 2001;41:43–47.
46. Hiraoka K, Nagata A. Modulation of the soleus H reflex with different velocities of passive movement of the arm. Electromyogr Clin Neurophysiol 1999;39:21–26.
47. Honore J, Demaire C, Coquery JM. Effects of spatially oriented attention on the facilitation of the H reflex by a cutaneous stimulus. Electroencephalogr Clin Neurophysiol 1983; 55:156–161.
48. Hultborn H. Plateau potentials and their role in regulating motoneuronal firing. Adv Exp Med Biol 2002; 508:213–218.

49. Hultborn H, Illert M, Nielsen J, Paul A, Ballegaard M, Wiese H. On the mechanism of the post-activation depression of the H-reflex in human subjects. Exp Brain Res 1996;108:450–462.
50. Hultborn H, Meunier S, Morin C, Pierrot-Deseilligny E. Assessing changes in presynaptic inhibition of Ia fibres: a study in man and the cat. J Physiol (Lond) 1987;389:729–756.
51. Iles JF. Evidence for cutaneous and corticospinal modulation of presynaptic inhibition of Ia afferents from the human lower limb. J Physiol (Lond) 1996;491:197–207.
52. Iles JF, Pisini JV. Vestibular-evoked postural reactions in man and modulation of transmission in spinal reflex pathways. J Physiol (Lond) 1992;455:407–424.
53. Iles JF, Roberts RC. Inhibition of monosynaptic reflexes in the human lower limb. J Physiol (Lond) 1987;385:69–87.
54. Jankowska E, Johannisson T, Lipski J. Common interneurones in reflex pathways from group 1a and 1b afferents of ankle extensors in the cat. J Physiol (Lond) 1981;310:381–402.
55. Jankowska E, McCrea D, Mackel R. Oligosynaptic excitation of motoneurones by impulses in group Ia muscle spindle afferents in the cat. J Physiol (Lond) 1981;316:411–425.
56. Kennedy PM, Inglis JT. Modulation of the soleus H-reflex in prone human subjects using galvanic vestibular stimulation. Clin Neurophysiol 2001;112:2159–2163.
57. Kiehn O. Plateau potentials and active integration in the 'final common pathway' for motor behaviour. Trends Neurosci 1991;14:68–73.
58. Knikou M, Conway BA. Modulation of soleus H-reflex following ipsilateral mechanical loading of the sole of the foot in normal and complete spinal cord injured humans. Neurosci Lett 2001;303:107–110.
59. Knikou M, Rymer WZ. Effects of changes in hip joint angle on H-reflex excitability in humans. Exp Brain Res 2002;143:149–159.
60. Kohn AF, Floeter MK, Hallett M. Presynaptic inhibition compared with homosynaptic depression as an explanation for soleus H-reflex depression in humans. Exp Brain Res 1997; 116:375–380.
61. Komiyama T, Kasai T. Changes in the H-reflexes of ankle extensor and flexor muscles at the initiation of a stepping movement in humans. Brain Res 1997;766:227–235.
62. Leonard CT, Matsumoto T, Diedrich PM, McMillan JA. Changes in neural modulation and motor control during voluntary movement of older individuals. J Gerontol A Biol Sci Med Sci 1997;52A:M320–M325.
63. Magladery JW, McDougal DB Jr. Electrophysiological studies of nerve and reflex activity in normal man. I. Identification of certain reflexes in the electromyogram and the conduction velocity of peripheral nerve fibres. Bull Johns Hopkins Hosp 1950;86:265–290.
64. Magladery JW, Porter WE, Park AM, Teasdall RD. Electrophysiological studies of nerve and reflex activity in normal man. IV. The two-neurone reflex and identification of certain action potentials from spinal roots and cord. Bull Johns Hopkins Hosp 1951;88:499–519.
65. McIlroy WE, Collins DF, Brooke JD. Movement features and H reflex modulation. II. Passive rotation, movement velocity and single leg movement. Brain Res 1992;582:85–93.
66. Misiaszek JE, Barclay JK, Brooke JD. Inhibition of canine H reflexes during locomotor-like rotation about the knee arises from muscle mechanoreceptors in quadriceps. J Neurophysiol 1995;73:2499–2506.
67. Misiaszek JE, Brooke JD, Lafferty KB, Cheng J, Staines WR. Long-lasting inhibition of the human soleus H reflex pathway after passive movement. Brain Res 1995;677:69–81.
68. Misiaszek JE, Cheng J, Brooke JD, Staines WR. Movement-induced modulation of soleus H reflexes with altered length of biarticular muscles. Brain Res 1998;795:25–36.
69. Misiaszek JE, De Serre SJ, Stein RB, Jiang W, Pearson KG. Stretch and H reflexes in triceps surae are similar during tonic and rhythmic contractions in high decerebrate cats. J Neurophysiol 2000;83:1941–1950.
70. Misiaszek JE, Pearson KG. Stretch of quadriceps inhibits the soleus H reflex during locomotion in decerebrate cats. J Neurophysiol 1997;78:2975–2984.
71. Morita H, Shindo M, Yamagawa S, Yoshida T, Momoi H, Yanagisawa N. Progressive decrease in heteronymous monosynaptic Ia facilitation with human ageing. Exp Brain Res 1995;104:167–170.
72. Nielsen J, Crone C, Hultborn H. H-reflexes are smaller in dancers from The Royal Danish Ballet than in well-trained athletes. Eur J Appl Physiol Occup Physiol 1993;66:116–121.
73. Paquet N, Hui-Chan CWY. Human soleus H-reflex excitability is decreased by dynamic head-and-body tilts. J Vestib Res 1999;9:379–383.
74. Pierrot-Deseilligny E. Assessing changes in presynaptic inhibition of Ia afferents during movement in humans. J Neurosci Methods 1997;74:189–199.
75. Pierrot-Deseilligny E, Mazevet D. The monosynaptic reflex: a tool to investigate motor control in humans. Interest and limits. Neurophysiol Clin 2000;30:67–80.
76. Prochazka A. Sensorimotor gain control: a basic strategy of motor systems? Prog Neurobiol 1989;33:281–307.
77. Riedo R, Rüegg DG. Origin of the specific H reflex facilitation preceding a voluntary movement in man. J Physiol (Lond) 1988;397:371–388.
78. Rudomin P, Schmidt RF. Presynaptic inhibition in the vertebrate spinal cord revisited. Exp Brain Res 1999;129:1–37.
79. Schieppati M. The Hoffman reflex: a means of assessing spinal reflex excitability and its descending control in man. Prog Neurobiol 1987;28:345–376.
80. Schneider C, Lavoie BA, Capaday C. On the origin of the soleus H-reflex modulation pattern during human walking and its task-dependent differences. J Neurophysiol 2000;83: 2881–2890.
81. Simonsen EB, Dyhre-Poulsen P. Amplitude of the human soleus H reflex during walking and running. J Physiol (Lond) 1999;515:929–939.
82. Simonsen EB, Dyhre-Poulsen P, Voigt M. Excitability of the soleus H reflex during graded walking in humans. Acta Physiol Scand 1995;153:21–32.
83. Staines WR, Brooke JD, McIlroy WE. Task-relevant selective modulation of somatosensory afferent paths from the lower limb. Neuroreport 2000;11:1713–1719.
84. Stein RB. Presynaptic inhibition in humans. Prog Neurobiol 1995;47:533–544.
85. Táboříková H, Sax DS. Conditioning of H-reflexes by a preceding subthreshold H-reflex stimulus. Brain 1969;209:155–158.
86. Trimble MH, Brunt D, Jeon H-S, Kim H-D. Modulations of soleus H-reflex excitability during gait initiation: central versus peripheral influences. Muscle Nerve 2001;24:1371–1379.
87. Wolpaw JR. The complex structure of a simple memory. Trends Neurosci 1997;20:588–594.
88. Wolpaw JR, Tennissen AM. Activity-dependent spinal cord plasticity in health and disease. Annu Rev Neurosci 2001;24: 807–843.
89. Wood SA, Gregory JE, Proske U. The influence of muscle spindle discharge on the human H reflex and the monosynaptic reflex in the cat. J Physiol (Lond) 1996;497:279–290.
90. Zehr EP. Considerations for use of the Hoffmann reflex in exercise studies. Eur J Appl Physiol 2002;86:455–468.
91. Zehr EP, Collins DF, Frigon A, Klakowicz P, VanGelder S. Modulation of Hoffmann reflexes in forearm muscles during rhythmic, cyclical human arm movement. Proceedings of the Movement and Sensation International Symposium, Cairns, Australia, Sept. 3–6, 2001.
92. Zehr EP, Hesketh KL, Chua R. Differential regulation of cutaneous and H-reflexes during leg cycling in humans. J Neurophysiol 2001;85:1178–1184.
93. Zehr EP, Stein RB. Interaction of the Jendrassik maneuver with segmental presynaptic inhibition. Exp Brain Res 1999; 124:474– 480.