same molecular approaches that have revealed the extent of the complexity can be used to resolve the accompanying issues of relevance to regulatory mechanisms and physiology.

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The modulation of human reflexes during functional motor tasks

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Spinal reflexes are often viewed as stereotyped motor patterns with limited scope for modification. This presumed invariance is contrasted to the greater adaptive possibilities found in longer latency reflexes or voluntary reactions. However, recent evidence suggests that even short-latency, largely monosynaptic reflexes show a high degree of modulation during simple human motor activities such as walking and standing, and that the pattern of modulation can be specifically altered for the different functional requirements of each activity.

In turning the pages of this magazine, voluntary commands are sent from higher centres such as the motor cortex to the α-motoneurons controlling the arms and fingers. Sensory feedback also comes from the skin, muscles and joints along sensory pathways to the brain and, by reflex, to the motoneurons. Do these various centres function largely independently or do they interact in complex ways? For example, during voluntary movements do higher brain centres also modulate the properties of reflex pathways? Is the modulation specific to and of functional importance for the task being performed? If so, what are the neural mechanisms used to produce this modulation? Answers to these questions, some of which have been

raised over many years[1], are beginning to emerge from studies of natural human motor activities.

One prominent view, proposed by Feldman and his colleagues (recently summarized in an open-commentary format[2]) is that the modification of reflexes is limited to a shift in the threshold of a curve relating joint angle and torque. This view was derived from experimental work on antagonistic muscle groups working about the elbow. For simplicity, the concepts are illustrated in Fig. 1 for a single muscle and its reflexes, as the relationship between muscle length as an input and force as an output. The shape of this relationship is defined by its threshold (the length at which a force output is first seen) and its slope. Note that the slope may be different near threshold than at higher output levels, but in Feldman's view the shape of the input–output curve is fixed. For this reason, he and his colleagues refer to the curve as the 'invariant characteristic'. Voluntary commands can then merely shift the whole curve along the x-axis (i.e. change its threshold).

The slope of the line relating length to force in Fig. 1 has the dimensions of stiffness. A contracting muscle has an intrinsic stiffness that is supplemented by reflex responses. However, muscles generate

force via sliding filaments and cross-bridges that have a restricted working range, so muscle force can suddenly drop if the cross-bridges are stretched beyond their elastic limit. This 'yielding' can be compensated, at least partially, by spinal stretch reflexes[3], so the combined properties of muscles and reflexes can behave more like a simple spring than would the muscles alone. The combination represents the resistance of the muscle or the limb to external disturbances, or more generally, taking inertial and viscous factors into consideration, the mechanical impedance of the muscle or limb. If the combined impedance of the neuromuscular and reflex systems has simple, invariant characteristics, as shown in Fig. 1, it might facilitate the control of voluntary movements by the brain (reviewed in Ref. 4).

Reflex modulation involving higher centres

However, an invariant relationship between sensory input and reflex output is not always desirable. An interesting example was studied by Nashner[5,6]. His subjects stood quietly on a platform (Fig. 2) that could either be translated forward or backward or rotated about a fixed axis. When the platform was translated backward, the ankle was flexed by the forward sway of the body and the ankle extensor muscles were stretched (Fig. 2A). A reflex contraction in these muscles would then extend the ankle and bring the subject back to the upright position. Such a correction would clearly be desirable to maintain an upright posture.

However, if the platform was rotated so as to flex the ankle (Fig. 2B), a stretch reflex in the ankle extensors would be counterproductive. Reflex contraction of the ankle extensors to restore the angle of the ankle would tend to throw the subject off balance in a backward direction. The electromyographic (EMG) responses of the muscle for four consecutive trials are shown in each part of Fig. 2. Clearly, the reflex response to the same sensory input (change in ankle angle) rapidly increased in the translation paradigm, where it was useful, and rapidly decreased in the rotation paradigm, where it was inappropriate.

These dramatic, adaptive changes in reflex amplitude are contrary to the views of Feldman and of Houk mentioned above, but are not conclusive. Only one level of activity (quiet standing) and a limited range of perturbations were used, rather than determining the entire input–output curve. Therefore, these changes may have been due to changes in reflex threshold, rather than in reflex gain. In addition, although the responses probably had a short enough latency to be reflex in origin, the latency from the onset of platform movement was considerably longer (by roughly a factor of two or more) than that of the monosynaptic stretch reflex to these muscles. A role for monosynaptic reflexes cannot be ruled out, because the changes in muscle length were not measured directly, but they were presumably quite slow, continuing for tens or hundreds of milliseconds. Of course, many additional pathways could be contributing to this reflex modulation, and Nashner[5] showed that some patients with cerebellar deficits could not modify their responses in the two tasks, implicating cerebellar structures in the modifications that take place between trials.

Other adaptive modifications of reflexes have been

clearly demonstrated. For example, the properties of the vestibulo-ocular reflex (VOR) can be profoundly modified as a result of wearing prisms that reverse the direction of the visual world or telescopic spectacles that change its size[7,8]. The time course of the VOR adaptation is slow, lasting a period of days or weeks, yet the latency of the reflex remains short. The normal latency is 14 ms in a monkey, consistent with a disynaptic pathway, and modifications are seen at a latency of 19 ms after VOR adaptation[9]. However, the difference of 5 ms allows enough time for information to get to the vestibular cerebellum, go through additional synapses and return to influence the VOR. The modifiability of the reflex does require the integrity of cerebellar and probably other CNS structures[10,11].

Modulation of short-latency reflexes

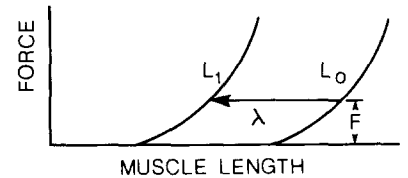Can short-latency, even monosynaptic pathways be modulated on a moment-to-moment basis during

Fig. 1. *Feldman's model in which the curve relating muscle force and length is 'invariant'. According to this model the CNS can merely shift the curve along the x-axis (i.e. change its threshold) without changing its shape. If the threshold is shifted by an amount λ, the length at which the muscle generates a force F that will just balance a load of this magnitude will be shifted from L_0 to L_1. This is the mechanism for postural adjustments in muscle length according to Feldman and his collaborators.* (Adapted from Ref. 2.)
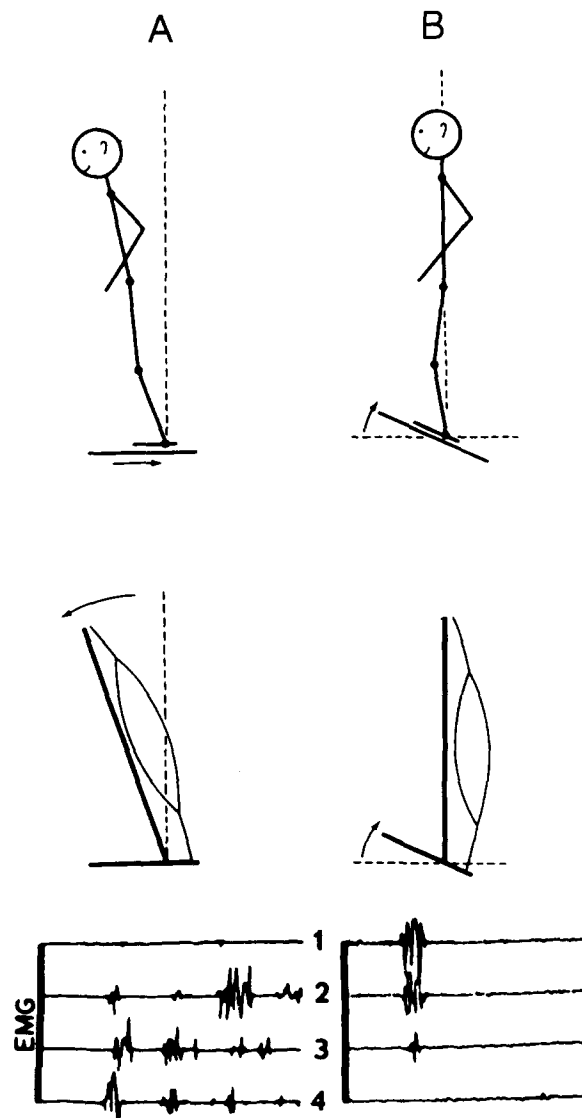

Fig. 2.
Schematic diagram of Nashner's experiment in which the ankle extensor muscles (indicated schematically) can be stretched a given amount by (A) translating the platform backwards or (B) rotating it about a fixed axis. In (A) the stretch reflex from these muscles will tend to bring the subject back to a stable, vertical position; in (B) it will tend to throw him backwards and off balance. In normal subjects, but not cerebellar patients, the reflex EMG in (A) rapidly increases over four successive trials, but in (B) rapidly decreases. (Adapted from Ref. 5.)

voluntary activity without requiring repeated trials over a period of time? To test this possibility, we electrically stimulated the tibial nerve[12] and recorded the EMG responses from the soleus muscle (an ankle extensor). If the stimulus is adjusted so that only some of the largest fibres are stimulated (Fig. 3A), two responses are observed. The first response, referred to as the M-wave, results from the direct stimulation of motor axons, whereas the second or H-wave results from stimulation of the largest sensory axons (group Ia fibres arising from the muscle spindle) which have a strong monosynaptic connection to α-motoneurons. The H-wave is largely, but perhaps not

exclusively[13], a monosynaptic reflex and can be elicited in a more reproducible way during a movement than the traditional tendon tap applied with a reflex hammer. It therefore provides a useful means of testing reflex modulation during behaviour.

During voluntary activity, a surface electrode behind the knee may still move relative to the tibial nerve it is intended to stimulate. However, any movement should affect the M-wave as well as the H-reflex. Thus, if stimulus levels that stimulate a constant percentage of motor fibres, as judged from the M-wave, are selected at each phase of the movement, then these stimuli probably also stimulate a constant percentage of muscle spindle sensory fibres.

Muscle spindles have complex sensory receptors that can respond to motor inputs from the two classes of γ-motoneurons (not shown in Fig. 3). The sensitivity of the afferents to muscle stretch can be selectively modulated by the pattern of activity in γ-motoneuron[14] and distinct patterns have been demonstrated in different rhythmic activities[15,16]. The tendon jerk may depend on both peripheral and central factors and so may be modulated to a somewhat different extent than the H-reflex[13]. Only the central factors measured by the H-reflex will be considered here, although results similar to those we will now discuss for H-reflexes during walking have recently been reported for tendon jerks[17].

Marked changes in the H-reflex do occur during a cyclic movement such as walking on a treadmill (Fig. 3C). The reflex increases markedly during the stance phase of the step cycle (but see Refs 18, 19), even when the M-wave and presumably the sensory stimulus is relatively constant throughout (Fig. 3B). Another interesting point is that the H-reflex usually increases approximately in parallel with the motor activity in the muscle, as measured by the rectified and filtered EMG record (Fig. 3D).

The parallel change in reflex response and total activity in the muscle has been observed in other experimental situations[20,21]. Is this modulation of reflexes automatically associated with the use of a muscle in a voluntary movement, or can the reflex be tailored specifically to the task? To test this possibility further, our subjects exerted various amounts of static force from standing quietly, to standing on the toes, to exerting near maximal activation of the ankle extensor muscles, such as the soleus. In other experiments, we changed the treadmill speed from 4km/h for walking to 8 km/h for running.

Fig. 4 summarizes the results (details in Refs 12, 22) for all three tasks. Not only were the M-waves matched between tasks (and hence the effective stimulus strength as before), but the reflexes are plotted as a function of the mean rectified surface EMG level. If reflexes were automatically adjusted to the level of activity during all voluntary movements, the reflex amplitude should be identical for the three tasks at a given level of activation of the soleus motor pool, and all the data should superimpose on a single curve. Clearly this is not found experimentally, which implies that even the shortest latency reflex pathway can be modulated specifically and independently of the level of motor activity. Other segmental reflexes, such as the disynaptic inhibitory reflex from muscle spindles to α-motoneurons in antagonistic muscles,
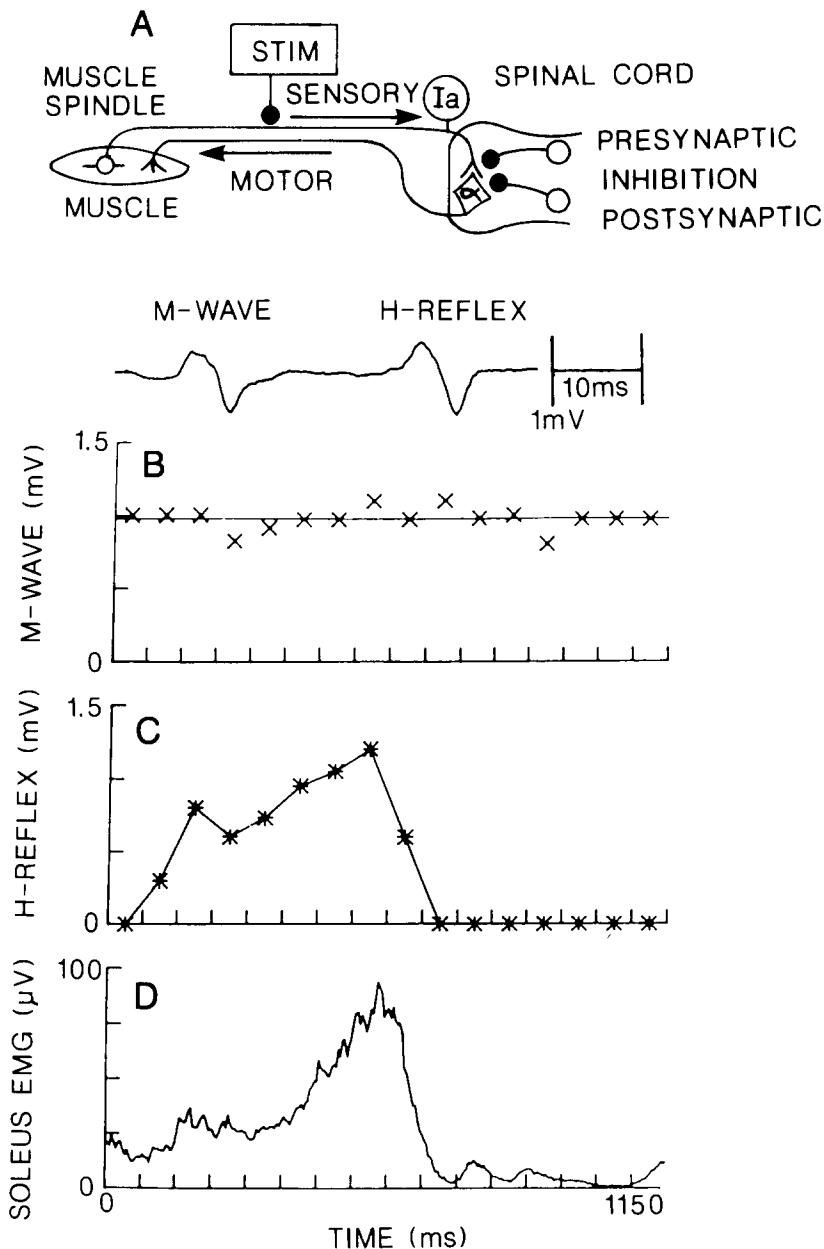
Fig. 3. (A) A stimulus to the tibial nerve produces two EMG responses in the soleus muscle, an M-wave from direct excitation of motor axons and an H-reflex from stimulation of the large Ia fibres from muscle spindles. These sensory fibres excite the α-motoneurons in the spinal cord by reflex, and produce a delayed response named after the German neurologist Hoffman, who first described it. Even this largely monosynaptic connection can be affected by presynaptic inhibition of the sensory terminals or postsynaptic inhibition of the α-motoneurons. (B) During walking, the stimulus is such that the M-wave remains fairly constant over the step cycle; (C) the H-reflex increases and decreases approximately in parallel with the activity in the muscle (D). A different time scale was used in (A) from that in (B) and (C).

can also be studied in humans using variants of these techniques[23]. Interestingly, our preliminary experiments suggest that this disynaptic reflex is not specifically modulated in different movements[24].

The difference between standing and walking involves a marked change in the y-intercept, and generally also a change in the slope (Fig. 4A), whereas the difference between walking and standing is mainly a change in slope (Fig. 4B). Note that the decrease of slope during running is not due to saturation of the motor pool, since it occurs at all EMG levels. Do the specific patterns of modulation really represent changes in reflex gain, or merely changes in threshold? The sensory volley could not be measured directly in our human subjects, but the M-wave is directly related to the number of motor fibres stimulated and presumably also to the number of sensory fibres stimulated by the same stimulus to the mixed nerve. Thus, plotting the H-reflex as a function of the M-wave (M–H curve) gives a measure of the input–output properties of the reflex.

M–H curves are shown in Fig. 5A for three different times during the stance phase. When a large fraction of the motor axons is stimulated (large M-waves), some α-motoneurons will be refractory and unable to respond to the afferent volley, so the H-reflex decreases because of occlusion. However, at the lower levels of the M-wave shown in this figure, the change in the H-reflex from the early stance phase to late stance represents a large increase in the slope of the M–H curve. Although both the M-wave and the H-wave may be related non-linearly to the actual input and output, the increase in slope can only result from a gain change in the central reflex transmission (excluding the peripheral effects of γ-motoneurons)[25]. Thus, the central gain of this largely monosynaptic reflex is modified substantially during the stance phase of locomotion.

It remains to be seen whether these effects are large enough to change substantially the slope of length–tension curves of muscles and reflexes, like those in Fig. 1. However, the potential functional value of these specific central gain changes can be readily appreciated. If the body sways forward during standing, as discussed in relation to Fig. 2A, a large reflex response s desirable to maintain a stable, upright stance. During walking, after the heel first contacts the ground (HC in Fig. 5C), the muscle shortens against a small load (the foot) until the foot is flat on the ground (FF). Once the foot is flat on the ground, the body begins to rotate over the ankle, thus stretching the contracting soleus muscle for most of the stance phase until the heel comes off the ground (HO).

The role of the soleus muscle (and the other ankle extensors) is to control the rate and extent of ankle flexion from FF to HO and to propel the body forward and upward. A large reflex would be most desirable to assist with this propulsive phase, and the reflex reaches its peak in the latter half of the stance phase. Since the muscle is being stretched during most of the stance phase, and the reflexes are operative, some of the output from the muscle during normal walking will arise from the stretch reflex.

When the toe comes off the ground (TO), the swing phase begins. The ankle is flexed to avoid dragging the toes on the ground and the soleus muscle is
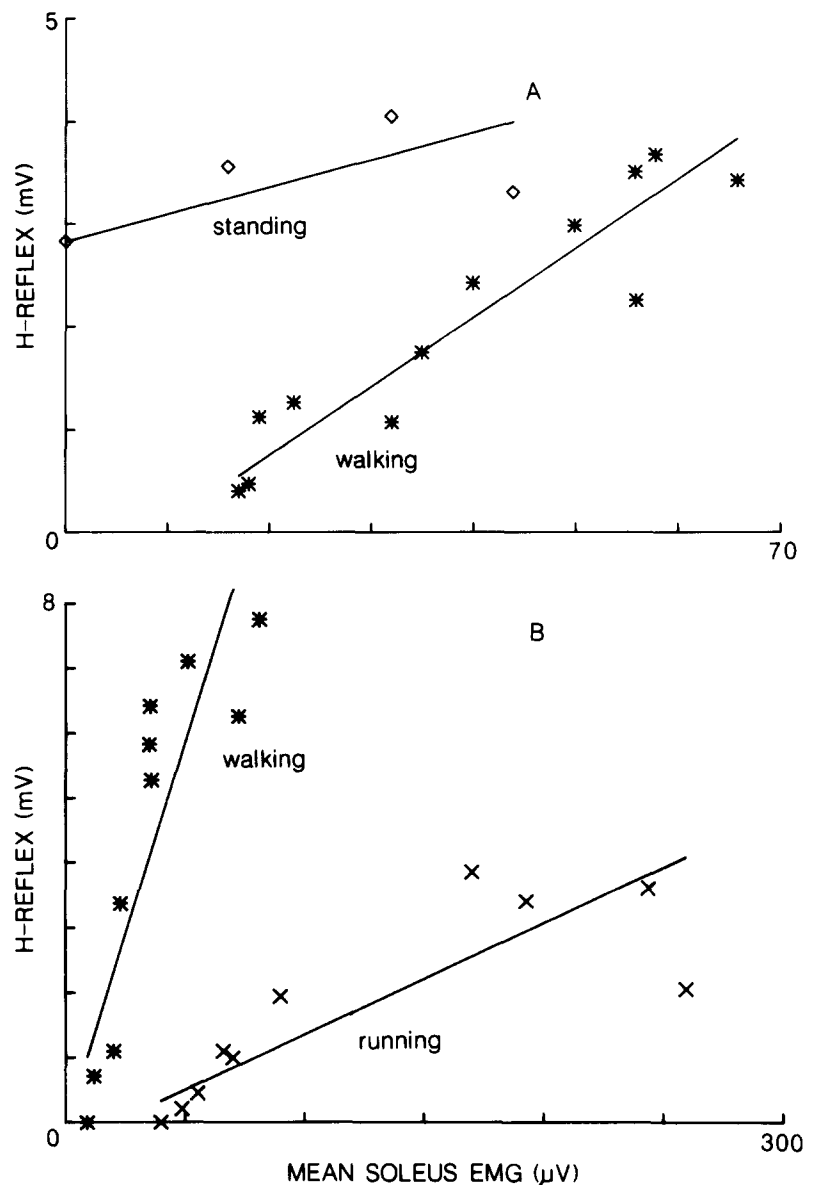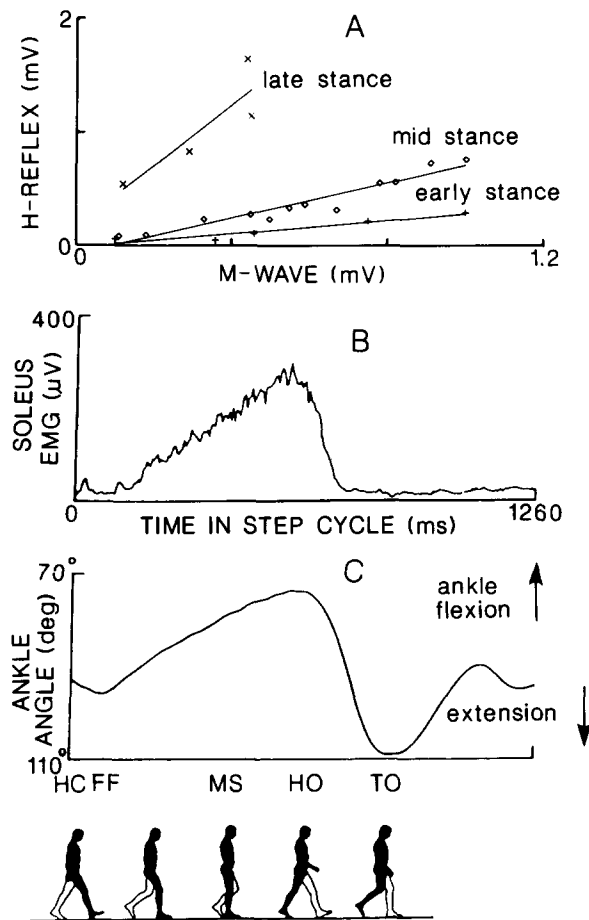

Fig. 4. Comparison in two subjects of the changes in the H-reflex (at a constant M-wave) for (A) standing and walking and (B) walking and running. The excitation level of the motoneurons is measured experimentally as the mean rectified level of the surface EMG. The difference between the H-reflexes during standing and walking involved a large change in y-intercept (A) whereas the difference between walking and running was mainly a change in slope (B). Straight lines have been fitted by the standard technique for minimizing the mean square deviation of points from the fitted line. The functional implications of these changes and possible neuronal mechanisms are discussed in the text.

stretched in the process. A stretch reflex would now be inappropriate, because it would counteract the ankle flexion. Thus, the parallel increase in the reflex and the muscle activity during the stance phase, and the virtual absence of a reflex during swing, as observed in Fig. 3, are closely matched to the functional requirements of locomotion. The same general pattern is observed in running as well as walking, but the slope for running in Fig. 4 is smaller than that for walking, for reasons that have yet to be elucidated (see Ref. 22 for suggestions).

Neural mechanisms

Although the functional importance of the difference in slope between walking and running (Fig. 4) needs further study, a simple neural mechanism can be

Fig. 5 (graphs A, B, C with labels: H-REFLEX (mV), M-WAVE (mV), late stance, mid stance, early stance; SOLEUS EMG (µV), TIME IN STEP CYCLE (ms) 1260; ANKLE ANGLE (deg), ankle flexion, extension, HC FF MS HO TO)

forearm contraction, which led him to suggest the invariance of Fig. 1. Perhaps only postsynaptic mechanisms were involved in the examples he considered. Whatever the mechanisms prove to be, the present results show clearly (1) that the human nervous system can adjust the reflex gain, even of a monosynaptic pathway, on a moment-to-moment basis; (2) that the modulation can occur independently of the level of motor output, and (3) that these adaptations have potential functional importance for the requirements of these tasks.

suggested (see Fig. 3A). If the level of presynaptic inhibition is increased throughout the stance phase of running compared with walking (see Ref. 25 concerning changes in presynaptic inhibition during human voluntary contraction), then the change in H-reflex gain would be expected. Inhibition of transmitter release from the presynaptic terminals of the muscle spindle afferents onto α-motoneurons would reduce the size of the EPSP produced in the motoneurons and hence the probability of discharges from motoneurons in response to the afferent volley. Computer simulations[26] show that the reflex would then be reduced at all levels of soleus EMG activity, as observed.

Postsynaptic inhibition onto α-motoneurons (Fig. 3A) could also decrease the reflex response, but would decrease the EMG activity at the same time. An additional source of excitation would have to be added to bring the EMG back to its control value. Under fairly general assumptions about the interaction of postsynaptic excitation and inhibition and the properties of the motoneuronal pool, both mathematical analysis and computer simulations indicate[26] that adding sufficient excitation would also restore the reflex response and not change the slope of the graph in Fig. 4.

Thus, the predictions from our analysis that need to be tested in animal experiments are: (1) the relation between the reflex response and EMG level should be independent of the mixture of postsynaptic mechanisms acting to produce motoneuron firing; and (2) presynaptic inhibition, on the other hand, should alter the size of the reflex response independently of the level of motor output. The first prediction is reminiscent of Feldman's results of studies on

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