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The effects of baclofen on the stretch reflex parameters of the cat

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Abstract Experiments were done in cats decerebrated at the precollicular postmammillary level to determine how a tonic increase of presynaptic inhibition of the intraspinal terminals of muscle spindle afferents changes the mechanical properties of the soleus stretch reflex (s.r.). Baclofen, a specific $GABA_B$ receptor agonist, was injected i.v. (1–2 mg/kg) so as to induce a tonic increase in presynaptic inhibition. The effects of baclofen on the stiffness and threshold of the s.r. were determined, respectively, from plots of stiffness vs background force and force vs length (length-tension plot). Baclofen, at these doses, had no effect on the excitation-contraction coupling properties of muscle or on the intrinsic stiffness-force relation. Changes of the soleus background force, required to obtain the stiffness vs force plots, were produced by stimulation of the contralateral common peroneal nerve or the posterior tibial nerve and occasionally by electrical stimulation in the area of the red nucleus. The stiffness of the s.r. as a function of the background force level was determined by stretching the muscle with a square pulse of 1–2 mm amplitude and 200–300 ms duration. The stiffness at each force level was calculated by dividing the change in force by the change in length, at a point where the force trace had stabilized. The length-tension relation of the s.r. was determined by stretching the muscle 12–17 mm at a constant rate of 1–2 mm/s. At all force levels, baclofen produced a significant decrease (40% or more) in the s.r. stiffness, within 10–15 min of injection as determined from the stiffness-force plots. The length-tension plots revealed that the decrease of s.r. stiffness was always accompanied by an increase in the s.r. threshold (typically 2–3 mm). It is suggested, therefore, that the s.r. threshold is not an independent variable, depending on the membrane potential of the α-motoneurons, and additionally on the level of presynaptic inhibition of the muscle spindle afferent terminals. The present results also imply that it may be possible for the CNS to adaptively modify the s.r. stiffness via presynaptic inhibition of the intraspinal terminals of muscle afferents. However, any such change of s.r. stiffness will be accompanied by a change in the s.r. threshold.

Key words Baclofen · Stretch reflex · Muscle stiffness · Spinal cord · Cat

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Introduction

The stretch reflex has been studied for at least 70 years (Liddell and Sherrington 1924), but what may be one of the most important mechanisms responsible for its regulation, presynaptic inhibition of the muscle spindle afferent terminals in the spinal cord (Eccles 1964), has only begun to be studied at the functional level in humans (e.g., Meunier and Pierrot-Deseilligny 1989; Lavoie et al. 1993). In animals, most studies of presynaptic inhibition have been involved with identifying the pathways which can produce presynaptic inhibition and the ionic mechanisms involved (see reviews by Bormann 1988; Rudomin 1990). A particularly important outcome of this work was the finding that presynaptic inhibition of muscle afferent terminals is mediated by specific interneuronal pathways (Eccles et al. 1962; Rudomin 1990; Jankowska 1992). However, the mechanical consequences of a change of presynaptic inhibition of muscle afferent terminals has not been investigated. The control of stretch reflex parameters (threshold and stiffness) is clearly the "raison d'être" of presynaptic inhibition in the stretch reflex. How presynaptic inhibition affects these parameters is not known. In fact, as commented upon by Matthews (1972), presynaptic inhibitory mechanisms have not, in general, been incorporated into the ideas of how the spinal cord controls movements precisely because of a lack of quantitative measures of its effects.

We previously suggested that the purpose of presynaptic inhibition in the stretch reflex pathway was to allow for a change in the gain of the latter, independently of the level of recruitment of the α-motoneuron pool (Capaday and Stein 1986, 1987a, 1989). A change of the central gain of the stretch reflex produced by a change of presynaptic inhibition implies that the stiffness of the stretch reflex must change. The stretch reflex would therefore generate proportionately more or less tension per unit change of muscle length, depending on the level of presynaptic inhibition. Thus, control of the level of presynaptic inhibition would allow for the adaptive control of the mechanical impedance at a single joint. The relation between length and tension of a muscle under stretch reflex control is reasonably linear (Granit 1958; Matthews 1959a). Thus, two parameters characterize the stretch reflex when studied in the length-tension space, the threshold (x-intercept) and the stiffness (slope). How these parameters are controlled by the CNS during posture and movement is central to current theories of motor control (see for example, Houk and Rymer 1981; Berkinblit et al. 1986). Three important mechanisms governing the stretch reflex input-output properties have been investigated: the effects of the fusimotor system (Matthews 1959b), reciprocal disynaptic inhibition (Matthews 1959b), and activation of descending motor pathways (Feldman and Orlovsky 1972). In all three cases, the major effect was a change of the threshold of the stretch reflex. These observations have led some researchers to suggest that the CNS cannot change the stiffness of the stretch reflex independently of the level of motor output (reviewed by Houk and Rymer 1981; Berkinblit et al. 1986; but see also Pompeiano 1960; Henatsch et al. 1976; Nichols and Steeves 1986).

In order to investigate the possible effects of presynaptic inhibition of muscle afferents on the stretch reflex parameters we have used the pharmacological agent baclofen (Lioresal). This compound is a specific $GABA_B$ receptor agonist and is known to increase the level of presynaptic inhibition of primary afferent terminals in the spinal cord (Edwards et al. 1989; Peng and Frank 1989a,b; Jiménez et al. 1991). Baclofen has no effect on intrinsic membrane properties or on the resting membrane potential of α-motoneurons, and presumably γ-motoneurons (Edwards et al. 1989). It is preferable to $GABA_A$ agonists such as muscimol because these may, in addition to increasing presynaptic inhibition, also decrease the amplitude of the action potential invading the Ia-terminals and produce postsynaptic inhibitory effects in the motoneurons (Peng and Frank 1989a,b). It should be noted, however, that $GABA_B$ receptors have been suggested not to mediate the presynaptic inhibition produced by segmental pathways (Stuart and Redman 1991). In any case, baclofen appears to be an ideal pharmacological agent for tonically increasing presynaptic inhibition of the intraspinal terminals of muscle spindle afferents and thus allow for measurements of the mechanical consequences on the actions of the stretch reflex. The use of such a drug to induce a tonic increase of presynaptic inhibition, rather than the more usual electrical activation of physiological pathways involved in presynaptic inhibition (Eccles 1964), is clearly simpler as well as appropriate for an initial steady-state analysis of the problem.

The present paper summarizes the effects of baclofen on the stretch reflex of decerebrate cats, studied in the length-tension space (Matthews 1959a,b) and the stiffness-force space (Hoffer and Andreassen 1981). An abstract of the present results was recently published (Capaday 1994).

Methods

Surgical protocol and preparation

This study was conducted in accordance with the guidelines of the council of the American Physiological Society. Data were obtained from 17 cats weighing between 2.5 and 3.5 kg. The animals were decerebrated at the precollicular postmammillary level. The surgical procedures were done under halothane anesthesia, which was discontinued after decerebration. The trachea was exposed and intubated. A canula was inserted in the right carotid artery for recording the blood pressure; the left carotid artery was doubly ligated. A cannula was also inserted into one of the external jugular veins to inject baclofen (1–6 mg/kg) and various solutions required for maintenance of the animal. Typically, 1 mg of dexamethasone was injected about 20 min prior to decerebration in order to minimize swelling of the brainstem. Immediately following decerebration, 10 ml 5% glucose in physiological saline was injected. An additional 5 ml of this solution was given every 2 h throughout the course of the experiments. If the blood pressure was lower than 60 mmHg, 5–10 ml of dextran (a plasma volume expander) was also given. All injected solutions had their pH adjusted to 7.4.

The triceps surae muscle group in the left hindleg was dissected free of the surrounding tissues. The soleus muscle was separated from the lateral gastrocnemius muscle up to its origin of insertion on the tibial bone. A small piece of the calcaneum was left attached to the soleus tendon and a double length of no. 2 silk suture material was tied around the tendon near the site of attachment to the calcaneum. Two Teflon-coated, multistranded, stainless steel wires were inserted into the soleus muscle about 2 cm apart, distal to the entry of the soleus nerve. The left leg was extensively denervated except for the nerves to the lateral gastrocnemius and soleus. The nerve to the lateral gastrocnemius was usually left intact because we found, as has been noted by others (e.g., Matthews 1972), that this resulted in stronger stretch reflex responses in the soleus. A pool was made with the skin flaps of the leg and filled with paraffin oil so as to cover the soleus and all the tissues of the leg. The separation of the lateral gastrocnemius from the soleus and the insulation properties of the paraffin oil insured that the electromyographic recordings (EMG) in the soleus (Matthews 1959a) were free of cross-talk.

Cuff electrodes used for stimulation, or recording, were placed on the left sciatic nerve and the anterior portion of the left tibial nerve. On the right side, cuff electrodes were placed on the common peroneal nerve and the posterior tibial nerve (i.e., distal to the popliteal fossa). The nerves were stimulated with 200-μs square wave pulses delivered through stimulus isolation units.

Measurements of stretch reflex parameters

A static length-tension curve of the soleus stretch reflex was obtained by slowly stretching the muscle at a constant rate of 1–2 mm/s, by up to 14–17 mm beyond the reflex threshold, and measuring the resulting increase in tension as a function of the

change in length (Granit 1958; Matthews 1959a,b). From such plots, the static stiffness (measured in N/mm as the Δ force/Δ length) and threshold (measured in mm) of the stretch reflex were determined after a least-mean-squares linear fit to the data points. These measurements are quite sensitive to changes in the stretch reflex threshold as noted by previous authors (e.g., Matthews 1959a,b; Feldman and Orlovsky 1972). The straight line fits to the length-tension values nearly always accounted for at least 80% of the total variance of the data (i.e., $r \geq 0.9$).

At the outset, we reasoned that these measurements may not be the most sensitive for revealing the effects of presynaptic inhibition on the stretch reflex stiffness. The stiffness of the stretch reflex seems to be weakly dependent on the initial muscle length and is much more dependent on the initial muscle force (Hoffer and Andreassen 1981). Therefore, in addition to the static length-tension measurements, dynamic stiffness-force measurements were also done. The soleus muscle was stretched by a square pulse of 1–2 mm amplitude and 200–300 ms duration and the change in force measured at a point where the force trace stabilized to a constant level (see Fig. 4), as was done previously by Hoffer and Andreassen (1981). The stiffness was plotted as a function of the mean background force measured 50 ms before the stretch. These experiments provided measurements of what may be termed the "dynamic stiffness" of the stretch reflex over nearly the whole range of recruitment of the α-motoneuron pool, and thus of muscle force output.

Experimental protocol

The soleus tendon was attached to a linear strain gauge transducer mounted on the coil of a DC motor. The motion of the coil (armature) was translational. The DC motor was controlled by an analog position control system. The stiffness of the position control system was 27 N/mm and the damping factor was set to obtain a critically damped step response. The force, length, and EMG activity of the soleus muscle were digitized at a sampling rate of 2000 samples/s and analyzed in real time on a 386 PC. The data was also simultaneously recorded on VCR tape for further analysis, when required.

Variations of the level of soleus force were produced by stimulation of the contralateral (right) common peroneal nerve or the posterior tibial nerve at a strength of 2–7 times the motor threshold; the stimulus rate was 25–70 stimuli/s. Stimulation of these nerves produce the classic crossed-extensor reflex, with flexion of the ipsilateral leg and extension of the contralateral one (Creed et al. 1932). In some experiments, stimulation in the area of the red nucleus (1 mm rostral and 2–3 mm lateral to the superior colliculus, 6–8 mm in depth), using stimuli of 200 μs duration and an intensity of 10–100 μA delivered through an isolated constant current unit, was also used to produce changing levels of soleus motor output (Hoffer and Andreassen 1981). The reader is referred to previous publications for typical records of soleus force output during the crossed-extensor reflex (e.g., Hoffer and Andreassen 1981; Capaday and Stein 1989). Stimulation of the posterior tibial nerve usually produced stronger and more sustained crossed extensor reflexes than stimulation of the common peroneal nerve, it also usually produced larger force outputs than stimulation of the brainstem.

Data reduction and analysis

For the length-tension measurements, the computer program generated the command ramp signal (velocity:1–2 mm/s, amplitude:14–17 mm), sampled the muscle force at every 1 mm length increment, and displayed the results graphically on the video screen. The least-mean-squares line was fitted to the acquired data points immediately after the end of the ramp stretch. This feature insured that the length-tension measurements were in fact reproducible from moment to moment in a given experimental situation. Only data points whose force value (y-value) exceeded the rms noise level (approximately 0.01 N) of the force transducer were included in the data set used for fitting the least-mean-squares line. The threshold and stiffness of the stretch reflex were determined from, respectively, the x-intercept and the slope of the fitted line. In all cases, the length-tension relation of the passive elastic components of the soleus muscle was subtracted. The latter was determined at the end of the experiment after the tibial nerve was cut. The contribution of the passive elastic component was usually rather small over the range of stretch amplitudes used, and its threshold well beyond that of the stretch reflex.

The data for the stiffness-force measurements were also acquired in real time. The initial data reduction consisted of averaging together responses to muscle stretch that occurred at nearly the same background force. The force range of the soleus was divided into force bins. Typically 20 force bins, with a bin size of 1 N, were used. In addition, there was always an extra force bin into which responses at zero background force were stored. The computer program measured the background force level from a 50-ms time segment prior to the stretch. The calculated background force value was used to determine in which force bin the force, rectified EMG, and unrectified EMG responses should be stored. All responses in the same force bin (typically in increments of 1 N) were averaged together. Thus, responses were sorted out as a function of the background force level at the time of the stretch. From this sorted data, the stiffness of the stretch reflex as a function of the background force was measured (see Fig. 4).

The intrinsic stiffness of the soleus muscle as a function of the background force was measured as previously described (Nichols and Houk 1976; Hoffer and Andreassen 1981). At the end of each experiment, the tibial nerve was cut above the nerve cuff and stimulated at various constant rates ranging from 12 to 40 Hz. At these rates, the soleus produces fused tetanic contractions upon which were superimposed the same stretches used in the reflex experiments. The data were sorted and analyzed as described above.

Results

Three main sets of observations are described in this section. Firstly, it is shown that baclofen has no effect on the process of excitation-contraction coupling, nor on the intrinsic relation between stiffness and force. Secondly, the effects of baclofen on the stretch reflex threshold and stiffness, measured in the length-tension space, are described. The section ends with a description of how the stiffness-force relation of a muscle under stretch reflex control is modified following the injection of baclofen.

In order to attribute the effects of baclofen on the mechanical properties of the stretch reflex as being due to its action(s) on the CNS, it is necessary to verify that it has no significant effects on intrinsic neuromuscular properties. Indeed, the process of excitation-contraction coupling in muscle is not affected by baclofen. The relation between the mean rectified EMG and force (Fig. 1), which is approximately linear, remains the same after injection of baclofen, at least over the range of doses used in the present experiments (1–6 mg/kg). The maximum twitch tension and M-wave responses can also be used to confirm this point. It can be seen in the two records at the bottom of Fig. 1 that neither the maximum twitch nor the maximum M-wave is affected by baclofen. In addition, the intrinsic stiffness-force relation of the muscle is not modified (Fig. 1).

Two examples of length-tension plots of the soleus muscle under stretch reflex control are shown in Fig. 2.

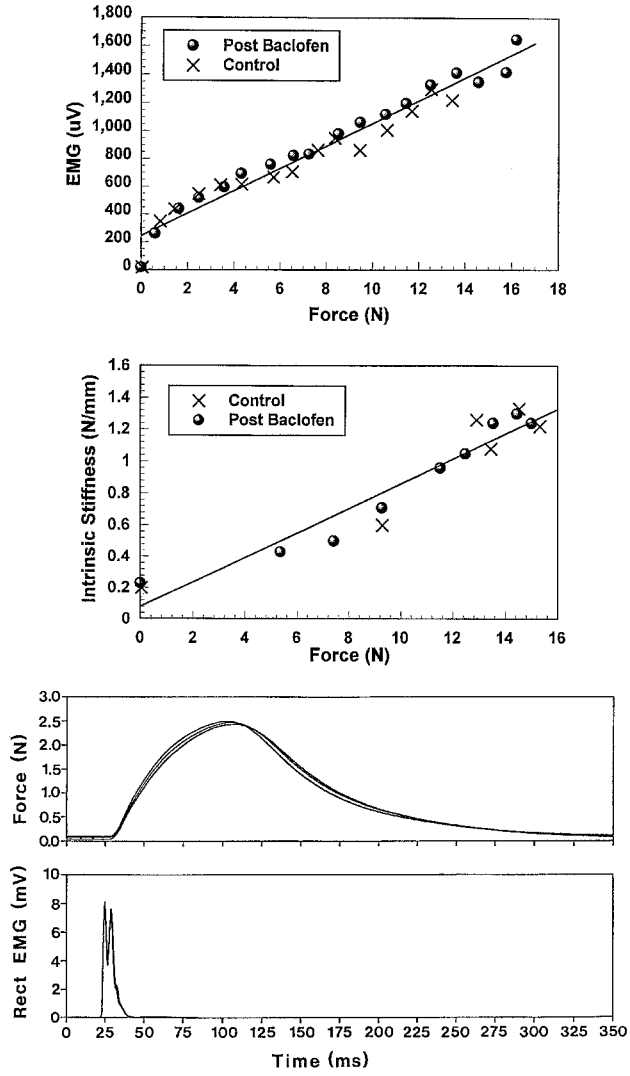

Fig. 1 Baclofen has no effect on excitation-contraction coupling and the intrinsic stiffness-force properties of muscle. The EMG vs force plot (*top*) and the maximum twitch-tension measurements (bottom two graphs) show that the process of excitation-contraction coupling in muscle is not affected by baclofen. The data points of the EMG vs force plot were obtained during a crossed-extensor reflex. The mean rectified (*Rect*) EMG was measured over a 50-ms period preceding the measurement of the force value. In addition, although not surprising, the intrinsic relation between stiffness and force (*middle*) is also not modified by baclofen

The data were obtained by slowly stretching the soleus muscle at a constant velocity (2 mm/s) and recording the tension at increments of 1 mm. Any force contribution from the passive elastic components of the muscle was subtracted from the total force at the corresponding length. The graphs thus show the active muscle force as a function of the stretch amplitude. The static stiffness (slope of the relation) and the threshold (x-intercept) of the stretch reflex are readily apparent in these graphs. In cat16, the soleus muscle was tonically active prior to the beginning of the stretch, whereas in cat29 it was quiescent but very near the reflex threshold. The stretch reflex threshold increased typically by 2–4 mm within 5 min following the injection of baclofen and was always accompanied by a decrease in stiffness. The examples shown in Fig. 2 are the final steady state length-tension plots following injection of 1 mg baclofen/kg. The final steady state values of the threshold and stiffness were usually attained within 30–40 min of the injection. Typically, the stiffness was decreased by 40–60% at this dose. Further injections of baclofen (e.g., an extra 1 mg/kg) lead to the complete inhibition of the tonic stretch reflex.

The most salient feature of the length-tension plots following baclofen injection was that the increase of the stretch reflex threshold was always accompanied by a decrease in its stiffness. The graphs shown in Fig. 3 present further details on this point. The length-tension plot at the bottom of the figure shows the changes of the tonic stretch reflex characteristics, as a function of time following the injection of 1 mg baclofen/kg. The reproducibility of the control length-tension relation is exemplified by superimposing two control curves obtained 5 min apart (Fig. 3, Cntrl 1 and Cntrl 2). Following the injection of baclofen, the threshold increases and the stiffness decreases until they reach their final steady state value, after some 40–45 min. Summary graphs showing the relation between the stiffness and threshold are shown at the top of Fig. 3. The negative threshold values shown in these graphs, indicating that there was tonic activity in the muscle prior to stretching, are extrapolated from the best fitting least-mean-squares line. They only serve as an expedient, stressing that the decreased stretch reflex stiffness following baclofen was associated with a increased threshold. All the data points obtained after administration of baclofen lie below and to the right of the control values. These graphs also summarize the well know fact that under control conditions the stiffness is nearly constant and independent of the threshold (Matthews 1959a,b). What is new in the present experiments is that baclofen activated a central neural mechanism capable of decreasing the stretch reflex stiffness, but not without also increasing the threshold. However, as can be deduced from the stiffness vs threshold graphs in Fig. 3, there probably is a transition zone along the threshold axis. Thus, large thresholds under control conditions, which indicate that the membrane potential of the motoneurons is relatively hyperpolarized, can be similar to those obtained soon after the injection of baclofen in circumstances were the motoneurons are relatively closer to threshold. What is clear, is that starting from a stable set of initial control conditions (e.g., Fig. 3 Cntrl 1 and Cntrl 2), baclofen will decrease the stiffness and increase the threshold of the stretch reflex relative to these initial conditions.

The tonic stretch reflex measurements described above were also complemented with so called "dynamic" measurements (Hoffer and Andreassen 1981) using small (1 mm) rapid length increments lasting 200–300 ms (Fig. 4). These length perturbations were applied at different force levels produced by the crossed-extensor reflex, or stimulation of the brainstem in the area of the

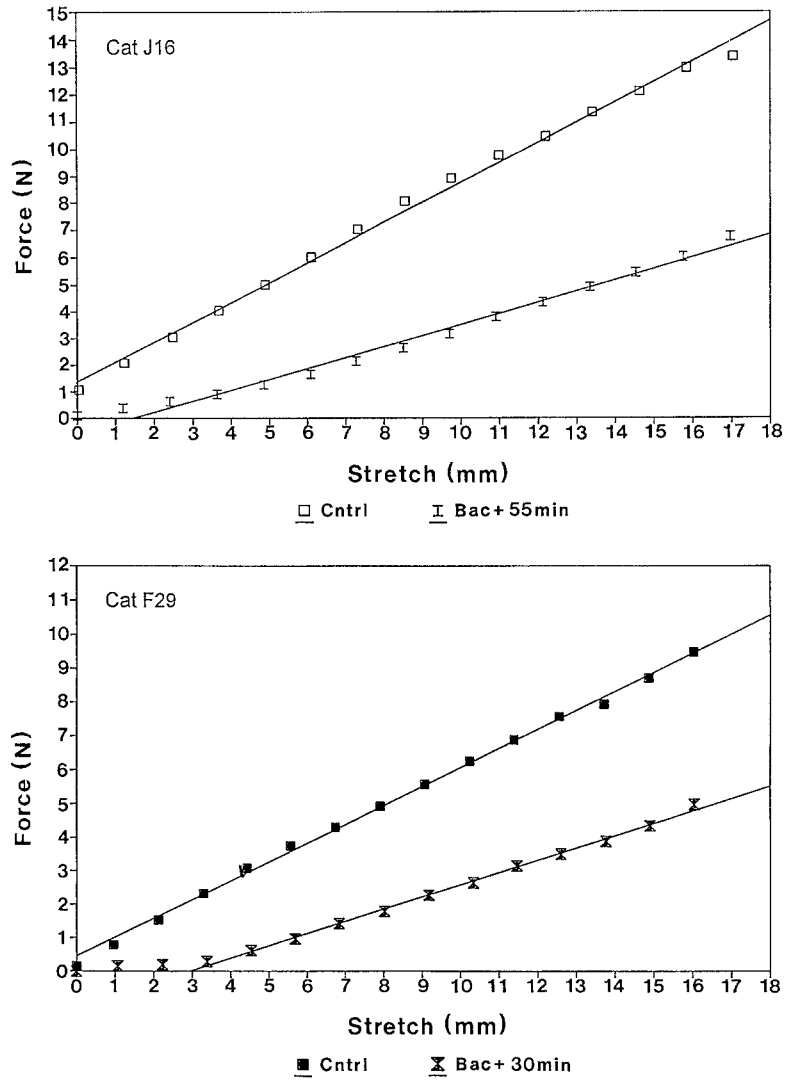

Fig. 2 Two examples of length-tension plots of the soleus muscle under stretch reflex control obtained in decerebrate cats. Two parameters characterize these plots, the threshold measured in mm and the stiffness measured in N/mm. Note that following injection of baclofen, the threshold increases and the stiffness decreases. Any force contribution from the passive elastic components of muscle was subtracted from the active force at the corresponding length

red nucleus (Hoffer and Andreassen 1981). In this way, a measure of the "dynamic" stiffness of the stretch reflex as a function of the background force could be determined and presented as stiffness-force plots (Fig. 5). The main reason for making these measurements was to determine whether the reduction of the stretch reflex stiffness produced by baclofen occurred over the whole range of force levels, thus insuring that the increased excitatory synaptic drive of the motoneurons could not counteract the inhibitory effects of baclofen (see Capaday and Stein 1989). If this were so, then two conclusions could be made from such an observation. Firstly, baclofen is likely to have an action presynaptic to the motoneurons, because if its only action were on the motoneurons (e.g., membrane hyperpolarization, intrinsic conductance changes, etc.) this can be offset by increasing the excitatory drive to the motoneurons (Capaday and Stein 1989; see also Hultborn et al. 1987). Furthermore, from a functional point of view, a reduction of the contribution of the stretch reflex to the total muscle stiffness, at all force levels, would provide further empirical evidence for suggesting the existence of a neural mechanism which may be capable of adaptive control of muscle stiffness.

Typical responses to small muscle stretches are shown in Fig. 4. In this example, there is a small (0.5 N) active background force prior to the stretch. The initial response to stretch, a sharp force transient, is due partly to inertial forces and partly to the short range elasticity of active muscle (Rack and Westbury 1974; Houk and Rymer 1981). The initial force transient is followed by a delayed and slower, twitch-like, increase of force due to the reflex EMG burst. A pause of activity always follows the large reflex burst and the tonic EMG activity resumes at a slightly higher level than the background prior to the stretch (Fig. 4). It is rather obvious that since the reflex force response is dynamic so too is the stiffness of the muscle during the course of the length perturbation. The stiffness may be measured anywhere along the reflex force response. We have followed the convention of Hoffer and Andreassen (1981) and measured the stiffness at a point where the force transient had stabilized (steady state), marked with the symbol "ss" in Fig. 4. In addition, the stiffness at the peak of the twitch-like reflex re-

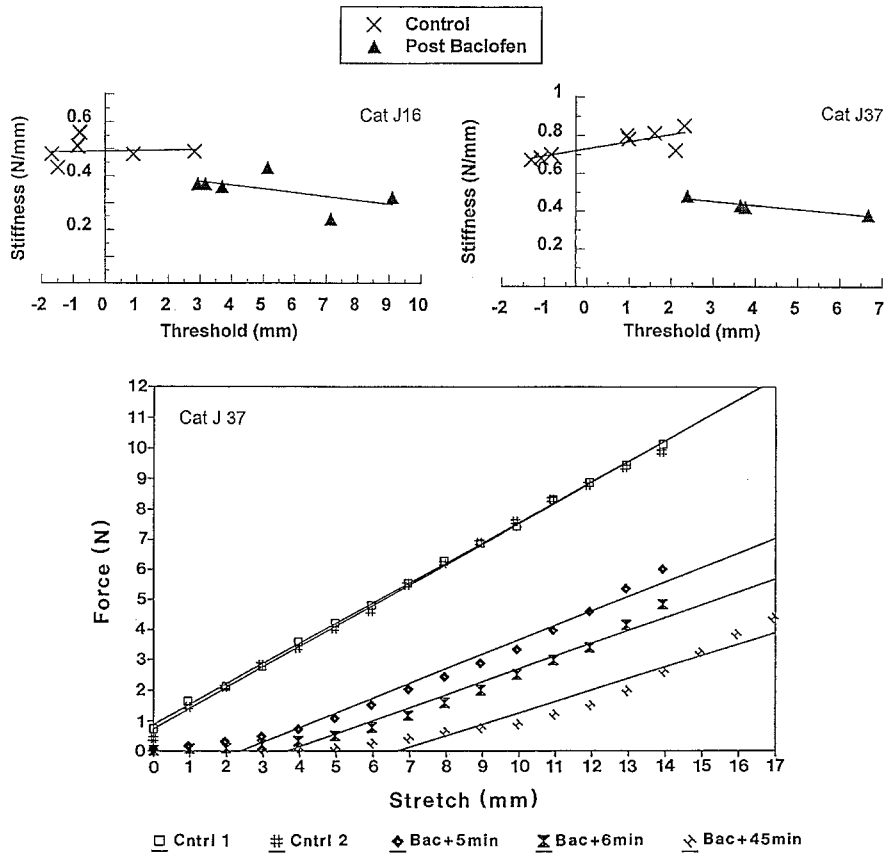

Fig. 3 Further examples of the effects of baclofen on the tonic stretch reflex parameters. The graph at the *bottom* of the figure shows that the increase of the stretch reflex threshold and the decrease of its stiffness occur rapidly after the injection of baclofen and progress with time, until a steady state is reached. A large enough dose of baclofen (e.g., 2 mg/kg) completely inhibits the tonic stretch reflex. The graphs at the *top* of the figure make the point that a decrease in the stretch reflex stiffness is always accompanied by an increase in its threshold (note different scales on *y*-axis)

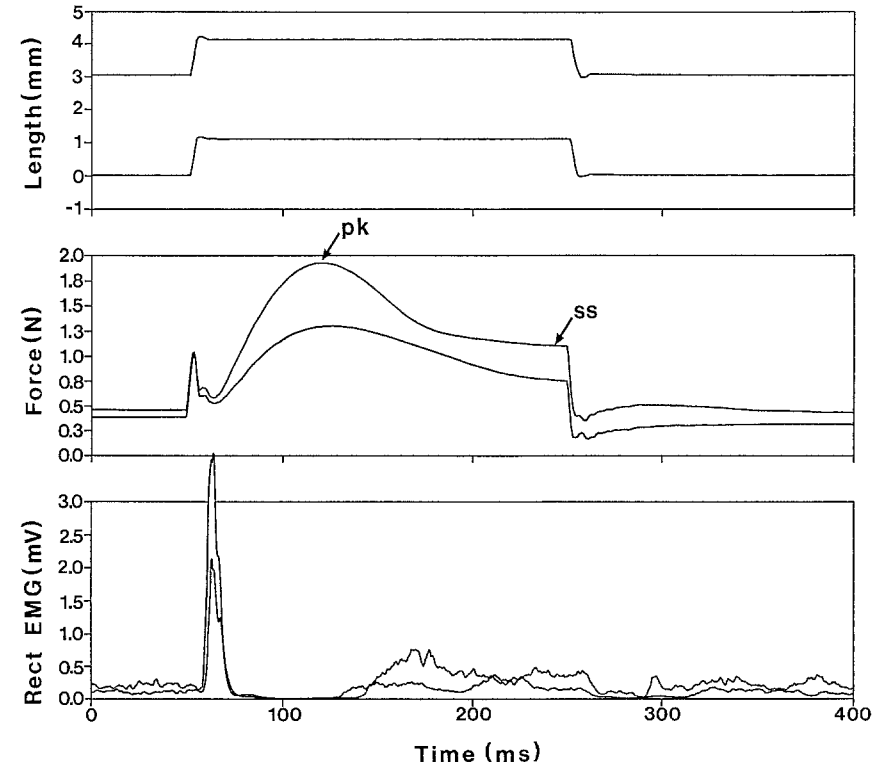

Fig. 4 To obtain measurements of stretch reflex stiffness as a function of the background force, the soleus muscle was stretched by a square pulse of 1 mm amplitude and 200–300 ms duration. In this example, the background force was varied by stimulating the posterior tibial nerve and eliciting a crossed-extensor reflex . The stiffness (ΔForce/Δlength) was calculated either as a steady state (*ss*) value at a time when the force transient following the stretch stabilized, or at the peak of the reflex force response (*pk*). Note that following injection of baclofen, the reflex EMG burst and the peak reflex force response to muscle stretch are decreased, as is the tonic EMG following the burst. In all cases, the increase of the stretch reflex threshold following baclofen was compensated by stretching the soleus muscle by the required amount (by 3 mm in this example)

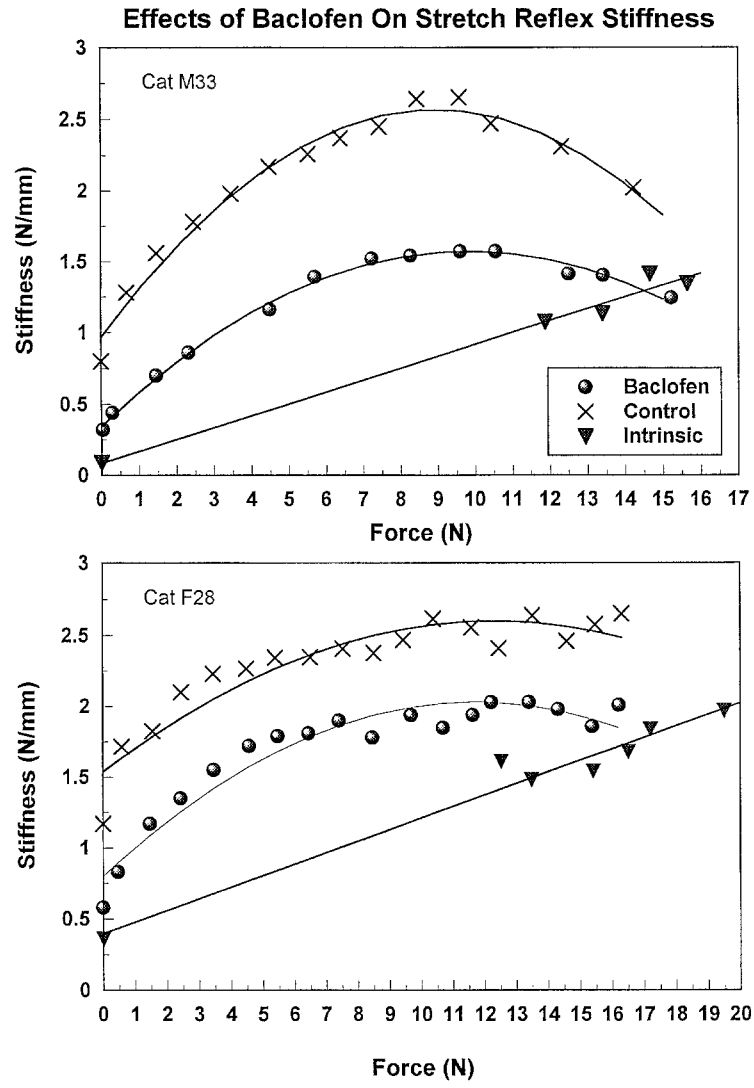

Fig. 5 Two examples of steady-state stiffness-force plots of the soleus muscle. The intrinsic stiffness-force relation of an areflexic muscle is linear and was obtained by electrical stimulation of the cut muscle nerve. The stretch reflex increases the stiffness of the muscle along a curve that can be fitted by a second order polynomial function (inverted parabola). Injection of baclofen resulted in a decrease of the reflex component of the total muscle stiffness at all background forces. In both examples, the variations of the background force were obtained by electrical stimulation of the contralateral posterior tibial nerve, so as to elicit a crossed-extensor reflex

sponse was also measured. As can be seen in Fig. 4, baclofen reduced the peak and steady-state stretch reflex stiffness.

After injection of baclofen, the reflex EMG burst and the tonic EMG activity following the burst are reduced, as is the reflex force response. It should be noted, as shown in Fig. 4, that the dynamic stiffness-force measurements after the injection of baclofen were done at the new reflex threshold by stretching the soleus muscle by the required amount (e.g., by 3 mm in the example of Fig. 4). The reflex threshold was determined from length-tension plots obtained just prior to beginning the stiffness-force measurements. These measurements are, therefore, estimates of stretch reflex stiffness, as such. That is, they are essentially independent of the increased stretch reflex threshold due to baclofen.

Two examples of how the stiffness-force relation of the soleus under control of the stretch reflex is modified following the injection of baclofen are shown in Fig. 5. The stiffness measurements shown in Fig. 5 are steady state values as shown in Fig 4. The relation is well fitted by a second order polynomial function (inverted parabola). The underlying reasons of this parabolic profile and its functional significance have been previously described in detail (Hoffer and Andreassen 1981). Baclofen decreased the contribution of the stretch reflex to the total muscle stiffness (ss and pk values) at all force levels. The example at the top of Fig. 5 was the more typical in that the largest change usually occurred in the range near the peak of the stiffness-force relation. The stiffness at the peak of the relation decreased by 25–50% within 30 min following injection of 1 mg baclofen/kg. Injection of larger dosages of baclofen (e.g., an additional 1–2 mg/kg) would further inhibit not only the stretch reflex, but also the crossed-extensor reflex, which we found to be the most effective method to produce variations of the soleus force over most of its range. Therefore, the values of the decrease in dynamic stiffness reported in the present experiment, although significant, are not estimates of the maximum possible decrease which may be obtained by injections of baclofen. Rather, they are typical of what may be obtained at doses that reduce the stretch reflex while also maintaining the crossed-extensor reflex operational, albeit at a higher

threshold. Thus, following baclofen, the stimulation strength necessary to elicit a crossed-extensor reflex of the same magnitude as in control conditions was always higher.

Discussion

Two main findings are reported in this paper. Firstly, baclofen produced an increase of the stretch reflex threshold and simultaneously a decrease in its stiffness, as revealed by the length-tension plots. Secondly, baclofen decreased the stretch reflex dynamic stiffness at all background force levels, as revealed by the stiffness-force measurements. There have been a few earlier reports that the stiffness of the stretch reflex can change under some conditions (Henatsch et al. 1976; Nichols and Steeves 1986). These changes either occurred spontaneously, and thus in no simply reproducible manner (Henatsch et al. 1976), or were observed in only two of six animals when the red nucleus was stimulated (Nichols and Steeves 1986). Furthermore, no particular neural mechanism(s) was ascribed to underlie these changes. The present results are the first clear demonstration that the stiffness of the stretch reflex can be changed in a reliable and reproducible way. The results also demonstrate that while it is possible to change the threshold of the stretch reflex without affecting its stiffness (Matthews 1959a,b; Feldman and Orlovsky 1972), the converse is not true. Thus, it appears that the stretch reflex stiffness cannot be changed without also changing its threshold. In the next section, it will be argued that the main mechanism responsible for these effects is a tonic increase of the level of presynaptic inhibition of the muscle spindle afferent terminals in the spinal cord. This is followed by a discussion of the functional implications of the present results for the basic mechanisms and theories of motor control.

Neural mechanisms underlying the observed effects of baclofen

It was shown in this study that baclofen does not affect excitation-contraction coupling, nor the intrinsic stiffness-force relation of muscle (Fig. 1). It would have been surprising for the latter relationship to be affected by baclofen, since the two variables are directly related to the number of attached cross-bridges (e.g., Zajac, 1989). Baclofen does not affect neuromuscular transmission between α-efferents and extrafusal fibers (Fehr and Bein 1974; Cedarbaum and Schleifer 1990). Presumably, based on what is known of the α-efferent to extrafusal fiber connection, baclofen should not affect the graded synaptic potentials produced in bag fibers by activity in the γ-efferents. However, this may require experimental verification. Finally, it is also known that baclofen does not affect the transduction mechanism of de-efferented spindles (Fehr and Bein 1974). Thus, the findings reported in this paper must be predominantly due to a central action of this drug. Baclofen may produce its effects at various sites in the remaining CNS structures of the decerebrate cat. The various possibilities, singly or in combination, include the following: presynaptic inhibition of the intraspinal terminals of the muscle spindle afferents, effects on the excitability of interneurons in the stretch reflex pathway (if any), effects on the γ-motoneurons, or effects on the brainstem nuclei contributing to decerebrate rigidity. As summarized in the Introduction, changes in γ-motoneuron activity (Matthews 1959b), activity in descending motor pathways of the brainstem (Feldman and Orlovsky 1972), and postsynaptic inhibition (Matthews 1959b), have all been reported to have as their main effect a change in the threshold of the stretch reflex, while the stiffness remains nearly constant. Thus, it seems reasonable to suggest that the present findings (a decrease of the stretch reflex stiffness and the associated increase of its threshold) are for the most part the result of baclofen-induced tonic presynaptic inhibition of the intraspinal terminals of muscle spindle afferents.

Possible inhibitory effects of baclofen on putative excitatory interneurons in the stretch reflex pathway are of particular interest in the present discussion. Little is known about putative excitatory interneuronal pathways contributing to the stretch reflex (Jankowska 1992), and thus there are as yet no quantitative measurements of the possible contribution such interneurons may make to the stretch reflex output (see the reviews by Matthews 1972; Sypert and Munson 1984). If such pathways do exist, and contribute substantially to the stretch reflex output, then the inhibition of these interneurons by baclofen would have an effect indistinguishable from that of presynaptic inhibition of muscle spindle afferents. In each case, the increased threshold and decreased stiffness would result from the recruitment of fewer motor units per unit length increment. However, it is clear that presynaptic inhibition of muscle afferent terminals do occur after injection of baclofen. Therefore, notwithstanding the potential contribution of interneuronal pathways to the stretch reflex, the length-tension and stiffness-force measurements are in any case likely to reflect true parametric changes produced by presynaptic inhibition. It will be important to determine the nature of the interneuronal pathways of the stretch reflex and the quantitative contribution they make to its output, if only because the stretch reflex is such a basic and integral neural mechanism of motor control.

Functional implications for normal motor control and spasticity

The main implication of the present results is that presynaptic inhibition of muscle spindle afferents is a potential neural mechanism that would allow for the adaptive control of the mechanical impedance at a single joint. In principle, there are three ways to modify the mechanical impedance of a controlled system: (1) the inertia or mo-

ment of inertia of the system may be changed, (2) the damping characteristics may be changed, and (3) its stiffness characteristics may be changed. At the level of single joints, the moment of inertia is unchangeable. Adaptive control of the damping characteristics requires control of the velocity sensitivity of the primary spindle afferents. The action of the dynamic γ-motoneurons on the primary spindle afferents is to increase the overall sensitivity of the receptor to stretch, not its velocity sensitivity per se (Matthews 1981). Finally, as mentioned in the Introduction, based on the experimental evidence available at the time (Matthews 1959a,b; Feldman and Orlovsky 1972; Nichols and Houk 1976) it was suggested that the stiffness of the stretch reflex may be a regulated but constant parameter (see the reviews by Houk and Rymer 1981; Berkinblit et al. 1986). Thus, in such a case, adaptive control of the stiffness at a single joint would not be possible. Partly as a result of this idea, several researchers have suggested that the co-contraction of antagonistic muscles acting at a joint is a means by which the mechanical impedance of a joint can be modified (e.g., Lacquaniti et al. 1982; Hogan 1984). However, it is now known that co-contraction increases the stiffness of the joint by no more than 30–50% of that which can be achieved by maximum activation of the agonist muscles only (Milner and Cloutier 1993). The present results point to the possibility that the CNS may be capable of modifying the mechanical impedance at a single joint, such as the ankle, by controlling the level of presynaptic inhibition of the muscle spindle afferents. For example, it has been suggested that the stiffness of the ankle is reduced during walking, independently of the background force, as a result of an increase of presynaptic inhibition of the muscle spindle afferents (Capaday and Stein 1987a,b; Stein and Capaday 1988). This would make the ankle more compliant during the stance phase of walking, thus allowing for the lengthening contraction of the ankle extensors under the load of the body, without inducing myoclonic contractions as result of a strong stretch reflex (Houk 1978; Morin et al. 1982; Stein and Capaday 1988). It should be noted that presynaptic inhibition would have a greater range of control action at low and moderate force levels than at higher force levels. This follows from the inverted parabolic relation between the stretch reflex stiffness and the background force (Fig. 5), since the stretch reflex contributes progressively less to the total muscle stiffness as the background force increases. The relatively low levels of muscle activity in the ankle extensors during walking would thus be within the range of greatest presynaptic inhibitory control.

A second implication of the present results is that the threshold of the stretch reflex is not an independent variable, as is for example suggested in the "λ-model" of motor control (see Berkinblit et al. 1986). It depends on the membrane potential of the α-motoneurons and on the existing level of presynaptic inhibition of the muscle spindle afferent terminals. However, not all of the increased stretch reflex threshold observed in the present experiments can be attributed to presynaptic inhibition of muscle spindle afferent terminals. Edwards et al. (1989) and Jiménez et al. (1991) have shown that baclofen has some effect on descending pathways in the ventromedial funiculus. However, these effects are weaker than those on primary afferent fibers. Nonetheless, since activity in these descending pathways is partly responsible for the increased muscle tone of decerebrate rigidity, a reduction of activity in these pathways will on its own increase the stretch reflex threshold.

Finally, it would be difficult to ignore the potential implications of the present results for the understanding and treatment of spasticity. The action of baclofen on the stretch reflex of spastic patients has only been determined by measuring the H-reflex in quiescent conditions (e.g., Latash et al. 1989). There was no simple reason to believe that during motor activity, once the threshold of the stretch reflex was exceeded, that its output would in fact be decreased by baclofen. The results described in this paper suggest that this would in fact be the case. Thus, the intensity of action of the stretch reflex would be diminished in the spastic patients during motor activity. The link between threshold and stiffness of the stretch reflex described in this paper is also relevant to resolving certain controversies related to what parameters of the stretch reflex are affected in spasticity. For example, Powers et al. (1989) have suggested that in spastic patients it is the stretch reflex threshold which is lowered, as a result of a more depolarized resting membrane potential of the α-motoneurons. On the other hand, Thilmann and colleagues (1991) have suggested that it is the stretch reflex stiffness which is increased in spastic patients. Our results imply that the two parameters are linked such that a change in the stiffness of the stretch reflex will also be accompanied by a change in its threshold, but that changes in the threshold without a change in the stiffness are possible.

There are other potential mechanisms by which the stretch reflex parameters can be modified. For example, if changes in the recruitment profile (Kernell and Hultborn 1990) of the motoneuron pool occur in different tasks, then the stretch reflex parameters will be automatically modified. Marked changes of the relation between trans-membrane current and discharge frequency of motoneurons, which may occur for example during locomotion (Brownstone et al. 1992), would also change the stretch reflex parameters. However, these are neither direct nor independent neural mechanisms specific for the control of stretch reflex parameters. The findings reported in this paper describe what may be expected if a change of presynaptic inhibition were to occur during a motor task. The challenge will be to clearly identify such tasks and correlate the neurophysiological changes with the mechanical changes.

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