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Neural Mechanisms Underlying the Clasp-Knife Reflex in the Cat II. Stretch-Sensitive Muscular-Free Nerve Endings

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SUMMARY AND CONCLUSIONS

1. The goal of this study was to determine the contribution of muscular free nerve endings to the clasp-knife reflex by comparing their response properties and reflex actions to the clasp-knife reflex.

2. The responses of single muscle afferents were examined in anesthetized cats using stretch and isometric contraction of ankle extensor muscles identical to those that evoked clasp-knife inhibition in decerebrated and dorsal spinal-hemisectioned cats.

3. Fifty-three stretch-sensitive mechanoreceptor afferents were identified as free nerve ending afferents based on their conduction velocities, location within the muscle, uniformity of response, and dissimilarity to other muscle proprioceptors. The afferent conduction velocities were in both the group III (56%) and group II (44%) range, including five fast-conducting group II afferents (>55 m/s).

4. The stretch response of stretch-sensitive, free nerve endings (SSFNEs) showed several characteristic features: *1*) afferents were excited only by large stretches that produced significant passive force; *2*) afferent activity began after a brief delay and exhibited segmentation of discharge during ramp stretch, a maximum at the end of ramp stretch, and rapid and complete decay during static stretch, and *3*) afferent response adapted to repeated stretches. These properties match those of clasp-knife inhibition described in the companion paper, except that the SSFNE segmentation and maximum were more pronounced and their decay during maintained stretch was more rapid.

5. Isometric contraction produced by electrical stimulation of the muscle nerve, which induced force-evoked inhibition in decerebrated and dorsal hemisectioned cats, also consistently excited SSFNEs. Stretch evoked greater excitation than contraction, indicating that both length and force contribute to SSFNE activity.

6. Stimulation of free nerve endings by squeezing the achilles tendon in cats exhibiting the clasp-knife reflex evoked powerful, homonymous inhibition and a flexion-withdrawal pattern of reflex action—that is, inhibition of extensor and excitation of flexor muscles throughout the hindlimb, which parallels the spatial divergence of the clasp-knife reflex.

7. Intrathecal application of capsaicin, which preferentially blocks the reflex actions of small afferent fibers, blocked clasp-knife inhibition in decerebrated, dorsal hemisectioned cats.

8. The similarities between the reflex actions and response properties of SSFNEs and the properties of the clasp-knife reflex suggest that SSFNEs mediate clasp-knife inhibition. The differences between the responses of SSFNEs and clasp-knife inhibition to stretch and contraction might be explained by spinal "low-pass" filtering, which may be accomplished by spinal interneurons. Thus the activity of SSFNEs in muscle and tendon appears sufficient to account for the features of the clasp-knife reflex, although additional contributions from Golgi tendon organs and secondary spindle afferents cannot be excluded.

INTRODUCTION

The clasp-knife reflex, which consists of brief excitation followed by powerful, long-lasting inhibition in homonymous and synergistic muscles, has been extensively investigated in both reduced animal preparations (Burke et al. 1972; Cleland and Rymer 1990; Rymer et al. 1979; Sherrington 1909), chronically spinalized animals (Nichols and Cope 1989; Sherrington 1909), and spastic human patients (Burke et al. 1971; Rademaker 1947). The identity of the sensory receptors responsible for clasp-knife inhibition has, however, remained controversial. The goal of our experiments was to determine whether the response patterns and reflex actions of muscular free nerve endings are sufficient to account for clasp-knife inhibition.

Golgi tendon organs, which are excited by stretch of active muscle (Houk and Henneman 1967; Stuart et al. 1970) and inhibit homonymous extensor motoneurons (Eccles et al. 1957), were first suggested by Matthews (1933) to mediate clasp-knife inhibition. However, recent investigations have questioned the magnitude of their contribution to clasp-knife inhibition for several reasons. First, the clasp-knife reflex typically has a length threshold longer than the length threshold of Golgi tendon organs in active muscle (Rymer et al. 1979). Second, the strength of force feedback that is presumably due to Golgi tendon organs in decerebrated, dorsal hemisectioned cats exhibiting the clasp-knife reflex is weak (Cath and Crago 1982). Third, the companion paper (Cleland and Rymer 1990) showed that several properties of the clasp-knife reflex—decay of inhibition during maintained stretch, lack of effect of release of stretch, adaptation to repeated stretches, and homonymous excitation during stretch of a flexor muscle—are not consistent with the known response properties and reflex actions of Golgi tendon organs (Houk et al. 1980; Proske 1981).

Burke et al. (1972) suggested that secondary spindle afferents were responsible for clasp-knife inhibition based on their finding that clasp-knife inhibition has an absolute length threshold (Burke et al. 1972) and that electrical stimulation of group II afferents in extensor muscles evokes homonymous inhibition (see Baldissera et al. 1981). However, Rymer et al. (1979) showed that the length thresholds

of secondary spindle afferents in cats exhibiting the clasp-knife reflex were poorly correlated with the length threshold of clasp-knife inhibition. Moreover, in the companion paper (Cleland and Rymer 1990) we showed that in contrast to secondary spindle afferents, clasp-knife inhibition decays during maintained stretch, adapts to repeated stretch, and is not significantly affected by the release of stretch. More important, isometric contraction, which should decrease rather than increase the activity of secondary spindle afferents, evokes similar patterns of inhibition. There is also evidence that the reflex actions evoked by electrical stimulation of group II afferents in the triceps surae muscles is produced by activation of a limited number of powerful afferents that most likely arise from muscular free nerve endings rather than secondary spindle afferents (see DISCUSSION). Thus secondary spindle afferents are unlikely to contribute to clasp-knife inhibition.

Recently, Rymer et al. (1979) hypothesized that muscular free nerve endings were responsible for clasp-knife inhibition. They showed that gentle pressure on the achilles tendon, which would likely only excite free nerve endings in the tendon, evoked strong inhibition in cats exhibiting the clasp-knife reflex. They also recorded from several non-spindle group II afferents that had temporal features broadly similar to the decreases in force and EMG in clasp-knife inhibition. Similarly, Mense and Meyer (1985) have shown that group III and IV muscle afferents can be excited by stretch and contraction within the physiological range, further supporting a possible role for these receptors in stretch-evoked inhibition.

The aim of this study was to test the hypothesis that muscular free nerve endings are responsible for clasp-knife inhibition by comparing the afferent response to muscle stretch and contraction with the analogous properties of the clasp-knife reflex. We further tested the involvement of muscular free nerve endings indirectly by pharmacologically blocking their reflex actions with capsaicin. Our results demonstrate that stretch-sensitive, free nerve ending afferents (SSFNEs) appear sufficient to account for clasp-knife inhibition. Previous reports of this research have been published in abstract (Cleland and Rymer 1983) and thesis (Cleland 1984) form.

METHODS

The experiments described in this paper used two different preparations. The reflex effects of tendon squeeze and capsaicin blockade were investigated in the decerebrated and dorsal spinal-hemisectioned cat, which is fully described in the companion paper (Cleland and Rymer 1990). The response properties of muscle afferents were investigated in the barbiturate-anesthetized cat, which is described below.

Animal preparation

Cats weighing 3–5 kg were anesthetized with a mixture of halothane, nitrous oxide, and oxygen. The trachea and external jugular vein were cannulated, and the femoral, sural, common peroneal, tibial (above the branches to the long flexor muscles), hamstring, and sometimes nerves to the hip were cut. Pentobarbital sodium was given intravenously, in a dose of 40 mg/kg, and gaseous anesthetic was withdrawn, allowing the cat to breath room air. Supplementary doses of pentobarbital sodium were given as necessary.

The cat was secured in a spinal frame by a head holder, a clamp on the L_2 spinous process, and hip pins and cup-shaped clamps on the femoral condyles and ankle malleoli. For the cats in which muscle afferents were dissected from the dorsal roots, a laminectomy was done from L_4–L_7 and the lateral gastrocnemius-soleus and medial gastrocnemius nerves dissected in continuity. The soleus and medial and lateral gastrocnemius muscles were dissected and the cat maintained as described in the companion paper (Cleland and Rymer 1990). At the end of the experiment, the cats were killed with an overdose of pentobarbital sodium.

Inputs and outputs

The inputs used to study the muscle afferents were identical to those used to study the clasp-knife reflex (Cleland and Rymer 1990). Muscle length was controlled by an AGAC-Derritron AV-50 mechanical vibrator and was measured with a linear variable differential transducer. Muscle length was specified relative to the maximum physiological length of each muscle. Isometric contraction was evoked by electrically stimulating the muscle nerve with bipolar platinum-iridium hook electrodes and pulses of 0.02-ms duration. Isometric force was modulated either by changing the frequency of stimulation within the normal physiological range (6–25 Hz) (Burke 1981) or by increasing the stimulus intensity over the range from 1.0–2.0 × threshold for muscle twitch. The stimulus intensity was always below threshold for the muscle afferent studied. The force produced by individual muscles was measured with a load cell mounted between the muscle and muscle stretcher.

The electromyograms (EMGs) were recorded with pairs of 75-μm, teflon-coated stainless steel wires, bared over the terminal 3–5 mm and inserted with hypodermic needles into separate portions of each muscle. Electrodes were placed in three flexor muscles acting at different joints (ankle, tibialis anterior; knee, semitendinosis; hip, iliopsoas) and six extensor muscles acting at different joints (ankle: soleus, lateral and medial gastrocnemius, flexor digitorum longus, plantaris). The semitendinosis, flexor digitorum longus, and tibialis anterior were left attached to the tendon, and the soleus, plantaris, and lateral and medial gastrocnemius were tenotomized.

Muscle receptors in the achilles tendon were preferentially excited by squeezing the distal portion of the tendon with a pair of fine forceps whose tips were covered with soft tubing to avoid damaging the tendon. To apply precisely localized pressure, small portions of the tendon were squeezed with fine forceps under microscopic control. Care was taken to minimize longitudinal tension that could excite distant receptors. When the receptive fields of muscle receptors were accessible, their sensitivity was quantified with von Frey hairs. Threshold was defined as the smallest force that produced an ~50% chance of the afferent discharging at least one action potential.

Muscle-afferent recording

Single muscle afferents were isolated from fine filaments teased from either dorsal root fascicles or from the muscle nerve. Electrical activity was recorded with a monopolar platinum-iridium electrode (referenced to regional skin), amplified, and filtered (100 Hz–10 kHz). Muscle stretch and direct mechanical pressure were used as search stimuli rather than electrical stimulation of the muscle nerve, which likely biased the sample of muscle afferents toward those afferents that were the most mechanosensitive. Because many group III and most IV mechanoreceptors have high mechanical thresholds (Mense 1986), the choice of search

stimulus may have contributed to the lack of any group IV mechanosensitive afferents and the large number of group II afferents.

Data acquisition and analysis

Experiments were controlled and data collected on-line by a Digital Equipment PDP 11/23 minicomputer. Muscle length and force were sampled at 100 Hz with a 12-bit A/D converter. The time of occurrence of action potentials was determined with a time-amplitude window discriminator and stored with a resolution of 100 μs. The dynamic features of the response were examined by ensemble-averaging afferent activity, force, and length from individual trials. Afferent activity was ensemble averaged by forming histograms, or probability-density functions (Matthews and Stein 1969), of the time of occurrence of each action potential. Afferent probability-density records were smoothed by computer with a Gaussian-weighted, 9-point, moving-average filter (Abeles 1982).

Conduction-velocity estimation

The conduction velocity of afferents teased from the dorsal roots was determined by electrically stimulating the afferent in the muscle nerve (bipolar, 0.02-ms duration, monophasic) and measuring both the conduction time and conduction distance. For afferents teased from the muscle nerve, the above method was impractical because of the lack of accuracy in measuring the conduction distance and interference from the stimulus artifact. Instead, two hook electrodes, separated by 5–10 mm, were placed under the muscle nerve between the muscle and the afferent recording site. The action potential of the muscle afferent was then used to trigger averages from the time-delayed neurogram recorded by the hook electrodes (Kanda et al. 1977). The difference in time between the peak of the two waveforms divided by the conduction distance yielded the conduction velocity. In some instances, the waveforms had different shapes, probably because the recording electrodes were placed at different positions relative to the nodes of Ranvier (Marks and Loeb 1976). In these instances, the positions of the recording electrodes were adjusted until similarly shaped averages were obtained for both electrodes.

Afferent identification

Identification of free nerve ending afferents was based on several overlapping criteria. Because most of the afferents had group III conduction velocities and novel response properties unlike other muscle proprioceptors, they undoubtedly arose from free nerve ending receptors (Matthews 1972; Mense 1986). Afferents with group II or unknown conduction velocities, but otherwise similar to group III free nerve ending afferents, were also likely to have arisen from muscular free nerve endings.

Primary spindle afferents were identified if the afferent had group I conduction velocity (>72 m/s) and responded to longitudinal, small-amplitude muscle vibration (100 μm, 160 HZ), which is a selective stimulus for primary spindle afferents in passive muscle (Brown et al. 1967). Golgi tendon organ afferents were identified if the afferent had group I conduction velocity, activity on the rising edge and peak-of-twitch contractions that persisted even when compliance was increased, and regular, spontaneous activity at long muscle lengths (Houk et al. 1971; Stuart et al. 1970). Secondary spindle afferents were identified if the afferent had group II conduction velocity (24–72 m/sec), responded to small stretches (e.g., 4 mm) beginning at short initial muscle lengths (−10 to −15 mm), did not respond to small-amplitude vibration, and had a spontaneous discharge at muscle lengths within the physiological range. Paciniform-like receptor afferents were identified if the afferent was not a primary spindle afferent and responded dynamically and reliably to brief, remote stimuli such as tapping on the hindlimb or recording table (Matthews 1972).

RESULTS

Fifty-three muscle afferents were identified as SSFNEs in 45 cats. The activity of 24 afferents was recorded from the muscle nerve and 29 from the dorsal roots.

Conduction-velocity distribution

The conduction-velocity distribution of SSFNEs is shown in Fig. 1. The solid bars indicate group III (6–24 m/s; $n = 24$, 56%), and the hatched bars indicate group II (24–72 m/s; $n = 19$, 44%) conduction velocities. In contrast to some previous studies (Boyd and Davey 1968; Hunt 1954; Jack 1978), we found many group II SSFNEs, several with fast conduction velocities (>55 m/s). No stretch-sensitive group IV afferents were found.

Pressure sensitivity

Nearly all (52/53) SSFNEs were classified as low-threshold mechanoreceptors because they responded to light stroking or pressure, in accordance with previously used definitions (Mense 1986). Only one high-threshold SSFNE, which responded weakly to strong, presumably noxious pressure, was found. A typical response to gentle squeezing of the tendon with fine forceps is shown in Fig. 2A.

All SSFNEs exhibited a maintained response to constant pressure and immediately stopped their discharge when pressure was removed. The average firing rate during the application of pressure was 19.4 Hz (±16.7 Hz SD, $n = 23$). The receptors whose receptive fields were accessible were extremely sensitive to light pressure, but those whose receptive fields were located in the proximal portion of the muscle or deep within the muscle could not be thoroughly examined. The receptive fields were usually small (1 × 1 mm), although distant stimuli were often effective because of the SSFNE's high sensitivity. Dynamic stimuli, such as stroking the muscle, were more effective than static stimuli,

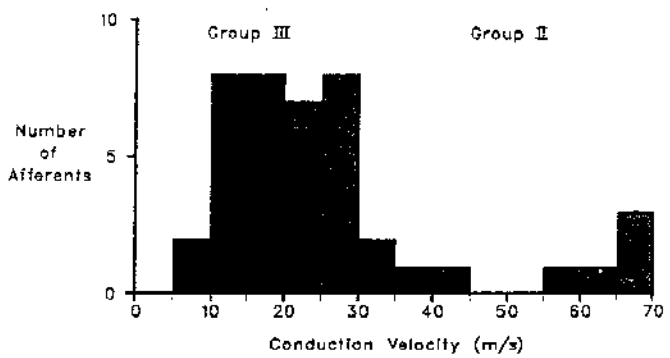

FIG. 1. Conduction-velocity distribution. Histogram shows the conduction velocities for 43/53 SSFNEs. Filled bars indicate group III (6–24 m/s) conduction-velocity afferents, and hatched bars indicate group II (24–72 m/s) afferents.

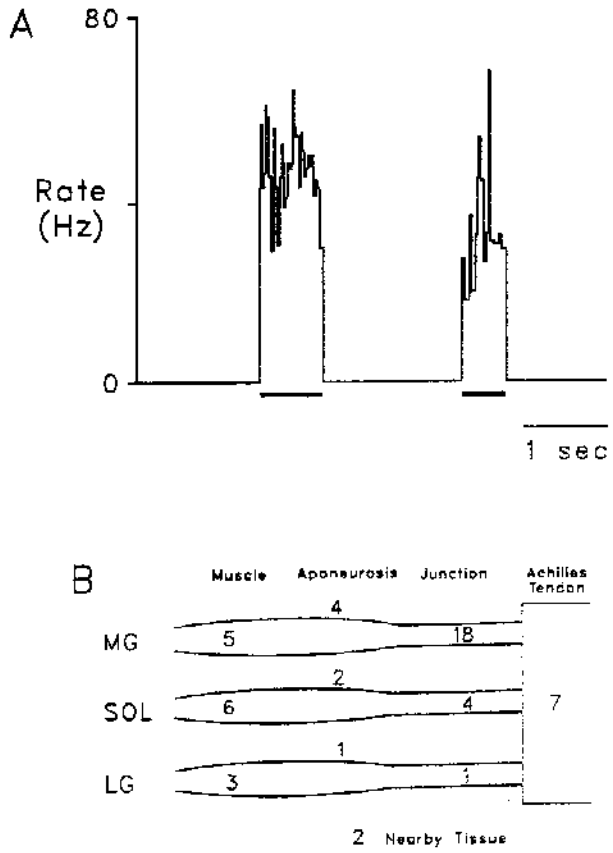

FIG. 2. Pressure response and receptive fields. *A*: SSFNE is powerfully excited by squeezing the soleus tendon with silicone covered forceps. Stimulus was firm but not noxious. Dark bars indicate the approximate duration of squeeze. Record is a single trial. *B*: schematic illustrates the location and types of receptive fields. From *right* to *left* are the achilles tendon, musculotendinous junction, aponeurosis, and muscle belly, with nearby tissue shown *below*. Specific muscles, when appropriate, are shown to the *left*. Numbers indicate the number of afferents that had each type of receptive field.

such as maintained blunt pressure. Receptive fields were never discontinuous.

The pressure sensitivity of five SSFNEs was quantified with von Frey hairs (most others could not be studied because their receptive fields were inaccessible). All five were extremely sensitive. The threshold, defined as a 50% likelihood of response, was 4.5-mg load for one SSFNE—the smallest von Frey hair available. The other four required only 166-mg loads.

Overall, the receptive fields of SSFNEs were distributed throughout the triceps surae muscles, tendon, and connective tissue. Figure 2*B* shows schematically their receptive-field locations, according to muscle, and location within the muscle or connective tissue. Unlike other proprioceptors, SSFNEs were not restricted to either muscle or tendinous connective tissue, which suggests a diversity in their sensitivity to whole muscle stretch or contraction. Although a number of SSFNEs had receptive fields within muscle or the surface aponeurosis, many SSFNEs were located in the distal portion of the common achilles tendon which is devoid of other proprioceptors, suggesting that SSFNEs could be preferentially excited by localized pressure to the tendon.

Muscle stretch

Ramp-and-hold stretches, identical to those used to evoke clasp-knife inhibition (Cleland and Rymer 1990), were imposed on the soleus and medial and lateral gastrocnemius. All 53 SSFNEs responded to stretch. A typical stretch response is shown in Fig. 3. The *third* record is a single trial, and the *bottom* record is a smoothed ensemble average of 20 trials. The response to stretch, even to maximum physiological length, was usually less than one-half the response to innocuous direct pressure.

TIME COURSE OF RESPONSE. Figure 3 also shows the typical time course of SSFNE activity, and Fig. 4 illustrates the range of stretch responses obtained. Before stretch, SSFNEs were either quiescent (32/53), irregularly active at low frequencies (<2 Hz; 19/53), or rarely tonically active (2/53; 4 and 20 Hz). After the onset of stretch, applied typically at 20 mm/s for 0.5 s, SSFNEs discharged after a brief latency (119 ± 10.8 ms, mean ± SD, $n = 45$). At the beginning of the hold portion of stretch, activity reached a maximum (30 ms from hold onset, ±12 ms SD, $n = 16$). During maintained stretch, the activity decayed either immediately (Fig. 4, *A* and *D*) or with a brief time course (Fig. 4, *B* and *C*). The mean time required to decay from the maximum by 50% was 0.79 s (from hold onset; ± 0.81 ms SD, $n = 37$). Some SSFNEs (12/53) exhibited a weak static response during the entire 3.5-s stretch.

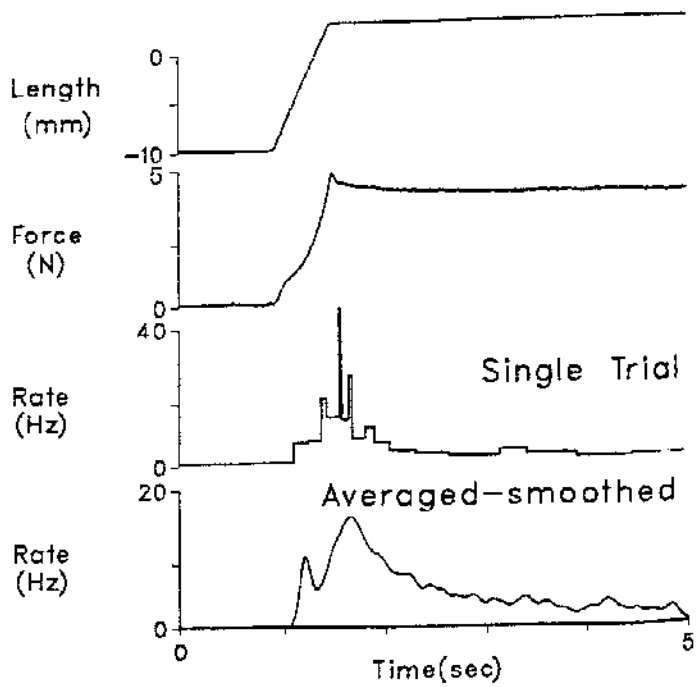

FIG. 3. Stretch response. Large-amplitude stretch of the soleus excites a SSFNE. *Third* record is a single trial, and *bottom* record is a smoothed ensemble average of 20 trials for the same afferent. Note that dynamic features of the afferent response, which include segmentation during ramp stretch, dynamic overshoot, and nearly complete decay within the displayed window, are clearer in the ensemble average.

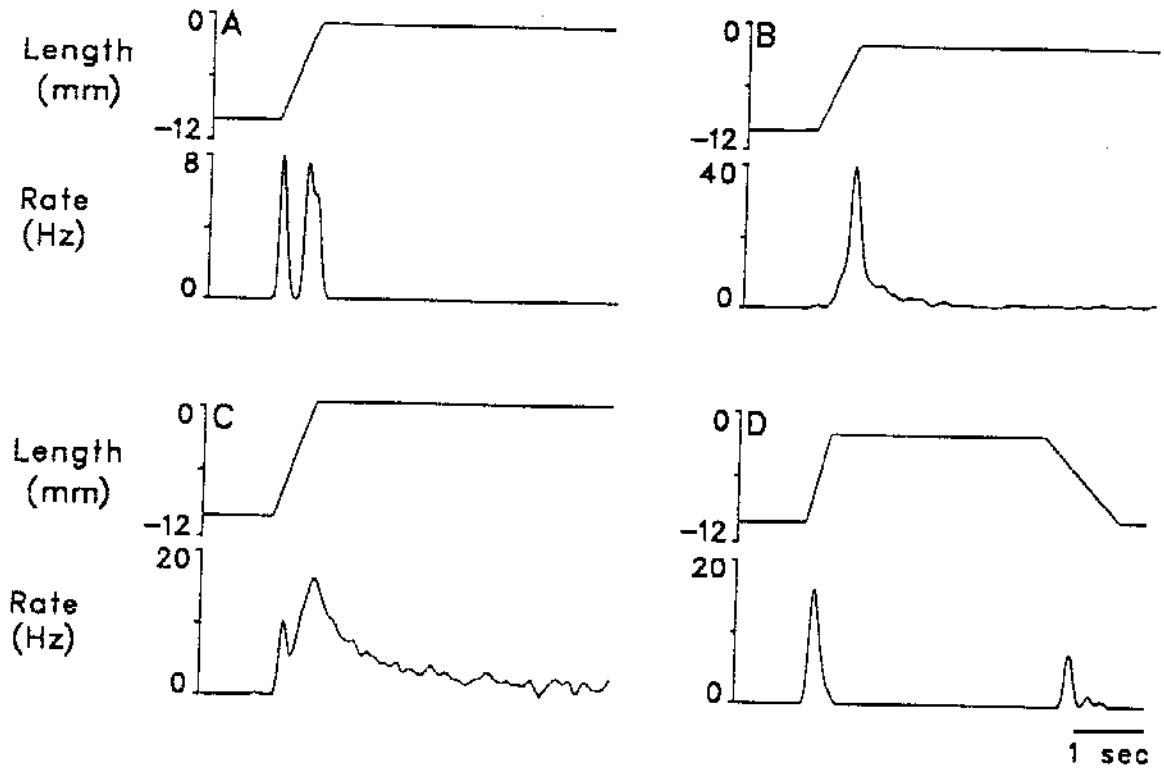

FIG. 4. Variability in time course of response. Each panel shows the response of a different SSFNE to similar muscle stretches. Each record is a smoothed ensemble average. Conduction velocities are 67 m/s and 56 m/s for the *top left* and *top right* afferents. Conduction velocity was not determined for the *bottom* 2 afferents.

SSFNEs often exhibited characteristic variations in their firing patterns. Most SSFNEs (20/23) displayed a double burst, or segmented, pattern of activity during ramp stretch (Fig. 4, *A* and *C*), and some SSFNEs (7/53) fired during release of stretch (Fig. 4*D*). The firing rates reached by SSFNEs were low and variable. The mean average rate during ramp stretch was 11.7 pulses/s (±10.7 Hz SD, n = 21; static force = 2.9 N, ±1.8 N) but varied from 150 Hz to only one action potential. Figure 4 shows two SSFNEs with significantly different firing rates (cf. Fig. 4, *A* and *B*; note difference in rate scale).

AMPLITUDE DEPENDENCE OF AFFERENT RESPONSE. The magnitude of SSFNE response increased with increasing amplitude of stretch. Figure 5 shows the response, recorded as the total number of action potentials elicited by ramp-and-hold stretch, versus the final length of stretch. Typically, SSFNEs responded only to relatively large amplitude stretches that generated significant passive force. A clear maximum or saturation was never reached. The shape of the relation between stretch amplitude and discharge rate was uniformly concave upwards and closely paralleled the relation between passive muscle force and amplitude of stretch. Similarly shaped relations were obtained for all eight SSFNEs that were studied with several different amplitudes of stretch.

The threshold stretch amplitude was defined as the amplitude of the smallest stretch that evoked a response. In Fig. 5, the threshold stretch corresponds to stretches that terminated at −7 mm. The mean threshold was −4.8 mm (±1.4 mm SD, n = 13). The threshold did not covary with conduction velocity or the muscle in which the receptor was located. None of the 53 SSFNEs responded to stretches that did not produce clear increases in passive force.

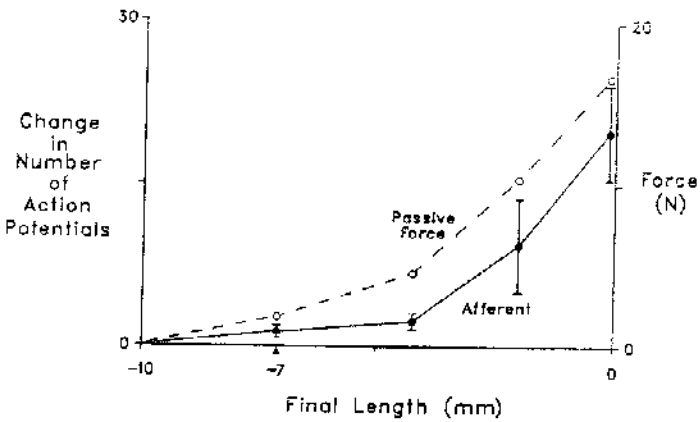

FIG. 5. Dependence on amplitude of stretch. SSFNE response, measured as the total number of action potentials evoked by stretch of the medial gastrocnemius, is plotted against the final length of stretch for stretches of increasing amplitude but constant duration (——, ●). There was no spontaneous activity at the initial length. Error bars are standard deviation for 2–10 trials. Passive force generated by stretch is shown by the dashed line connecting the open circles. Error bars for force measurements are not shown because they were so small that they would fall within the symbol. Length threshold for this afferent, −7 mm, is indicated by the arrow.

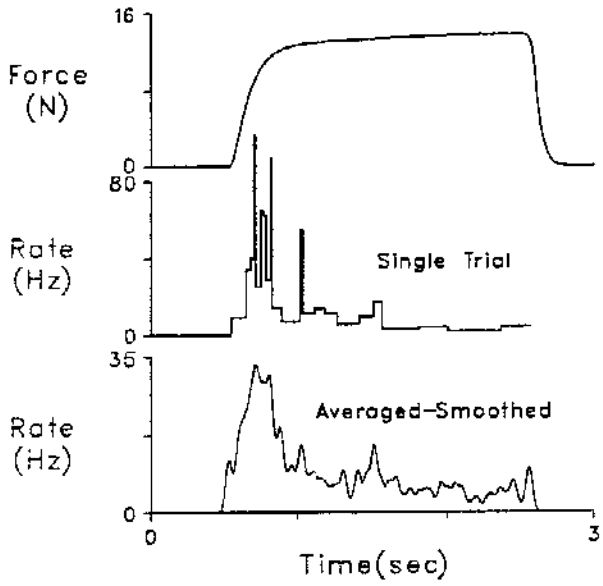

FIG. 6. Isometric-tetanic contraction. Isometric contraction of the soleus was produced by electrical stimulation of the muscle nerve (30 Hz) at an intensity below threshold for the SSFNE afferent. *Middle* record shows a single response of the SSFNE and the *bottom* record is a smoothed ensemble average of 12 trials.

Isometric contraction

Isometric contraction, identical to that which induced force-evoked inhibition in decerebrated dorsal hemisectioned preparations, was produced by low-intensity electrical stimulation of the muscle nerve, subthreshold for the SSFNE afferent. Nearly all (86%; 32/37) of the SSFNEs were excited by isometric contraction. Figure 6 shows a typical single trial and a smoothed ensemble average of 12 trials. The response consisted of a maximum that decayed to a maintained response during the plateau of the force tetanus. At the end of the tetanus, the activity immediately returned to the initial level. The average maintained response rate was 17.9 Hz (±13.8 Hz, n = 25; static force = 7.9 N, ±9.9 N). Although most SSFNEs displayed this pattern, seven discharged only on the falling phase of the tetanus and one discharged on both the rising and falling phase. The SSFNEs that responded during declining contraction differed from those that were activated by stretch release. All SSFNEs responsive to tetanic contraction also responded to twitch contraction.

Afferent activity depended critically on the dynamics of isometric contraction. Figure 7*A* shows that a smaller, unfused contraction produced a greater response than a larger, fused contraction. Similar results were obtained in 5/6 SSFNEs tested. These results suggest that SSFNEs have a high dynamic sensitivity to force, which is consistent with the maximum firing rate occurring at the onset of tetanic contraction (Figs. 6 and 7, *A* and *B*).

Different SSFNEs had different sensitivities to changes in force and length. Although the mean firing rate during stretch (11.7 Hz) was less than during contraction (17.9 Hz), stretch produced a much smaller increase in force (1.9 N, ±1.8 SD, n = 21) than contraction (11.7 N, ±10.7 SD, n = 21). When the increases in force produced by contraction and stretch could be matched, most SSFNEs (27/38) were more strongly excited by stretch. Figure 7*B* shows that

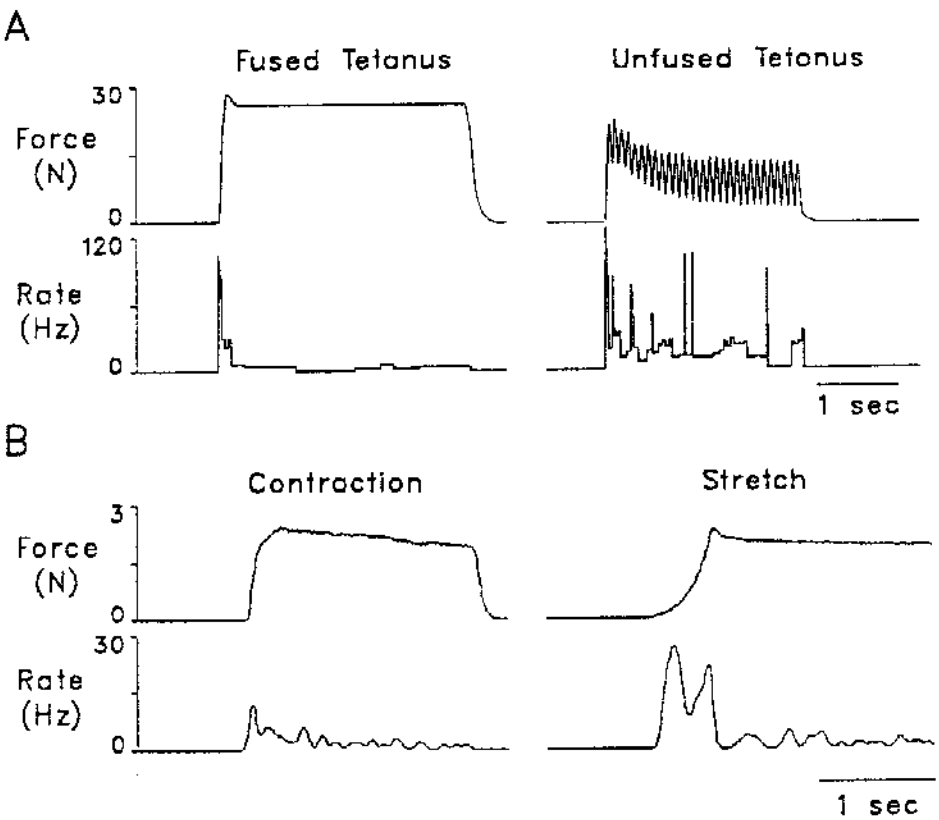

FIG. 7. Dependence on type of muscle force. *A*: on the *left*, fused contraction of the medial gastrocnemius produced by 50-Hz stimulation of the muscle nerve evokes a weak response in the SSFNE. On the *right*, an unfused tetanus (12.5 Hz) producing less force evokes a significantly greater response. Unsmoothed single trials. *B*: on the *left*, tetanic contraction of the soleus (20 Hz) evokes a typical response in the SSFNE. On the *right*, stretch of the same muscle in the same experiment produces less force but a greater response. Records are smoothed ensemble averages of 10 and 12 trials. Afferent conduction velocity was 8 m/s.

stretch that produced a small force (1.5 N) evoked a greater afferent response than isometric contraction that produced an even greater force (2 N). Only 7/38 SSFNEs were more strongly excited by contraction than stretch. These results show that the stretch response cannot be explained solely by the accompanying increase in force, implying that length per se contributes to the excitation of SSFNEs.

Rate adaptation

A striking and consistent characteristic of SSFNEs was that most (36/42) adapted swiftly to repeated stretch. Figure 8*A* shows the adaptation of a SSFNE during a series of eight trials. In spite of similar stretch and force profiles, the response decreased by trial 11 to nearly 10% of the initial response. The solid line connecting the filled circles in Fig. 8*B* shows the time course of adaptation for the same SSFNE shown in Fig. 8*A*. Most adaptation occurred between the first and second trial, with 80% adaptation occurring by trial 6. The decay of the clasp-knife reflex (redrawn from Fig. 12 in Cleland and Rymer 1990), shown by the thin line connecting the open circles, shows a similar time course. In contrast, neither the Golgi tendon organ (—— connecting ▲) nor secondary spindle afferent (—— connecting ■) showed any adaptation. The mean trial by which 50% adaptation occurred was trial number 4.8 (±2.0 SD, n = 15). The average trial at which nearly maximal adaptation was reached was 9.7 (±2.9 SD, n = 12). Adaptation did not significantly depend on the amplitude of stretch. None of the four secondary spindle afferents nor the one Golgi tendon organ recorded showed rate adaptation with repeated stretch.

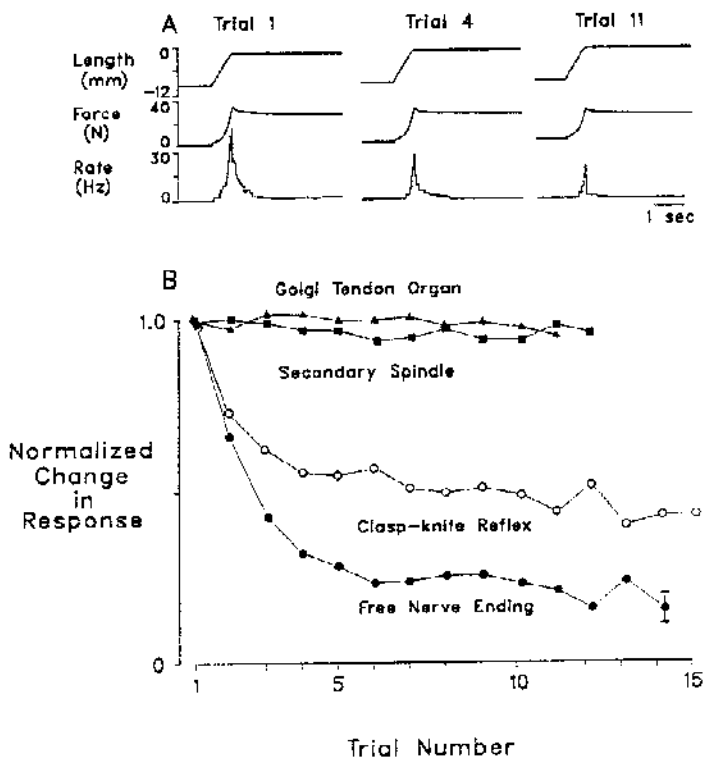

FIG. 8. Adaptation. *A*: repeated stretch of the medial gastrocnemius evokes progressively weaker responses. Each trial was separated by 30 s, and entire series was preceded by 3 min of rest. *B*: response, measured as total number of action potentials evoked by stretch and normalized to the first trial, is graphed against trial number. Solid line connecting filled circles is the relation for the unit shown in *A*. Each point is an average of 9 trials. Standard deviation, shown for the last point, was similar for all points. In contrast to the SSFNE, a Golgi tendon organ (—— connecting ▲) and secondary spindle afferent (—— connecting ■) show no adaptation. Each point for these 2 afferents is the average of the change in peak dynamic and steady-state firing rate from a single trial. For comparison, adaptation of the clasp-knife reflex, estimated by the decrease in homonymous excitation evoked by stretch of the tibialis anterior (taken from Fig. 12 in Cleland and Rymer 1990), is indicated by the solid line connecting open circles. SSFNE afferent conduction velocity was 53 m/s.

Reflex actions

To predict the contributions of SSFNEs to clasp-knife inhibition, it is necessary to determine their reflex actions as well as their response properties. To evaluate the sign, strength, and spatial divergence of the reflex actions of muscular free nerve endings, we performed the following experiments in decerebrated, dorsal hemisected cats that exhibited the clasp-knife reflex. Because the common achilles tendon is rich in free nerve ending receptors but essentially devoid of other proprioceptors, we used tendon squeeze to preferentially excite free nerve ending afferents. Similar responses could be obtained by lightly stroking the muscle surfaces and aponeuroses.

HOMONYMOUS REFLEX ACTIONS. Homonymous reflex actions of SSFNEs in the soleus or medial gastrocnemius were examined in 17 experiments. The consistent finding was that tendon squeeze powerfully inhibited EMG and force. Inhibition typically outlasted the stimulus by several seconds. Anesthetizing the tendon with lidocaine (5%) abolished the inhibition, verifying that receptors in the tendon were responsible for the inhibition, rather than remotely located muscle receptors. Like muscle stretch, tendon squeeze did not evoke inhibition in decerebrated cats with intact spinal cords. When a flexor, the tibialis anterior, rather than extensor tendon was squeezed in one experiment, powerful homonymous excitation rather than inhibition was obtained.

SPATIAL PATTERN OF REFLEX ACTIONS. In three experiments the spatial pattern of reflex actions evoked by tendon squeeze was investigated. EMG was recorded in three flexor muscles acting at different joints (ankle, tibialis anterior; knee, semitendinosis; hip, iliopsoas) and six extensor muscles acting at different joints (ankle: soleus, lateral and medial gastrocnemius, flexor digitorum longus, plantaris). Squeeze of the Achilles tendon inhibited extensor muscles and excited flexor muscles throughout the hindlimb.

Figure 9 shows single trials in which the iliopsoas, semitendinosis, and tibialis anterior were excited and the soleus and medial gastrocnemius and plantaris were inhibited by tendon squeeze. This pattern of reflex action was identical to the clasp-knife pattern evoked by stretch or contraction (Cleland and Rymer 1990). Similarly, the identical pattern, inhibition of extensor and excitation of flexor muscles, was obtained when a flexor tendon was squeezed. In one experiment the leg was left nearly intact, verifying that the reflex effects did not depend on extensive dissection that

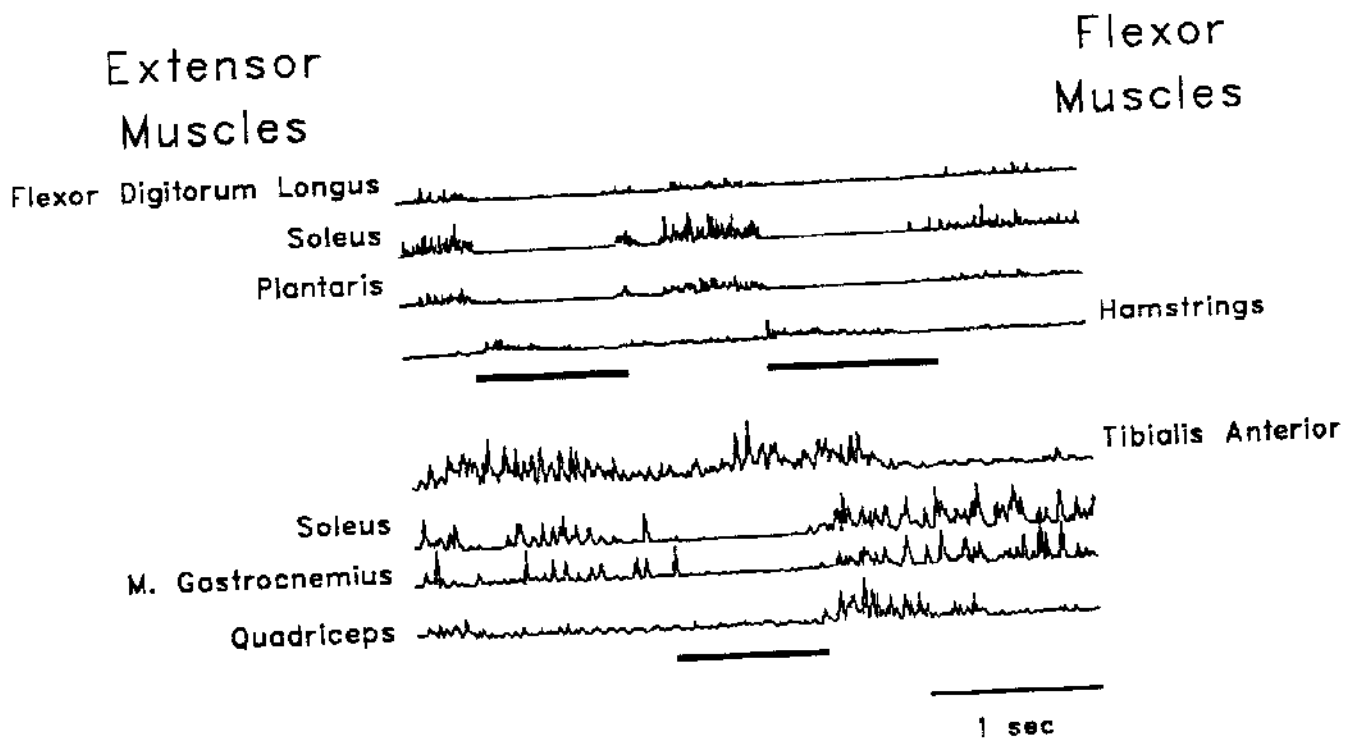

FIG. 9. Reflex actions. Soleus tendon was squeezed in 2 different trials (*top* and *bottom* sets of records) in a decerebrated and dorsal spinal hemisectioned cat. Semitendinosis, flexor digitorum longus, and tibialis anterior were left attached to the tendon, and the soleus, plantaris, lateral and medial gastrocnemius were tenotomized. EMG in extensor muscles was inhibited, and EMG in flexor muscles was increased. Each panel is a single trial.

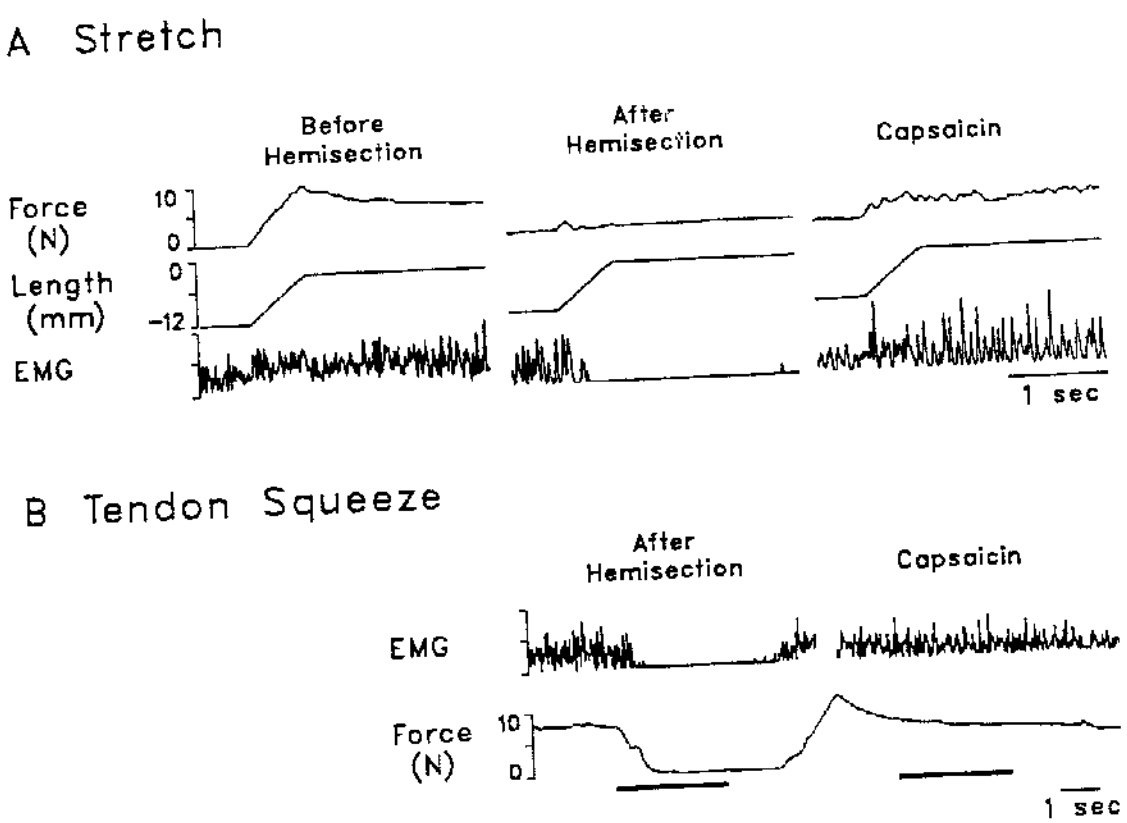

FIG. 10. Capsaicin blockade. *A*: *left* and *middle* panels show stretch of the soleus in a decerebrated cat before and after dorsal spinal hemisection. *Right* panel shows the stretch response shortly after 100 mg of capsaicin was applied intrathecally to the L_7–S_1 spinal junction. *B*: reflex actions of squeeze of the achilles tendon after hemisection (*left*) and subsequent to application of capsaicin (*right*). Dark bars indicate the approximate duration of squeeze. Same experiment as shown in *A*.

could alter the properties of the muscle receptors responsible.

Capsaicin blockade

If muscular free nerve endings mediate clasp-knife inhibition, then pharmacologic blockade of their reflex actions should abolish clasp-knife inhibition and restore the stretch reflex. Capsaicin (100 μg, dissolved in 10% Tween and 10% alcohol), which preferentially blocks the reflex action of small afferent fibers (Fitzgerald 1983), was applied intrathecally through a catheter to the L_5–S_1 portions of the spinal cord. Figure 10*A* shows that before hemisection, stretch evoked the typical excitatory stretch reflex. After hemisection, excitation was replaced by clasp-knife inhibition. Capsaicin then abolished the inhibition, restoring the stretch response to near prehemisection levels. Figure 10*B* shows that the inhibition evoked by tendon squeeze was also abolished by capsaicin, further supporting the interpretation that capsaicin eliminated clasp-knife inhibition by blocking the reflex action of free nerve ending afferents. Similar results were obtained in two experiments. In two other experiments, the effects of capsaicin were insufficient to abolish either clasp-knife inhibition or tendon-squeeze–evoked inhibition, further supporting the correlation between clasp-knife inhibition and the inhibition evoked by SSFNEs in the tendon.

DISCUSSION

Identification of muscle-receptor afferents

There are several lines of evidence which suggest that SSFNEs arose from free nerve endings in the muscle and tendon.

First, the conduction velocities of most SSFNEs were in the group III range, and free nerve endings are the only known muscle receptor with group III conduction velocity (Matthews 1972). The remaining afferents whose conduction velocity was measured were in the group II range, which also contains free nerve ending afferents (Barker et al. 1962; Paintal 1960; Rymer et al. 1979).

Second, the response properties of SSFNEs were similar to those of muscular fine–caliber afferents, generally accepted to arise from free nerve endings (Andres et al. 1985; Hinsey 1927; Stacey 1969). Fine-caliber afferents also respond to stretch and contraction within the physiological range (Mense and Meyer 1985). Although Mense (1986) and others have emphasized their generally poor mechanosensitivity, the high prevalence of stretch responsiveness in our study is resolved by realizing that we used muscle stretch and contraction rather than electrical stimulation of the muscle nerve as our search stimuli. Consequently, we were biased toward finding mechanosensitive afferents and missing non-mechanosensitive afferents, which includes most group IV afferents (Mense 1986).

Third, SSFNEs had relatively uniform response properties that differed from the properties of primary spindle, secondary spindle, Golgi tendon organ, and paciniform-like receptor afferents. Unlike spindle afferents, SSFNEs completely adapted to large, maintained stretch and were excited by isometric contraction that presumably caused internal muscle-fiber shortening. Unlike Golgi tendon organs, SSFNEs had a pronounced dynamic response to ramp stretch and completely adapted to stretch. Paciniform-like receptors can be excluded because they are more dynamically sensitive than SSFNEs. Muscular free nerve ending afferents, which constitute up to 75% of all muscle-receptor afferents (Stacey 1969), are the only other type of receptor found in muscle. Although any conclusion about the morphology of the receptors must be based on indirect evidence, the most likely hypothesis, based on their response properties and conduction velocities, is that SSFNEs arose from free nerve endings in muscle and tendon.

Are muscular free nerve ending receptors responsible for clasp-knife inhibition?

Although the clasp-knife reflex was first described almost 70 years ago, the muscle receptors responsible for clasp-knife inhibition are still not known. Golgi tendon organs (Matthews 1972) and secondary spindle afferents (Burke et al. 1972), once favored, are now considered unlikely sources (see DISCUSSION in Cleland and Rymer 1990). Currently, muscular free nerve endings appear the most likely possibility, but definitive evidence has been lacking. Our results, discussed in detail below, show that SSFNEs have response properties and reflex actions similar to clasp-knife inhibition and that blockade of their reflex actions abolishes clasp-knife inhibition. Thus stretch-sensitive, muscular free nerve endings appear sufficient and perhaps necessary for clasp-knife inhibition.

RESPONSE PROPERTIES. The response properties of SSFNEs were similar to clasp-knife and force-evoked inhibition in four ways. First, short stretches, which would not have evoked clasp-knife inhibition, did not excite SSFNEs. Instead, both the SSFNE activity and clasp-knife inhibition were only evoked by long stretches that approached maximum physiological length and generated appreciable force. Second, the time course of SSFNE activity and clasp-knife inhibition was also similar. Both demonstrated a similar onset latency (117 vs. 118 ms), segmentation during the ramp portion of stretch, dynamic overshoot at the completion of the ramp, decay during maintained stretch, adaptation to repeated stretch, were unaffected by release of stretch, and sometimes showed an OFF response. (The reason most afferents were unaffected by release is that their activity usually had completely ceased before release.) Third, isometric contraction, which evokes clasp-knife-like inhibition, also consistently excited SSFNEs. The time course of activity of force-evoked inhibition and SSFNE activity were also similar, both exhibiting a maintained response during contraction and occasionally an OFF response at the end of contraction. Fourth, both clasp-knife inhibition and SSFNE activity showed a greater response to stretch than contraction for matched forces.

On the other hand, there were some differences between SSFNE responses and the clasp-knife reflex. Clasp-knife inhibition had less pronounced EMG segmentation during the ramp portion of stretch, a smaller and later maximum

(152 vs. 30 ms after start of hold) at the end of ramp stretch, and decayed much more slowly during maintained stretch than did SSFNE activity (3.1 vs. 0.77 s to 50% reduction). Similarly, inhibition evoked by contraction exhibited a smaller initial peak and unlike the SSFNEs persisted beyond the end of contraction. These revealing differences may be due to interneuronal "low-pass filtering" of SSFNE activity. This appears likely because spinal interneurons have been found that are significantly excited by SSFNEs and have a time course of activity that closely parallels clasp-knife inhibition (Cleland et al. 1982).

REFLEX ACTIONS. The reflex actions evoked by tendon squeeze were likely to be representative of the reflex actions evoked by SSFNEs, because stimuli that would excite SSFNEs elsewhere in the muscle also evoked similar inhibition. Tendon squeeze appeared to excite free nerve ending receptors in the tendon preferentially, because spindle and Golgi tendon organ afferents were not consistently excited by such a stimulus, and lidocaine applied to the tendon blocked the reflex actions. Thus tendon squeeze is a preferential stimulus for tendon free nerve endings.

We found that the reflex actions of tendon squeeze, evoked in the same animal that demonstrated a clasp-knife reflex, closely paralleled the clasp-knife reflex. Homonymous and synergistic extensor muscles were powerfully inhibited, and flexor muscles were excited throughout the hindlimb by tendon squeeze of both extensor and flexor muscles. These results are consistent with previous attempts in other preparations to stimulate the tendon mechanically (Fulton and Pi-Suner 1928; Paintal 1961; Rymer et al. 1979; Sherrington 1909) or electrically (McCouch et al. 1950), although Golgi tendon organs may have also contributed to the reflex effects in these other preparations. Similarly, electrical stimulation of group II and III muscle afferents also evokes the same pattern of reflex action in fully spinalized cats (Eccles and Lundberg 1957; Holmqvist and Lundberg 1961; Lloyd 1943).

CAPSAICIN BLOCKADE. Capsaicin preferentially affects unmyelinated and small-myelinated sensory afferents (Fitzgerald 1983) but has not been shown to have any affect on large-myelinated afferents (Nagy et al. 1983). Furthermore, a likely mediator of capsaicin's actions, substance P (Holzer 1988), is found in small dorsal root ganglia cell bodies that give rise to small-unmyelinated and myelinated afferents but not in large dorsal root ganglia cell bodies that give rise to large-myelinated afferents (Hokfelt et al. 1976). Because free nerve endings have small-unmyelinated and myelinated axons and contain substance P (Marley and Livett 1985), our results showing that capsaicin significantly blocks clasp-knife inhibition supports the view that muscular free nerve endings are necessary for clasp-knife inhibition. Furthermore, the correlation between block of clasp-knife inhibition and block of reflex inhibition evoked by preferential stimulation of free nerve endings with tendon squeeze further implicates free nerve endings. The lack of complete elimination of clasp-knife inhibition is not surprising, because even high doses of capsaicin fail to completely block unmyelinated afferents (Holzer 1988; Nagy et al. 1983).

Do the effects of electrical stimulation of group II afferents arise from secondary spindle or free nerve ending receptor afferents?

Most investigations of the reflex actions of secondary spindle afferents have used electrical stimulation of the muscle nerve at group II intensities and argued that contributions from other group II afferents in the triceps surae muscles are negligible (e.g., Lundberg et al. 1987). Indeed, although group II afferents probably arising from free nerve endings have been extensively described for other muscles (Abrahams et al. 1984; Jack 1978; Paintal 1960; Stacey 1969), some studies (Boyd and Davey 1968; Hunt 1954; Jack 1978) claimed that there were almost no group II afferents from the medial gastrocnemius or soleus that did not arise from secondary spindle afferents. However, others have described group II and even group I afferents in the soleus and medial gastrocnemius that most likely originated from muscular free nerve endings (Barker et al. 1962; Paintal 1960; Rymer et al. 1979).

We found that 44% of our population of SSFNEs had group II conduction velocities (24–72 m/s; 23% if group II is defined as 30–72 m/s). Furthermore, the group II afferents described in those studies and those studied here span the entire group II range of conduction velocities. These results further demonstrate that the nerves to the triceps surae muscles contain group II afferents that do not arise from secondary spindle receptors. Although possibly few in number, non-spindle group II muscle afferents presumably arising from muscular free nerve endings may have powerful reflex actions (Cleland and Rymer 1990; Lundberg et al. 1987) and be responsible for many of the reflex actions previously attributed to secondary spindle afferents.

Functions of muscular free nerve endings

The functions of muscular free nerve endings are only partly understood. Their response to mechanical and chemical stimuli and the reflex actions of group III and IV muscle afferents suggest that they are involved in cardiovascular and respiratory regulation, perception of muscular pain, and reflex regulation of muscle activity (Mense 1986).

Our results show that the mechanosensitivity of SSFNEs is significantly different from other muscle receptors. SSFNEs are only weakly excited by stretch and contraction, vary widely in their relative sensitivity to stretch and contraction, are strongly influenced by the type of contraction, and adapt to repeated stretches. Other studies have shown that the mechanosensitivity of muscular free nerve endings is enhanced by fatigue (Hayward et al. 1988) and inflammation (Grigg et al. 1986). Furthermore, mechanosensitive free nerve ending receptors also respond to metabolic products and ionic alterations associated with exercise (Mense 1986). Consequently, SSFNEs are unlikely to provide the CNS with simple information on whole-muscle properties. Instead, they may signal local stress or strain in the muscle, tendon, or connective tissue, such as conveyed by Ruffini receptors in the joint capsule (Grigg and Hoffman 1984). When local stress or strain becomes excessive,

SSFNEs could evoke a flexion-withdrawal reflex that would unload the limb and presumably relieve the excessive stress or strain (Cleland and Rymer 1990). The effects of fatigue and inflammation could then be viewed as adaptive modulation that would lower the threshold for the SSFNE-evoked, flexion-withdrawal reflexes.

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