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Excitability Changes of Extensor Motoneurons and Primary Afferent Endings During Prolonged Stimulation of Flexor Afferents*

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Summary. Long trains of electrical stimuli supramaximal for Group I fibers of PBST nerves were used to study the effect on GS pathway. Inhibition of GS monosynaptic response occurred during PBST stimulation: however, decline in the inhibition developed with time despite the constancy of the inhibitory input monitored from the dorsal root. The level of recovery of the monosynaptic reflex at steady state depended upon the frequency of PBST stimulation, the higher the frequency the more complete the recovery. The effect of increasing the frequency of GS stimulation was to increase the inhibitory effect from PBST. Enhanced excitability of GS primary afferent endings in monosynaptic contact with homonymous motoneurons occurred and decreased parallel to the recovery of the monosynaptic response. When present, the polysynaptic response evoked by stimulating GS peripheral nerves increased during PBST stimulation in an inverse relation to changes in the monosynaptic response. Intracellular recordings from GS motoneurons usually revealed no change in membrane potential or in excitability of postsynaptic membrane to direct stimulation. Increased delay of intracellular GS spike potential was observed during PBST stimulation. The amount of this shift can be accounted for by polysynaptic activation of the same motoneuron.

Key Words: Monosynaptic response — Primary afferent depolarization — Spinal cord — Cat

Introduction

Inhibition of the monosynaptic response, which occurs in extensor nerves of the ankle following activation of afferent fibers from flexor muscles of the knee, has been thought to be due primarily to presynaptic inhibition (Eccles *et al.*, 1962b). This view is based on the initial observation of Frank and Fuortes (1957) who found no changes in membrane potential or excitability of the gastrocnemius motoneurons during this inhibition. Further investigations from Eccles' laboratory (summarized in Eccles, 1964) revealed that the inhibition of gastrocnemius and soleus (GS) excitatory postsynaptic potentials (EPSP) is due to depolarization of

the primary afferent terminals which are in monosynaptic contact with motoneurons (Eccles *et al.*, 1961b; Eccles *et al.*, 1962a).

However, the view that primary afferent depolarization is the main mechanism responsible for this inhibition is not consistent with results from Granit's laboratory (Granit *et al.*, 1964a and b). In fact, as a consequence of stretching the flexor muscle of the knee, hyperpolarization of the postsynaptic membrane, inversion of the depolarizing noise toward hyperpolarization and decreased excitability of extensor motoneurons of the same limb were found. From additional studies Granit (1968) and Kellerth (1968) concluded that, although presynaptic inhibition may exist, it has no physiological significance.

Despite the attention given this inhibition and its underlying mechanism there have been only fragmentary results (Eccles *et al.*, 1961b and Decandia *et al.*, 1968) on the effects of long trains of conditioning stimuli on the monosynaptic response. In these studies we investigated the effects of prolonged electrical stimulation of Group I afferents of the posterior biceps-semitendinosus nerves (PBST) on the excitability of GS motoneurons and homonymous primary afferent endings. Under these conditions both extracellular and intracellular recordings were used.

Methods

The results were obtained from twenty-four cats anesthetized with pentobarbital sodium (35 mg/kg, i.p.) and spinalized at thoracic level, T12. The lumbar enlargement of the spinal cord and nerves to the gastrocnemius-soleus (GS) and posterior biceps-semitendinosus (PBST) muscles were exposed on the left side. The ipsilateral ventral roots from L5 to S2 and the peripheral nerves were cut distally. When required, supplementary doses (30 mg) of anesthetic were injected i.p. The spinal cord and the isolated nerves were covered with warm mineral oil and the rectal temperature was maintained at 37.0 ± 0.5°C.

For fifteen cats single test stimuli, maximal for Group I fibers, were applied continually to the GS nerve and the mono- and polysynaptic responses were recorded from L7 or S1 ventral root. The frequency of stimulation was initially the highest which did not reduce the maximal monosynaptic response. The absolute value of the frequency was found to be different for different cats, but never higher than once every 2 sec. The magnitude of the test stimuli having been set, conditioning stimulation was delivered to PBST nerves at four different frequencies: 300, 200, 100, or 50 shocks per sec. The conditioning periods were initiated at intervals of 70—80 sec and had a duration of about 30 sec. The conditioning frequency was maintained constant during three or four 30 sec trains, and in subsequent trials the other frequencies were used in turn. Supramaximal stimuli for Ia + Ib fibers were used to maintain unchanging afferent volleys which were recorded through a monopolar electrode on L7 or S1 dorsal root. In the second phase of the experiment, the frequency of the test stimulation was increased. As reported by Jefferson and Schlapp (1953) the amplitude of the monosynaptic response was found to decrease as the frequency increased. When stabilization in amplitude was reached, the same conditioning experiments were performed as described above.

The excitability of the primary afferent endings in monosynaptic contact with the GS motoneurons was tested by stimulating through micropipettes which were inserted into the GS motoneuron nuclei as described by Decandia *et al.* (1967). The pipettes were filled with 4 M NaCl and had a resistance of 1 MΩ. According to Wall's method (1958) brief electrical stimuli were applied to the motoneuron nuclei at submaximal intensity and the antidromic responses were recorded from the GS nerves. The stimuli were applied continually once every 2 sec. Testing of the excitability was carried out on three of the fifteen animals during conditioning experiments, but not simultaneously with the recording of the ventral root response.

To facilitate the analysis all responses were recorded on FM tape (Ampex SP 300) with synchronizing signals on a parallel channel. Monosynaptic responses were then analyzed by

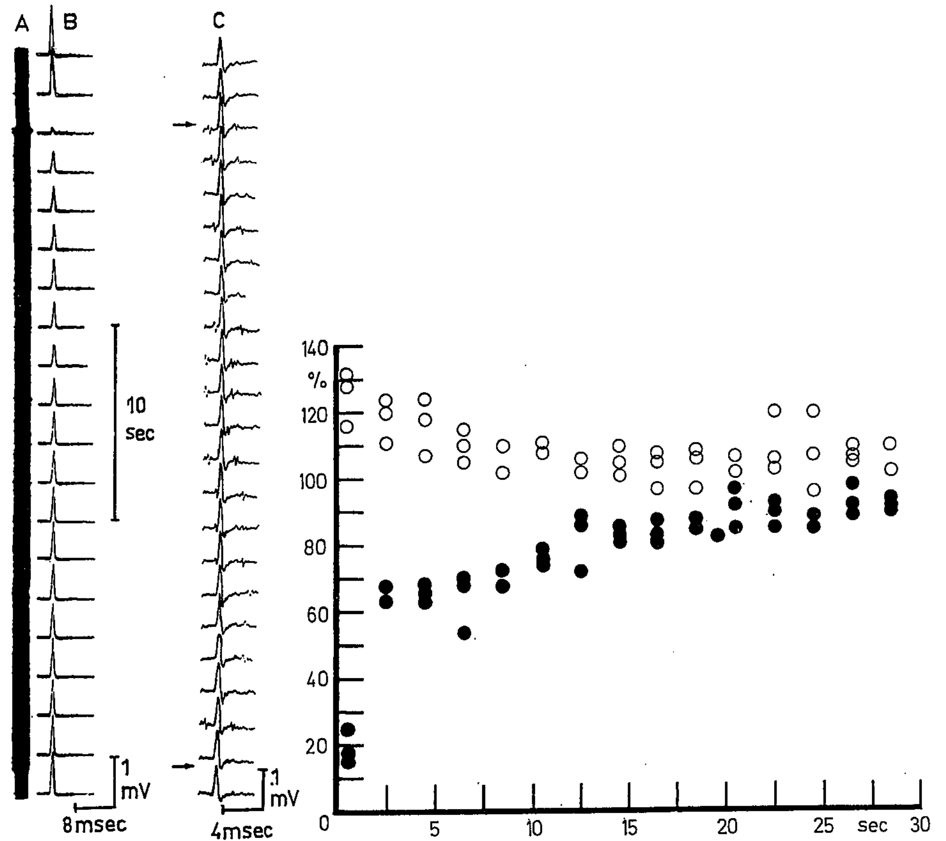

Fig. 1. *Effect of long-lasting stimulation of PBST nerves.* Effects on GS monosynaptic reflex response (column *B*) and GS antidromic volley (column *C*). Column *A* shows the afferent volleys from PBST nerves. The frequency of PBST stimulation is 300/sec (dense line). PBST stimulation period for the antidromic volleys is represented by the two arrows. In the graph, the time course of recovery of the monosynaptic reflex (filled circles) and excitability of primary afferent endings (open circles) is reported for a frequency of PBST stimulation at 300/sec. The amplitude of spike potential is expressed as percent of the mean control values obtained at 0.5/sec. Results from three different trials are plotted

playing the tapes into an IBM 1800 computer which was programmed to recognize the monosynaptic response, measure its amplitude, calculate its percent change from mean control values and plot these changes as a function of conditioning time.

For intracellular recording nine of the twenty-four cats were prepared, in addition, with bilateral pneumothorax to avoid artifacts and movement of the spinal cord. Conventional glass micropipettes filled with 3 M KCl and having a resistance of 3—5 MΩ were used. Forty-four motoneurons, monosynaptically activated by GS Group I fibers were studied. During an experiment PBST stimulation was at just supramaximal intensity for Group I fibers and at a frequency of 300/sec. To test directly the excitability of GS motoneurons during PBST activation, brief pulses of current at threshold intensity were applied through the same recording micropipette arranged in a bridge circuit (Araki and Otani, 1955). The intensity was considered to be threshold when the stimulus-response ratio was 2:1 at resting condition. The membrane potential also was measured with a DC amplifier at high gain throughout PBST conditioning.

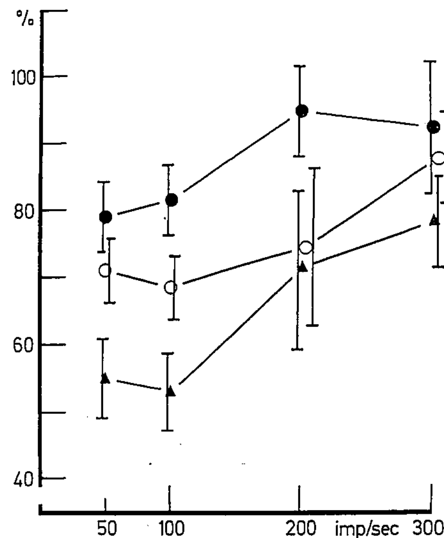

Fig. 2. *Plateau values of GS monosynaptic reflex as a function of frequency of conditioning (PBST) and testing (GS) stimulation.* Each point represents the mean value of the amplitude of conditioned monosynaptic reflex responses at plateau as expressed in percent of the mean control value. Vertical lines represent the standard deviation. The graph shows that the amount of recovery of GS monosynaptic reflex is a direct function of PBST frequency and an inverse function of GS frequency. The three curves have been obtained for GS stimulation frequency at 0.5/sec (filled circles), 0.66/sec (open circles) and 2/sec (triangles)

Results

Monosynaptic Reflex Response

As expected (Eccles *et al.*, 1962b), stimulation of PBST afferent fibers at high frequency reduced the amplitude of the monosynaptic response evoked by stimulating the GS afferent fibers. However, partial recovery from inhibition as a function of time occurred despite the persistence of constant conditioning input. An example of these changes is shown in Fig. 1 for a preparation in which only the monosynaptic reflex (column B) appeared. Column A consists of a continuous recording of afferent conditioning volleys from PBST activation at 300/sec. The graph of Fig. 1 contains corresponding computer plots of the percent change of the amplitude of the monosynaptic response as a function of conditioning time for three trials (solid circles). After a large initial inhibition, decline in inhibition developed until it reached a plateau in about 20 sec. A few curves were approximately linear before reaching a plateau. Typically the initial inhibition and the recovery plateau were greater at higher conditioning frequencies.

For a given frequency of conditioning stimulation the level of the recovery plateau was dependent on the frequency of the test stimulation. This interdependence is illustrated in Fig. 2 for a preparation in which it was possible to use three different test frequencies. It was difficult to obtain such data, since the variability of the monosynaptic response increased greatly at higher test frequencies and yielded irreproducible conditioning curves. At least two test frequencies were used successfully with each cat.

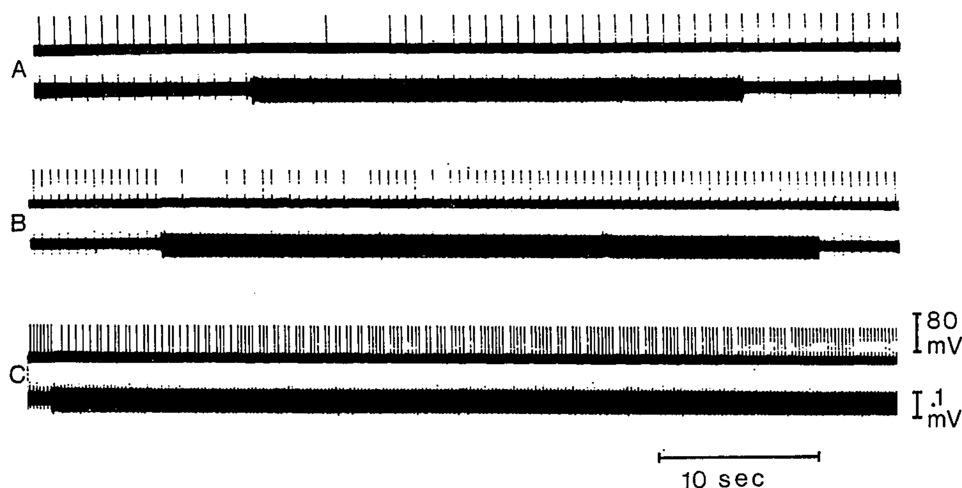

Fig. 3. *Effects of inhibitory activation on intracellularly recorded responses.* Intracellular recordings from a motoneuron (top trace of each pair of recordings) monosynaptically actived by GS stimulation and extracellular recordings from L7 dorsal root of afferent volleys from both GS and PBST nerves (bottom trace). The frequency of stimulation is 300/sec for PBST (heavy line) in all the recordings and 1, 2 and 5/sec for GS in *A*, *B*, and *C* respectively. The results show that the duration of inhibition by PBST, i.e. lack of spikes, depends upon the frequency of GS stimulation

Each point of Fig. 2 represents the mean of all amplitude values obtained for the plateau expressed as percent of the mean control value for that test frequency. The plateau value is seen to be a direct function of the conditioning frequency and an inverse function of the test frequency.

Excitability of Ia Afferent Terminals

Testing the excitability of the GS primary afferent terminals after the method of Wall (1958) revealed increased excitability during the conditioning stimulation of PBST nerve. However, a tendency to recover towards the control value occurred as a function of time. Column C of Fig. 1 illustrates these changes as reflected in the antidromic discharge of GS Ia afferent fibers for PBST conditioning stimuli of 300/sec (between arrows). As reported for inhibition of the monosynaptic reflex, the degree of facilitation depended on the frequency of conditioning stimulation. Recovery of the amplitudes of both the monosynaptic and antidromic responses obtained in the same cat have a parallel time course (see graph of Fig. 1).

Polysynaptic Reflex Response

During PBST activation the area of the polysynaptic response usually increased in proportion to the decrease in amplitude of the monosynaptic response, as described before (Decandia *et al.*, 1968). No attempt has been made to analyze this phenomenon quantitatively.

Intracellular Recordings from GS Motoneurons

In these studies the inhibition during PBST activation becomes evident when spike potentials fail to appear in response to the GS afferent volleys. Such dropouts

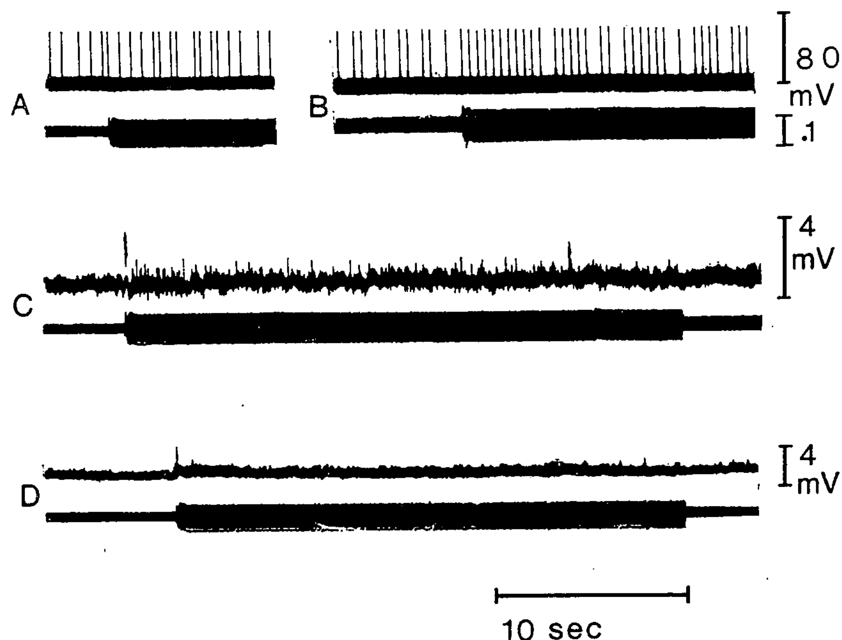

Fig. 4. *Effect of PBST stimulation at 300/sec on excitability and membrane potential of a GS motoneuron.* Intracellular stimulation (*A*) at threshold intensity (about 50% of stimuli yield responses) shows no changes in excitability of postsynaptic membrane during PBST activation since no change in stimulus-response ratio occurs. *C* and *D* are examples of the membrane potential recorded at high gain. While *C* shows no change in membrane potential during PBST activation, in *D* slight depolarization occurs with a tendency to recover to resting value as a function of time. A large EPSP-like deflection occurred with PBST stimulation in *C* and *D* as well as an increase in the synaptic noise. In *B* the effect of PBST stimulation is to increase the excitability of postsynaptic membrane as revealed by increased frequency of spike potentials to intracellular threshold stimulation

are evident in Fig. 3*A*, *B* and *C* where a GS stimulus was given at 1, 2 and 5/sec respectively. During PBST stimulation at 300/sec (indicated by the increased thickness of the lower recording of each pair) the dropouts are more apparent at the beginning of the conditioning period and occur less frequently as the stimulus is maintained. For the monosynaptic response recorded from the ventral root, the amount of inhibition at plateau was increased with increased test frequency; for the single cell, this phenomenon is apparent as a longer duration of inhibition for increased test frequency.

Usually, direct stimulation of the GS motoneuron during PBST stimulation revealed no change in excitability. The stability of the cell as measured through direct stimulation is illustrated in Fig. 4A. The cell was caused to fire 50% of the time to threshold stimuli at control conditions. Upon activation of PBST pathway there was no increase in the number of dropouts in the transition between control and conditioning period. Figure 4C illustrates the membrane potential of the same motoneuron as monitored at high gain. The stability is indicated by the constancy of membrane potential. Occasionally (3% of total trials), the same motoneuron experienced a small shift in the membrane po-

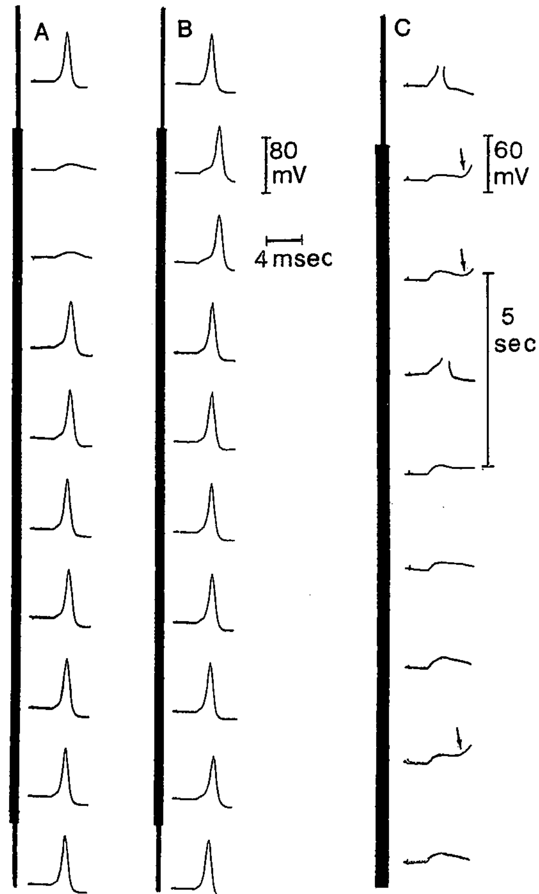

Fig. 5. *Intracellular recordings from two different motoneurons monosynaptically activated by GS peripheral stimulation.* Vertical trace on the left of each pair of columns contains afferent volleys from PBST nerve at 300/sec (heavy line). Stimulation of PBST nerves increases the delay of spike potentials as well as the amplitude of EPSPs at firing level. A, B are recorded from the same motoneuron. In *A* the first two spikes fail to appear during PBST stimulation. The series of recordings in *C* are taken from another motoneuron. In this case the stimulation of GS nerve produces a delayed response (indicated by arrows) in the falling phase of the EPSP as a consequence of PBST stimulation

tential towards depolarization. This shift was transient with a tendency to recovery to control value within a few seconds (Fig. 4D). Even when there was no shift in the membrane potential with inhibition, at high gain amplification an increase in the synaptic noise was always present (Fig. 4C). Further evidence for this excitatory influence was the appearance at the beginning of the slow transient depolarization of a relatively large EPSP-like deflection (Fig. 4C and D). In addition, for the same cell, there was an occasional increased firing index when testing the excitability by intracellular stimulation (Fig. 4B). In one motoneuron, decreased excitability as well as a shift in membrane potential towards hyperpolarization was observed for an intensity of PBST stimulation 3 times

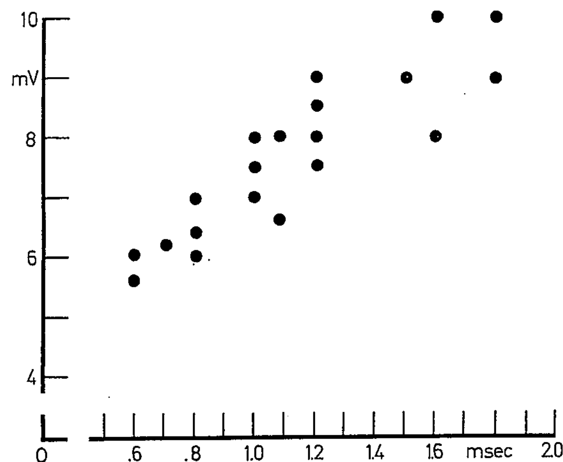

Fig. 6. *Relation between amplitude and duration of GS EPSPs at firing level during conditioning stimulation of PBST nerves at 300/sec.* Results are obtained from a single motoneuron for which four different conditioning trials were repeated. Control values are in the range of 6 mV in amplitude and 0.6 msec in duration. During conditioning stimulation shifts of these parameters occur up to 10 mV and 1.8 msec

maximal for Group I fibers. Again these changes were transient and disappeared when the intensity of conditioning stimuli was decreased to just above maximal for Group I fibers.

The possibility of a shift from mono- to polysynaptic firing was sought in responses of single GS motoneurons during PBST activation. As expected, at the beginning of PBST conditioning the motoneuron response failed to appear as seen in the second and third sweeps during the conditioning period of Fig. 5A. The spike reappearance is characterized by an increased delay which returns progressively to control values. Even in cases where spike inhibition is not evident (Fig. 5B) the spike may be markedly delayed. To examine the firing level as a function of magnitude of the delay, recordings were made at high gain. An increase does occur and is evident in the first few responses for the conditioning period.

The firing level also decreases as a function of time. The quantitative relationship between EPSP amplitude and the delay was measured for one motoneuron during several conditioning trials. The results which are plotted in Fig. 6 show a linear relationship. All motoneurons analyzed in this way showed a shift in the delay of more than 0.6 msec at the beginning of conditioning stimulation; shift as great as 2.0 msec were observed (Fig. 5C).

Discussion

The time course of changes in the monosynaptic extensor reflex with prolonged flexor inhibition can best be interpreted as resulting from a decrease in the effectiveness of presynaptic inhibition. This interpretation is based primarily on the parallel changes in excitability of the primary afferent endings, results of intracellular testing and concepts evolved by Eccles *et al.* (1963). The possibility that the initial inhibition could arise from direct pathways to motoneurons as reported by Granit

et al. (1964a and b) is probably not pertinent here for in their studies the experimental conditions were different: the flexor and extensor afferent pathways were activated asynchronously by stretching the muscles.

Our experiments do not reveal mechanisms involved in the decline in inhibition of the monosynaptic response and recovery of the excitability of the primary afferent endings. Since the PBST afferent volleys were constant throughout the conditioning period, the following possible events within the spinal cord can account for them: 1) depletion of chemical transmitter in the inhibiting pathway as has been suggested for the neuromuscular junction (Del Castillo and Katz, 1954) and the primary afferent endings in monosynaptic contact with motoneurons (Curtis and Eccles, 1960); 2) accomodation of postsynaptic membrane of the inhibiting pathway as reported for motoneurons (Araki and Otani, 1959); 3) Desensitization of postsynaptic receptors to the chemical transmitter as in the case of the postsynaptic membrane of neuromuscular junctions (Thesleff, 1959); and 4) an unknown active process such as habituation (Wickelgren, 1967) or inhibition of inhibitory neurons (Lundberg, 1964). Any one of these mechanisms could account for the quantitative relationship between recovery of monosynaptic response and frequency of conditioning stimulation. Greater uneffectiveness of these possible mechanisms, in fact, is expected as the frequency of inhibiting impulses increases. The same processes are considered, of course, responsible for the decreasing excitability of the primary afferent endings which parallels the recovery of the monosynaptic response.

Markedly good agreement exists between the studies from ventral root recordings and individual motoneurons: escape from inhibition of intracellular spike potential and longer duration of inhibition with increased test frequency were found.

Possibly, the increased synaptic noise (Fig. 4C) and the occasional appearance of slight depolarization (Fig. 4D) with the initiation of PBST conditioning can be related and due to generation of a dorsal root reflex by the early strong depolarization of GS primary afferent endings. Such a reflex conceivably could evoke an excitatory postsynaptic potential in the motoneurons (Eccles *et al.*, 1961a and b). Alternatively, since the conditioning stimulation was supramaximal for Group I fibers in order to assure constant Group I input, fibers with higher threshold such as Group II could have excited GS motoneurons as reported by Wilson and Kato (1965).

The observed increase in the area of the polysynaptic response as a consequence of inhibition of the monosynaptic response would result from greater responsiveness of GS motoneurons to polysynaptic chains if the monosynaptic pathway is inhibited presynaptically or if the excitability of polysynaptically activated motoneurons increases because of release from Renshaw (1941) inhibition.

The intracellular studies revealed with PBST inhibition a shift in latency of spike potential sufficient to be interpreted as a change from mono- to polysynaptic activation. Speculation on the physiological significance of the mono-polysynaptic activation of the extensor motoneurons by the afferent pathway is difficult. However, there is good evidence for its existence both in the present series of experiments as well as in the literature (Granit *et al.*, 1957; Tsukahara and Ohye, 1964; Cook *et al.*, 1965). That Group Ia fibers are responsible for such activation is evi-

dent from experiments in which both Group Ib (Granit, 1950; McCouch *et al.*, 1950; Hunt, 1952; Laporte and Lloyd, 1952; Jansen and Rudjord, 1964) and Group II fibers (Hunt, 1954; Laporte and Bessou, 1959; Bianconi *et al.*, 1964a, b) were found to be inhibitory on homonymous motoneurons. Since the intensity of stimulation in our experiments was just maximal for Group I fibers, it is unlikely that afferent fibers other than Group II were activated. Therefore, we conclude that Ia afferents from extensor muscles of the ankle have both mono- and polysynaptic connections with homonymous motoneurons.

In view of the finding of Coombs *et al.* (1957) that the firing level as monitored on the EPSP for various intensities of afferent bombardment was constant, it was surprising that this level increased with PBST inhibition. With increased firing level the EPSP slope was always decreased, allowing the possibility for accomodation to occur for the large delay seen here. In our view, accomodation would increase the threshold and, furthermore, a new threshold for polysynaptic activation could come into play.

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