EARLY POST-TETANIC POTENTIATION AND LOW FREQUENCY DEPRESSION OF SOME GROUP I REFLEX ACTIONS

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ABSTRACT

Group I reflex functions, namely monosynaptic reflex transmission, facilitation of synergists, and direct and disynaptic inhibition, show early post-tetanic potentiation following conditioning with a brief, high frequency, tetanus. Of these reflex functions, monosynaptic transmission always shows low frequency depression. Direct inhibitory pathways, and therefore inhibitory junctions, are insensitive to low frequency depression. The fact that direct inhibition can be potentiated shows it to be sufficiently labile that a decrease in efficacy at inhibitory junctions during repetitive activity should be revealed. Disynaptic inhibition often shows low frequency depression. As it is likely that inhibitory junctions in the direct and disynaptic pathways are similar, the low frequency depression of disynaptic inhibition is probably due to the properties of the excitatory relay between afferent fibers and interneurons in that pathway. Facilitation between synergists is often more depressed when the conditioning and testing volleys are nearly simultaneous than when they are separated by 1 to 1.5 msec. This result indicates that an early and rapid phase of action, responsible for homonymous and heteronymous transmission, is more sensitive to low frequency depression than is residual facilitation. In general, reflex transmission is more sensitive than are other aspects of action by group I fibers to events concurrent with and following repetitive activation.

INTRODUCTION

Effectiveness of monosynaptic reflex transmission has long been known to vary inversely with the rate of stimulation which is used to evoke the response under study. The depressed excitability which follows a single orthodromic volley was described by Brooks, Downman, and Eccles (1950), while the depression which accompanies repetitive activation of a monosynaptic pathway was first studied extensively by Jefferson and Schlapp (1953). Recent work (Lloyd and Wilson, 1957) has shown that the period of depression which follows motoneuron response can be divided into two phases: (1) early, or high frequency, depression, lasting approximately 100 msec. and due largely to subnormality in motoneurons; (2) late, or low frequency, depression, lasting as long as 20 seconds and presynaptic in origin. Degree of late depression depends upon a number of factors influencing reflex excitability, but the phenom-

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enon itself is regularly found in all preparations. The origin of late depression has been ascribed by some authors to reduced synaptic efficacy caused by depletion of chemical mediator (Beswick and Evanson, 1957). However, increases in stimulation frequency lead first to enhanced depression and subsequently to early post-tetanic potentiation (Beswick and Evanson, 1955), a sequence of changes difficult to explain by hypotheses postulating transmitter depletion. Lloyd and Wilson (1957) have suggested that late depression may originate in an action of presynaptic terminals upon motoneurons. This depressant action would be counteracted by the hyperpolarization of the terminal regions of the afferent nerves which is produced by repetitive activity. Following high frequencies of stimulation the hyperpolarization becomes predominant and gives rise to early post-tetanic potentiation.

Beswick and Evanson (1957) recently have studied low frequency depression of direct inhibition and of facilitation between synergistic muscles. They find that direct inhibition is not susceptible to low frequency depression, but that mutual facilitation of two synchronously evoked synergistic reflexes usually is. The experiments to be described here concern themselves with a further analysis of the effects of repetitive activation on various reflex actions of group I afferent fibers. A report of these experiments was made to the American Physiological Society in September, 1957 (Wilson, 1957).

Methods

Decapitate cats were used in all experiments. Laminectomy was performed in the usual manner, and the appropriate ventral roots were cut distally for recording. The spinal cord was covered by a pool of warm mineral oil, the temperature of which was kept steady throughout the experiment. A number of peripheral muscle nerves then were prepared for stimulation.

Early Potentiation.—All of these experiments involved the conditioning (facilitation, inhibition) by one pathway of the monosynaptic reflex elicited by stimulation of another pathway. Tetanization of the conditioning pathway led to changes in the ability of a later volley in this pathway to condition the test reflex (early potentiation of facilitation or inhibition). Simultaneously, early potentiation of transmission was also obtained: tetanization of the conditioning nerve is followed by increases in the monosynaptic reflex elicited by a subsequent single volley in this same nerve (Eccles and Rall, 1951; Lloyd, 1952).

One stimulator, also used to trigger the oscillograph sweep, was used to provide a gate for a second stimulator which was set to deliver a train of shocks, of desired frequency and duration, to the nerve used for conditioning. A delayed trigger in the oscilloscope provided, at any desired time after the start of the sweep of the first beam, a pulse which was used to trigger (1) the second beam and (2) two other stimulators, one of which provided a single conditioning stimulus, the other the test shock. In this manner, a conditioning and a testing shock, kept in constant time relation to each other, could be delivered at a variable interval after the end of a previous tetanic burst. In all cases, the conditioning complex, consisting of a tetanus

and subsequent single conditioning shock, was delivered to one nerve and the test shock to another. The procedure which was followed in measuring early potentiation of transmission and facilitation or inhibition, and which led to results such as those shown in Figs. 2 to 4, is illustrated in Fig. 1. In every experiment a large number of test reflexes, not preceded by the single conditioning shock, were recorded first (Fig.

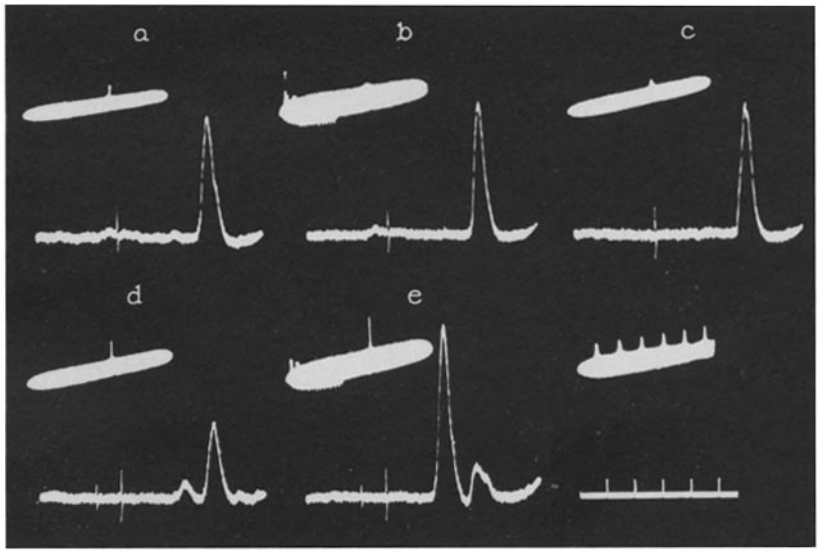

FIG. 1. Illustration of experiment on early potentiation of direct inhibition, with gastrocnemius inhibiting deep peroneal. The stimulus artifacts and reflex responses are shown at a very slow sweep speed on the upper beam; the lower beam shows, at a fast sweep speed, that part of the first beam on which the reflex responses appear. The duration of the conditioning tetanus, and the interval between the tetanus and subsequent conditioning-testing pair are measured on the upper beam. The size of the test reflex and of the monosynaptic reflex resulting from stimulation of the conditioning pathway, as well as the interval between the single conditioning stimulus and the test stimulus, are measured on the lower beam. For further explanation, see text. Time marker for upper beam, 100 msec.; for lower beam, 1 msec.

1 *a*), every sixth or seventh being preceded by a tetanus of the conditioning pathway (Fig. 1 *b*). In some cases the effect of such a tetanus was a severe depression of the test reflex at the shorter intervals (150 to 200 msec.) used in the experiments. The frequency and intensity of the conditioning tetanus then were so adjusted that the effect of this tetanus on the test response was either absent or small when compared to the changes observed during potentiation. Then, the test system was stimulated at intervals of one shock every 7 seconds. The first two test responses were unconditioned (Fig. 1 *c*). The next two test shocks were preceded at an appropriate interval by a single conditioning volley (Fig. 1 *d*). Finally, such a conditioning-testing pair

was preceded by a tetanus of the conditioning nerve (Fig. 1 *e*). Ten such sequences were photographed at each of various intervals after the end of the tetanus. Thus, every point on a graph, such as those in curve B of Fig. 2, is derived from twenty control unconditioned test responses, twenty conditioned tests, and ten conditioned tests preceded by a tetanus. In experiments such as the one illustrated in Fig. 2, where changes in two different responses are being measured, the test reflex and the monosynaptic reflex resulting from stimulation of the conditioning pathway were recorded in the same ventral root. Temporal separation between the two reflexes was sufficient so that both could be measured (Figs. 1 *d*, 1 *e*). Tetani at frequencies of 500 to 800/second and approximately 200 msecs. in duration were used. Following each tetanus, at least 1 minute was allowed to elapse before the next sequence was begun. With such spacing the effects of the tetanus had worn off before the start of the next determination.

Low Frequency Depression.—To study direct inhibition, disynaptic inhibition, and facilitation, control measurements of the degree of conditioning were obtained first. This was done by delivering the conditioning and testing shocks, in fixed time relation to each other, at low frequency, usually 0.1 or 0.2/second. The test stimulus then was kept at this frequency, while the frequency of the conditioning stimulus was raised. Whenever a test shock was inserted during the train of conditioning stimuli, it always followed a conditioning shock by the fixed time interval used throughout the experiment. The highest rate of repetition used in the conditioning system was 4/second, a frequency which has always been found to give considerable depression of homosynaptic transmission. The control and conditioned test responses, as well as the monosynaptic reflex response to the conditioning volley, were recorded in the same or neighboring ventral roots.

RESULTS

1. Early Post-Tetanic Potentiation of Group I Reflex Functions

Following short, high frequency, tetani, synaptic transmission is greatly enhanced, with the maximal effect observed approximately 150 msec. after the end of the tetanus (Eccles and Rall, 1951; Lloyd, 1952). Thus, while repetitive stimulation causes depression of reflex transmission and more rapid stimulation causes greater depression, still further increase in the frequency of activation leads to a reversal from increased depression to early post-tetanic potentiation (Beswick and Evanson, 1955). The same phenomena have been looked for in pathways which subserve direct inhibition, disynaptic inhibition, and monosynaptic facilitation between synergists.

Fig. 2 shows the results of two experiments on direct inhibition. In this, as in all subsequent figures, 100 per cent inhibition or facilitation refers to the level of conditioning obtained in the controls. Increments in inhibition or facilitation, expressed in terms of the control level, are plotted upwards. Decrease in inhibition or facilitation, where present, is plotted downwards in all graphs. In both of the experiments illustrated, the monosynaptic reflex evoked by stimulation of the deep peroneal nerve served as the test system and one or both

branches of the gastrocnemius nerve were used for conditioning. In the first experiment, it was possible to measure the early potentiation of the monosynaptic reflex discharge evoked by the conditioning volley (dots-A) and the early potentiation of direct inhibition (circles-B). In the second experiment, early potentiation of inhibition only was measured (triangles-B). It can be seen that both reflex transmission and direct inhibition are potentiated, the former being much more powerfully affected. Figs. 3 and 4 show that the disynaptic inhibition of gastrocnemius motoneurons by afferent volleys in the

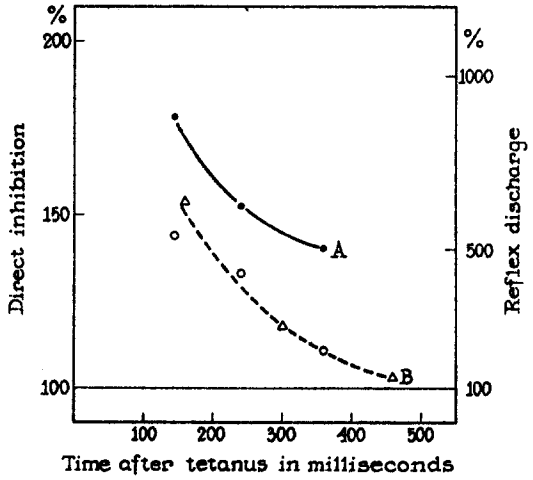

FIG. 2. Combined result of two experiments on early potentiation of direct inhibition, with gastrocnemius inhibiting deep peroneal in both cases. Curve A shows potentiation of gastrocnemius monosynaptic reflex discharge, curve B potentiation of direct inhibition. In the first experiment (circles, dots) the control level of inhibition was 37 per cent, the conditioning-test interval 0.9 msec. A tetanus 220 msec. in duration, at 650/sec., was used. Temperature 37°. In the second experiment (triangles) control inhibition was 29 per cent, stimulus interval 1.0 msec. Tetanus was 240 msec. at 800/sec. Temperature 36.5°. Note different ordinate scales used in the figure. For further explanation, see text.

nerve to flexor longus digitorum (Laporte and Lloyd, 1952), and also facilitation between synergists, in this case the two heads of gastrocnemius, can be potentiated in a similar way. A regular observation, illustrated in Figs. 2 to 4, was that early potentiation of reflex discharge is more striking than early potentiation of other group I reflex functions.

2. Effect of Repetitive Stimulation on Direct and Disynaptic Inhibition

All the experiments on direct inhibition involved interaction between the antagonistic ankle flexors and extensors. The nerves to the two heads of

gastrocnemius and the deep peroneal nerve were used interchangeably for testing and conditioning, and the interval between the conditioning and testing volleys was set routinely for maximal inhibition. Stimuli just supramaximal for group I were used throughout.

A series of experiments has confirmed the observation of Beswick and Evanson (1957) that direct inhibition is not modified in degree by increase in the frequency of the conditioning response. This is the case even though simultaneously recorded homosynaptic reflex transmission may be strongly de-

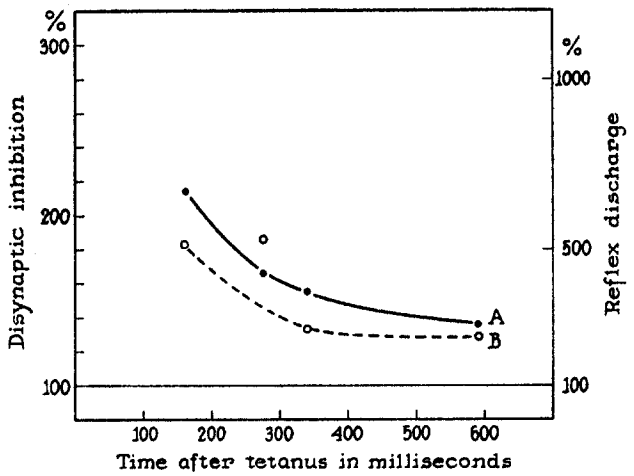

FIG. 3. Effect of a tetanus 220 msec. in duration and at the frequency of 600/sec. on the disynaptic inhibition exerted by a volley in the nerve to flexor longus digitorum on gastrocnemius monosynaptic reflex. Curve A shows potentiation of flexor longus monosynaptic reflex discharge, curve B potentiation of disynaptic inhibition. Control level of inhibition 47 to 59 per cent. Stimulus interval 1.4 msec. Temperature 36.7°. The measurement made 270 msec. after the end of tetanus was affected by a shift in gastrocnemius controls.

pressed. An experiment which illustrates this finding is shown in Fig. 5. Although some changes in the depth of inhibition have been seen, consisting at different times of small and irregular increases or decreases in the inhibition, unequivocal low frequency depresssion of direct inhibition, increasing with increasing frequency, has not been observed.

Similar experiments have been performed with the disynaptic inhibition of gastrocnemius monosynaptic reflexes by afferent volleys in the nerve to flexor longus digitorum. Fig. 6 illustrates an experiment in which disynaptic inhibition clearly showed low frequency depression. Although low frequency depression of the disynaptic inhibitory pathway was not found in all instances, it was

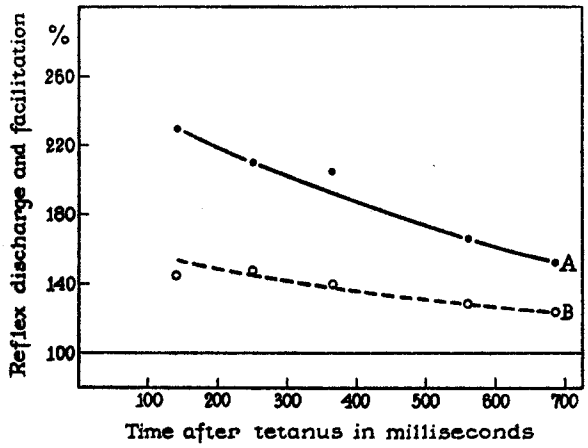

FIG. 4. Effect of tetanus 290 msec. in duration at the frequency of 700/sec. on facilitation of lateral gastrocnemius reflex by medial gastrocnemius volleys. Curve A shows potentiation of medial gastrocnemius reflex discharge, curve B potentiation of facilitation. The control degree of facilitation varied due to changes in the size of the test reflex, but did not go below 50 per cent. Stimulus interval 1.5 msec. Temperature 36.5°.

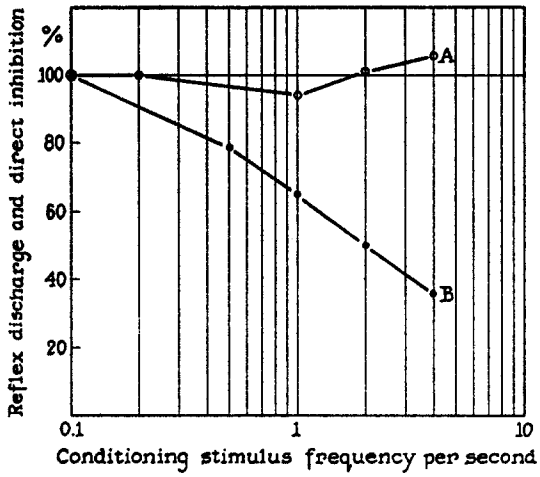

FIG. 5. Effect of frequency changes on the direct inhibition of the gastrocnemius reflex by a volley in the deep peroneal nerve. Test shock frequency 0.1/sec. Control inhibition level 67 per cent, stimulus interval 0.9 msec. Temperature 36.6–38.0°. Curve B shows effect of increasing the frequency of the conditioning stimulus on the monosynaptic reflex evoked by this stimulus. Curve A shows the lack of low frequency depression of direct inhibition.

seen frequently enough to show this pathway sensitive to changes brought about by repetitive stimulation.

As first described by Renshaw (1941), discharge of motoneurons, whether evoked antidromically or orthodromically, may exert significant inhibitory action on the excitability of neighboring motoneurons. This type of inhibition, which is best described as recurrent inhibition (Brooks and Wilson, 1958), can play no role in those of the present experiments which involve interaction of gastrocnemius and tibialis anterior, as it has been shown that the inhibitory action is restricted to nuclei in close proximity within the same segment of the spinal cord (Renshaw, 1941). Antidromic

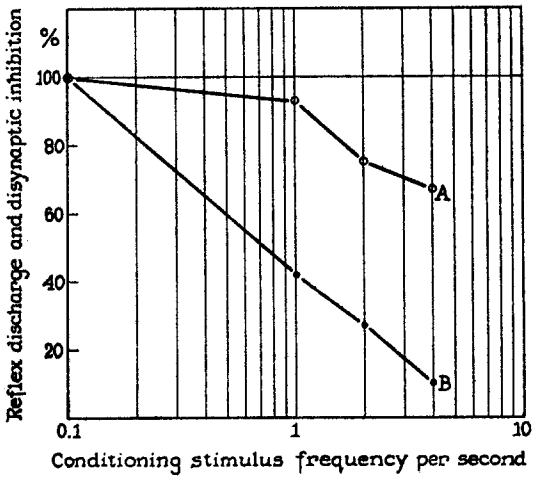

FIG. 6. Low frequency depression of the disynaptic inhibition of gastrocnemius reflex by stimulation of the nerve to flexor longus. Test shock frequency 0.2/sec. Control inhibition level 42 to 48 per cent, stimulus interval 1.4 msec. Temperature 36°. Low frequency depression of reflex transmission in the conditioning pathway is shown in curve B, low frequency depression of disynaptic inhibition in curve A.

stimulation of gastrocnemius or tibialis anterior nerves exerts no inhibitory effect on the motoneurons of the antagonist (Renshaw, 1941; Eccles, Fatt, and Koketsu, 1954). A somewhat different situation prevails, however, in the case of interaction between flexor longus and gastrocnemius, as these two nuclei may be in sufficiently close proximity to each other in the ventral horn that discharge of flexor longus motoneurons may exert an inhibitory action on some gastrocnemius motoneurons (Eccles, Fatt, and Koketsu, 1954). If discharge of flexor longus cells does condition gastrocnemius motoneurons, it would superimpose an additional inhibitory effect on the disynaptic inhibitory action. Such added inhibition would be decreased rather than increased at higher frequencies, for the number of flexor longus motoneurons that discharge is decreased. Recurrent inhibition acts with a very short latency. Although very brief, the interval between conditioning and test volleys in the disynaptic inhibition experiments is such that the discharge of flexor

longus motoneurons might occur sufficiently in advance of the arrival of the test volley to permit recurrent inhibition of the test system to take place. For several reasons, however, it seems that this type of interaction can be discounted as a factor in these experiments. Firstly, the response of flexor longus motoneurons to the conditioning volley usually appeared only in the seventh lumbar ventral root, whereas the test response of gastrocnemius motoneurons, while seen in both seventh lumbar and first sacral roots, was measured in the latter; thus, the two discharges involved pertained to different segments. Secondly, low frequency depression of disynaptic inhibition varied in degree during some experiments. If change in recurrent inhibition were an important factor in the observed low frequency depression of disynaptic inhibition, changes in the latter should be correlated with changes in the low frequency depression of the reflex response to the conditioning volleys. Such a relationship was not observed. Finally, it has been demonstrated that recurrent inhibition is an important factor only in such cases in which the test response is weak, the antidromic volley powerful (Lloyd, 1946). In the present experiments the test response was generally powerful, and antidromic inhibitory effects would again be minimized. For all these reasons, it can reasonably be assumed that any frequency-dependent changes in the depth of disynaptic inhibition at various frequencies of stimulation of the conditioning pathway are not due to changes in recurrent inhibition and do represent true low frequency depression of the disynaptic inhibitory path.

3. Low Frequency Depression of Facilitation

The facilitating action which a group I volley, evoked simultaneously with the test volley, exerts on the monosynaptic reflex of a synergic muscle is depressed by repetitive activation of the conditioning pathway (Beswick and Evanson, 1957). This low frequency depression of facilitation has been investigated further in the present experiments.

Variable results were obtained in the early experiments. While reflex response to the conditioning volleys was consistently depressed, facilitation was sometimes reduced, at other times irregularly affected. Even when low frequency depression of facilitation was observed, this depression was always less powerful than the simultaneously measured depression of reflex transmission. It seemed possible that lack of regularity in the effect of frequency on the facilitating potentiality of group I volleys might in part be due to the variable (from one experiment to another) 1 to 1.5 msec. interval between conditioning and testing volleys. In order to test this possibility, a series of experiments was performed in which degree of low frequency depression was measured at different conditioning-test intervals, and, therefore, at different strengths of facilitation. For these experiments preparations were picked in which stimulation of one branch of gastrocnemius, to be used for testing, evoked a monosynaptic reflex, and in which stimulation of the other branch evoked no visible reflex response, but did result in facilitation of the test reflex.

Fig. 7, which demonstrates a common experimental finding, shows an experiment in which two depression curves were obtained. In one case, conditioning

and test stimuli were almost synchronous; in the other, the two shocks were separated by 1.3 msec. It can be seen that in the former case (curve B) there is low frequency depression of facilitation, but that this depression is reduced in degree as the interval is increased (curve A). In some preparations increasing the interval within the range studied, namely .1 to 1.5 msec., had no effect on the depression. Greater intervals were avoided, since even with volleys just supramaximal for group I, there is, at these greater intervals, interference from reflex actions other than the facilitation under study.

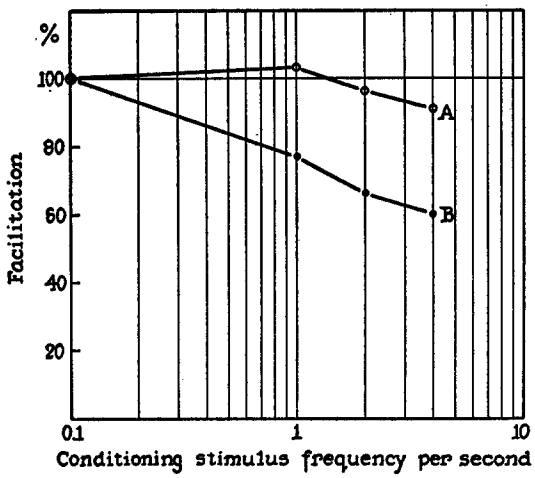

FIG. 7. Low frequency depression of the facilitation of one branch of gastrocnemius by the other. In A, stimulus interval of 1.3 msec., control facilitation 75 to 105 per cent. In B, interval of 0.1 msec., control facilitation 750 to 790 per cent. Test shock frequency 0.1/sec. Temperature 37.0°.

DISCUSSION

Early post-tetanic potentiation has been linked to hyperpolarization of presynaptic terminals (Lloyd, 1952). The efficacy of all such terminals should be similarly affected by hyperpolarization. Therefore, the only requirement for overt increased action in any given pathway following a short, high frequency tetanus appears to be the existence of an adequate subliminal fringe. The finding that early potentiation exists in all of the actions studied, namely direct inhibition, disynaptic inhibition, and monosynaptic facilitation, is evidence of the presence of such a fringe.

The irregular changes in the depth of direct inhibition which have been observed occasionally following changes in the frequency of conditioning stimulation can probably be ascribed to excitability fluctuation in the spinal cord. Absence of low frequency depression in the direct inhibitory pathway

sheds no light on the question of the presence or absence of an interneuron in this path, since the interneurons studied by Eccles, Fatt, and Landgren (1956), which they assume to be involved in the direct inhibitory action, are capable of responding to high frequencies of stimulation. Therefore, as pointed out by Beswick and Evanson (1957) the presence or absence of low frequency depression in the direct inhibitory path depends upon the properties of the inhibitory junctions at the motoneuron. Beswick and Evanson have suggested different explanations to account for the absence of low frequency depression at this point. One possibility put forward by these authors is that the hypothetical inhibitory transmitter substance is so potent, that even if depleted, it is still capable of exerting an inhibitory action too powerful for the excitatory volley to overcome. Alternatively, they suggest that the distribution of inhibitory synaptic knobs is dense enough to make up for depletion. Both of these basically similar explanations, by suggesting that decrease in inhibitory action would not be revealed, also imply that increase in inhibitory action should have no visible effect. This, however, is not the case. The experiments on early potentiation show that direct inhibitory action can be enhanced, just as it is during late post-tetanic potentiation (Lloyd, 1949). Since inhibition can be potentiated, it must be sufficiently labile to reveal decreases in effectiveness at the inhibitory junctions. It is, therefore, likely that there is no reduction of efficacy at inhibitory junctions during repetitive activity. Thus, as suggested by Beswick and Evanson as a third possibility, if indeed inhibition is mediated by a transmitter substance, this substance is not significantly susceptible to depletion.

It is reasonable to suppose that the properties of the inhibitory junctions of the direct and disynaptic pathways are similar. Such a view is supported by recent pharmacological evidence which shows that tetanus toxin abolishes direct, disynaptic, and other inhibitory actions in a similar manner (Brooks, Curtis, and Eccles, 1957). On this basis, it appears probable that low frequency depression of disynaptic inhibition is due to the properties of the excitatory relay from primary afferent fibers to the interneurons in this pathway. The absence of low frequency depression in the direct inhibitory pathway and its presence in the disynaptic path emphasize another difference in the behavior of these two types of inhibition.

Beswick and Evanson's finding that low frequency depression of facilitation is usually present when the conditioning and test shocks to synergic nuclei are almost synchronous has been repeated in the present experiments. Facilitation is at its peak with the shortest conditioning-test interval, and as this interval is lengthened, facilitation is, of course, decreased. In studies on low frequency depression of synaptic transmission, it was found that decreasing the reflex by reducing the afferent input, or by warming the preparation, increased low frequency depression (Lloyd and Wilson, 1957). Similarly, one might suppose that a decrease in the intensity of the facilitation effected by increasing the

interval between conditioning and testing shocks would result in greater, rather than lesser susceptibility to low frequency depression. Such a result has not been obtained. On the contrary, following increases in stimulus interval, depression of facilitation, although sometimes unaffected or irregularly affected, was commonly decreased. A reasonable explanation of this observation is that increasing the conditioning-test interval changes the process acting to facilitate the test reflex from one quite susceptible to low frequency depression to another much less susceptible. It is known that group I afferent fibers make heteronymous connections with synergic motoneurons and, under certain conditions, are able to cause these to discharge (Alvord and Fuortes, 1953; Lloyd, Hunt, and McIntyre, 1955). There is thus an always present heteronymous transmitter action, which, although usually inadequate to bring about discharge, can enhance the response of a motoneuron pool to homonymous stimuli (Hunt, 1955). Hunt (1955) has shown that transmitter potentiality of impulses decays greatly within a few tenths of a millisecond, and Eccles and his collaborators also state that impulses are generated only during the phase of incrementing depolarization produced by the ionic current across the subsynaptic membrane (Eccles, 1957). Thus while some authors postulate that excitation can be accounted for entirely in terms of the level of depolarization of the membrane (Frank and Fuortes, 1956), there is some agreement that impulse generation results from a phase of action of very short duration. Residual facilitation, on the other hand, is based on a longer lasting phase decaying exponentially with a time constant of approximately 4 msec. (Lloyd, 1946). Therefore, with increasing stimulus intervals, enhancement of motoneuron discharge by the convergent action of synergist group I fibers can be considered to be due at first mainly to heteronymous transmitter action, and later mainly to residual facilitation. The results of the present experiments indicate that the low frequency depression of facilitation observed when the conditioning and test shocks are nearly synchronous is largely due to depression of events which underly heteronymous transmission. The lesser depression at greater intervals indicates that the process underlying residual facilitation is less sensitive to low frequency depression than the event responsible for transmitter action.

The occurrence of early potentiation and the lack of low frequency depression in the direct inhibitory pathway again raise the question of the origin of low frequency depression. The inconsistency of the evidence for transmitter depletion at excitatory terminals has been discussed by Lloyd and Wilson (1957). This inconsistency, together with lack of reduced efficacy at inhibitory terminals, supports the view that transmitter depletion may not be an important event during low frequency repetitive activation.

Impulses in group I fibers lead to excitatory, inhibitory, and facilitatory actions on motoneurons. In general, it appears that the rapid excitatory phase

involved in synaptic transmission, both homonymous and heteronymous, is much more susceptible to low frequency depression and to the effects which follow repetitive activation than are the phenomena responsible for other actions of group I fibers.

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