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PRESYNAPTIC INHIBITION OF THE CENTRAL ACTIONS OF FLEXOR REFLEX AFFERENTS

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Inhibition of flexor reflexes by repetitive stimulation of contralateral nerves persists for several seconds (Sherrington & Sowton, 1915) and for as long as 300 msec after a single contralateral volley (Samojloff & Kisseleff, 1927; Eccles & Sherrington, 1931*b*). Subsequently it was found that single ipsilateral volleys also sometimes produced prolonged inhibition of flexor reflexes (Forbes, Querido, Whitaker & Hurxthal, 1928; Gerard & Forbes, 1928; Eccles & Sherrington, 1931*a*), reaching a maximum at about 20 msec and persisting for as long as 400 msec. This prolonged ipsilateral inhibition was observed whether the conditioning and testing volleys were in the same or in different afferent nerves. It was recognized that ipsilateral inhibition was responsible for the so-called 'jet' type of flexor reflex, in which the reflex response to the first volley of a repetitive train is much larger than the response to each of the subsequent volleys (Creed, Denny Brown, Eccles, Liddell & Sherrington, 1932, p. 91). A further observation was that in addition to this prolonged ipsilateral inhibition of flexor reflexes there was a distinct type of inhibition with a total duration of less than 50 msec (Eccles & Sherrington, 1931*a*). The identification of this latter type as an example of post-synaptic inhibition conforms with the observation that volleys in high threshold muscle and joint afferents produce in motoneurones inhibitory post-synaptic potentials at least 50 msec in duration (Eccles, 1953, Fig. 55; Eccles & Lundberg, 1959*a*; Kostyuk, 1960*b*). It will be shown below that presynaptic inhibition is responsible for at least the greater part of the more prolonged type of inhibition.

In view of the similarity of time courses of the slow positive potentials (P waves) recorded from the cord dorsum and of the ipsilateral inhibition of flexor reflexes, Gasser & Graham (1933) asked 'whether the positive potential may not be connected with the process responsible for inhibition'. In a further investigation Hughes & Gasser (1934) provided additional evidence that the size and time course of the P wave produced by a

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conditioning volley in different experiments could be correlated with the size and time course of the depression both of the N waves and of the reflexes that are produced by a subsequent testing volley. It was postulated that the responses of interneurones were not fully recovered until all traces of the P wave had died out. This prolonged depression of interneuronal responsiveness was later attributed to the positive after-potential that followed their initial spike discharge (Gasser, 1937), but it was not shown how this positive after-potential could give rise to the P wave of the cord dorsum. Barron & Matthews (1938) postulated that the P wave was produced by the same potential generator in the cord that gave the dorsal root potential (DRP); and, furthermore, in agreement with Gasser and his collaborators, that this generator was responsible for inhibition; but it was suggested that this inhibition was brought about by electric currents which caused blockage of conduction in the collateral branches of interneurones.

In recent years the evidence relating both the DRP and the P wave of the cord dorsum to a central inhibitory action has been lost sight of, because the interneuronal theory of inhibition developed by Gasser (1937) and by Bonnet & Bremer (1939) and by Bremer & Bonnet (1942) could not explain inhibition of monosynaptic reflexes (Lloyd, 1941, 1946; Renshaw, 1941, 1942), and also because there was such convincing evidence that central inhibition was due to the post-synaptic action of special inhibitory synapses (Eccles, 1953, 1957, 1961*a*; Fatt, 1954; Bremer, 1957; Fessard 1959; Kostyuk, 1959). It was generally assumed that there was merely an incidental relationship between duration of interneuronal action and the DRP on the one hand and the post-synaptic inhibitory action of interneurones on the other. As a consequence it could be stated that the DRP was of 'no functional significance' (Fatt, 1954). This position is no longer acceptable because there is now very strong evidence that presynaptic depolarization causes a diminution in the effectiveness of excitatory synapses (Hagiwara & Tasaki, 1958; Eccles, Kozak & Magni, 1961; Eccles, 1961*a*, *b*; Eccles, Magni & Willis, 1962; Eccles, Kostyuk & Schmidt, unpublished observations), being in fact responsible for presynaptic inhibition of the monosynaptic excitatory action of Group Ia impulses on motoneurones (Frank & Fuortes, 1957; Frank, 1959; Eccles, Eccles & Magni, 1961; Eccles, Schmidt & Willis, 1962). It will be appreciated that the much larger presynaptic depolarizations produced by cutaneous afferent volleys are likely to be still more potent in depressing the synaptic excitatory actions of impulses in these fibres. Thus the association of both the P wave and the DRP with reflex depression (Gasser & Graham, 1933; Hughes & Gasser, 1934; Barron & Matthews, 1938) must now be re-examined to discover if this depression is an example of presynaptic inhibition.

In the present paper it will be shown that, in accord with a recent prediction (Eccles, 1961*b*), there is very strong evidence that the inhibitory actions of cutaneous volleys are attributable to the depolarization that is observed as the DRP, and thus that they are examples of presynaptic inhibition. There is also evidence that the cutaneous and Group II and III muscle afferents are linked together into a single system that both produces and receives presynaptic inhibition. Possibly this system is co-extensive with the system of afferents producing flexor reflexes, the flexor reflex afferents (FRA). Finally, it will be shown that Group I muscle afferents very effectively produce presynaptic inhibition of all central actions of FRA volleys, though there is virtually no action in the reverse direction (see Eccles, Magni & Willis, 1962).

METHODS

The experiments, on anaesthetized cats, were similar to those of the preceding paper (Eccles, Kostyuk & Schmidt, 1962) except for the additional procedures involved in recording flexor reflexes and the discharges in the dorsolateral funiculus of the same side. The flexor reflex discharge was always recorded monophasically in the nerve supplying the knee flexor muscles, posterior biceps and semitendinosus. Since both dorsal and ventral roots were intact, it might be objected that some of the observed reflex discharge could be a dorsal root reflex (DRR) occurring in the muscle afferent fibres. However, the temperature of the animal was never subnormal, the usual range being 38–39° C, so DRRs would be depressed; and in any case, even at low temperatures, cutaneous volleys are very poor generators of DRRs in muscle afferent fibres (Eccles, Kozak & Magni, 1961). The dorsolateral funiculus was prepared for monophasic recording by transecting the spinal cord at the L2 level and then stripping off the dorsal columns to mid-L4 level. The dorsolateral funiculus could then be dissected off the remainder of the cord from L2 to L4 levels and lifted on to recording electrodes, one just beyond its origin from the cord and the other on its severed rostral end (see Laporte, Lundberg & Oscarsson, 1956).

On account of the extreme asynchronism in the discharge of impulses, the size of a flexor reflex cannot be assessed by measurement of the height of the monophasic spike potential in the nerve to a flexor muscle. Some procedure of integration is necessary in order to measure the actual size of the reflex discharge. In earlier investigations the isometric muscular contraction provided the integration; alternatively, integration has been effected by measuring with a planimeter the area of the monophasically recorded action potential in the nerve to a flexor muscle (Wilson, 1955; Mark & Steiner, 1958). We have been saved from this laborious procedure by an integrator designed by Mr J. S. Coombs. When precautions are taken to ensure that the recording of the spike responses of a nerve or tract is monophasic, the integrated records give a measure of the total number of impulses in the individual fibres regardless of their asynchronism. Integration was not employed in assessing the sizes of the initial spike in the dorsolateral funiculus, for this was monosynaptically generated and consequently had a relatively constant time course; hence it was allowable to use the height as a measure of size in the way that is customary with monosynaptic reflex discharges into ventral roots.

The nomenclature of the nerves with abbreviations are given in the Methods of the preceding paper (Eccles, Kostyuk & Schmidt, 1962; this volume, p. 239).

RESULTS

Inhibition of flexor reflexes

In Fig. 1A, B the integrated potential curves (lower traces) are seen to rise during the flexor reflex discharges, which are displayed on the upper traces. The integrator is so designed that the potential thereafter slowly

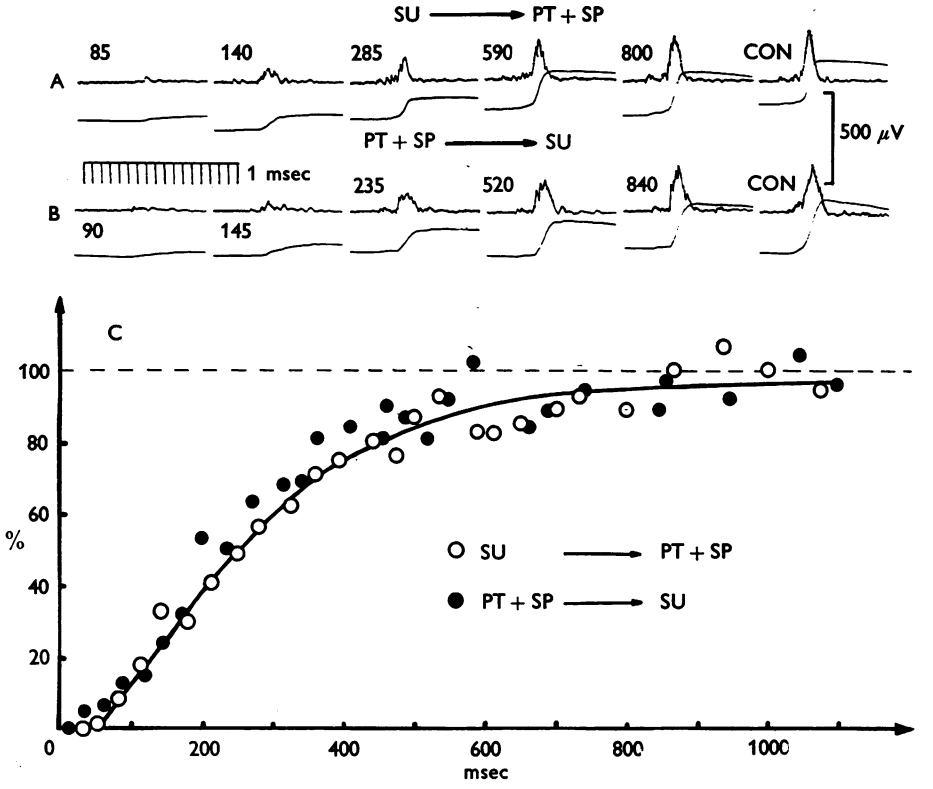

Fig. 1. Flexor reflex inhibition by a single cutaneous volley. The flexor reflex was evoked by a single volley in another cutaneous pathway and was recorded monophasically from the nerve to PBST muscle. The specimen records in A and B show in the upper line the reflex discharge which is integrated in the lower line. The numbers indicate the intervals (msec) between the conditioning and testing volleys, which are specified above the respective series. In this and all subsequent figures arrows indicate action of conditioning volley on testing volley. PT and SP are combined to give about the same flexor reflex response (control (CON) in A) as SU alone (CON in B). In C the amplitude of the integrated spike is plotted as percentage of control values for various intervals between the two volleys. Open circles correspond with A, filled circles with B, the curve being drawn for the open circles. Stimulus strength for all nerves was 4 times threshold. Stimuli were applied every 4·5 sec. In A and B the voltage scale is for the monosynaptic reflexes; same time scale (msec) for all records.

decays, as shown in the control records of Fig. 1A, B; thus automatic erasure is ensured between observations made at intervals longer than 1 sec. On account of this spontaneous decay it is important to measure the size of the integrated potential at a fixed time which is chosen to coincide with the usual summit of the integrated curve.

In testing for inhibition of flexor reflexes it is desirable to employ different afferent nerves for the conditioning and testing volleys so as to avoid, at least for the first synaptic relay, the changes that repetitive activation causes in synaptic efficacy (Curtis & Eccles, 1960). For example, a single volley in one cutaneous nerve can be employed to condition the reflex response produced by another cutaneous volley (Fig. 1A); and, as in Fig. 1B, the reverse sequence can also be investigated. Each afferent volley alone produced almost the same size of flexor reflex, and it is seen in Fig. 1C that there was virtual identity of the respective inhibitory curves. With lengthening of the testing interval there was a progressive decline of inhibition until recovery was almost complete with testing intervals of about 500 msec, though some depression was probably present even at 1000 msec. Often there was facilitation of the reflex discharge when the testing intervals were less than 20 msec (cf. Eccles & Sherrington, 1930, 1931*a*). Reflex depressions such as those illustrated in Fig. 1 were invariably observed when a volley in a cutaneous nerve was employed to condition the flexor reflex produced by a volley in another cutaneous nerve.

Earlier investigations (Eccles, Magni & Willis, 1962) had shown that cutaneous volleys had virtually no action in depolarizing Group I muscle afferents and so producing presynaptic inhibition of monosynaptic reflexes. It might therefore be expected that there would also be no action in the reverse direction. However, as is shown in Fig. 2A, Group I volleys from some muscles are very effective in inhibiting flexor reflexes with the characteristic long duration observed for conditioning by cutaneous volleys. Preliminary investigation has shown that, just as with presynaptic inhibition of Group I actions, the afferent volleys from flexor muscles are particularly potent. For example, when pitted against the same test reflex Group I PDP volleys in Fig. 2A caused almost four times as much inhibition as Group I GS volleys in Fig. 2B. Increase of the GS stimulus, so that conditioning was effected by 4 Group I+II+III volleys, greatly intensified the reflex depression (Fig. 2B, filled circles). Correspondingly, there was a large increase in presynaptic depolarization, as shown by the DRP (Eccles, Kostyuk & Schmidt, 1962, Fig. 2A, B). It may be inferred that much of this DRP was produced by depolarization of FRA fibres, particularly cutaneous fibres.

In general, the present investigation has fully confirmed the earlier investigations on the inhibition of flexor reflexes. There is a remarkable

similarity in the time courses of all these examples of inhibition. Group I volleys produced a depression of the monosynaptic EPSP and reflex discharge, which usually had a duration in excess of 200 msec (Eccles, Eccles & Magni, 1961; Eccles, Schmidt & Willis, 1962). It is seen in Fig. 2 that the depression of the flexor reflex runs the same time course whether produced by Group I or by Group I + II + III volleys. The inhibition of the flexor reflex by cutaneous volleys runs a slower time course, but, as suggested in the Discussion, the prolonged tail of the inhibitory curve may be otherwise explained.

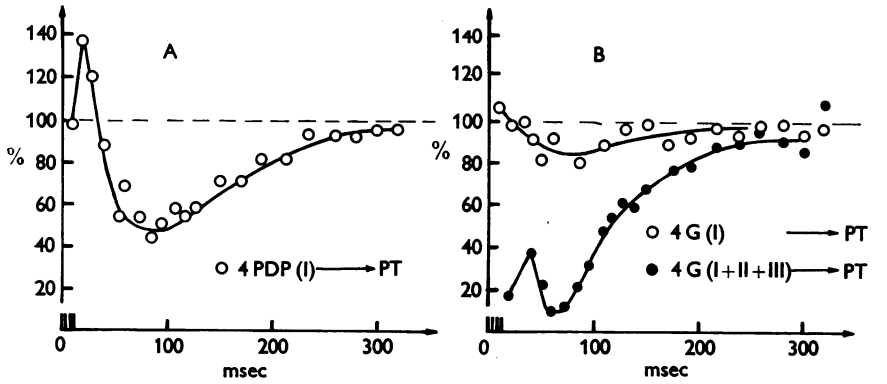

Fig. 2. Inhibition of a flexor reflex by conditioning volleys in muscle nerves. The flexor reflexes evoked by a single volley in the PT nerve were recorded monophasically as in Fig. 1, and the integrated reflex discharges were plotted as in Fig. 1C as percentages of the mean control value. In A the flexor reflex was conditioned by 4 volleys (at 220/sec) of Group I strength in PDP. In B open circles show the effect of 4 volleys set up by a stimulus of Group I strength in GS, and filled circles by a stimulus of Group III strength (40 times threshold) on the same reflex. The intervals are measured between the arrival times at the spinal cord of the first muscle volley and the PT volley.

Inhibition of discharges evoked by flexor reflex afferents into the dorsolateral funiculus of the same side

It must not be assumed that the inhibition of flexor reflexes, as described in the preceding section, is necessarily an example of presynaptic inhibition. Since there is at least one interneurone on the central pathway, it is possible that some interneurones are common to both the conditioning and testing pathways, and that the inhibition is due to depression of these interneurones consequent on their discharge in response to the conditioning volleys, as postulated by Gasser (1937). Furthermore, depression could also occur in the synaptic efficacy of those interneurones that are common to both conditioning and testing pathways, just as occurs with repetitive activation of synapses on motoneurones (Curtis & Eccles, 1960). It is

important therefore to determine if there is a comparable inhibition of the monosynaptic discharges that are evoked by FRA volleys.

The requisite conditions are provided by the monosynaptic discharges which impulses in alpha cutaneous fibres produce in the dorsolateral funiculus of the same side (Laporte *et al.* 1956; Oscarsson, 1958). Five subdivisions of this monosynaptic pathway have been recognized (Lundberg & Oscarsson, 1960, 1961); in two the relay cells are close to the segmental level of entry of the afferent fibres into the cord; the other three are subdivisions of the dorsal spino-cerebellar tract, the relay cells being in Clarke's column several segments more rostral. In testing for presynaptic inhibition it was desirable to exclude this latter group because the depolarization that appeared as the DRP and which gave maximal cord potentials close to the segmental level of entry (Bernhard, 1952, 1953; Eccles, Schmidt & Willis, unpublished observations) probably would be greatly attenuated for presynaptic terminals several segments more rostrally in Clarke's column. As described in Methods, this exclusion was effected by excising the dorsal columns down to L4 segmental level, and preparing the dorsolateral funiculus for recording from the level of cord section at L2 down to the upper L4 level.

As is shown in Fig. 3A, B (CON), a cutaneous volley in the SU nerve evoked a mass discharge in the dissected dorsolateral funiculus that began with a fairly synchronous spike with the latency expected for monosynaptic activation. Subsequently there was a prolonged discharge, which is characteristic of the responses of these tract cells (Laporte *et al.* 1956; Haapanen, Kolmodin & Skoglund, 1958; Wall, 1959; Hunt & Kuno, 1959; Eccles, Eccles & Lundberg, 1960; Kostyuk, 1960*a*; Armett, Gray & Palmer, 1961). There is evidence that much of this discharge is attributable to delayed excitation through polysynaptic pathways.

When preceded by a volley in the other cutaneous nerve (SP) there was depression of the monosynaptic discharge for testing intervals ranging from the briefest at 29 msec to beyond 150 msec, as may be seen in the plotted curve (open circles) for the series partly illustrated in Fig. 3. Furthermore, in Fig. 4 it is seen that a similar inhibitory curve was obtained for the reverse sequence of conditioning and testing volleys. In both Figs. 3 and 4 the delayed discharges were more depressed than the monosynaptic. This depression is displayed to better advantage in the integrated records which are illustrated in Figs. 3B and plotted in Fig. 3C (filled circles). Again, approximately similar curves were obtained when the order of the testing and conditioning volleys was reversed (Fig. 4C), though the monosynaptic discharges were relatively more depressed and the delayed discharges relatively less. Recovery from depression of the delayed discharges in Figs. 3C and 4C occupied at least 300 msec; and in

general it can be stated that delayed discharges always displayed a deeper and longer depression than did monosynaptic discharges.

In some experiments there was initially no detectable depression of the monosynaptic discharge, but with a deepening of the anaesthesia depression always developed. These observations are readily understood when it is realized that the monosynaptic activation of the tract cells by a cutaneous volley is so powerful that all cells are supramaximally excited for the monosynaptic discharge, while the later repetitive discharge is a very sensitive detector of inhibitory action which would be effective both in slowing the frequency and suppressing the terminal discharges. Deepening

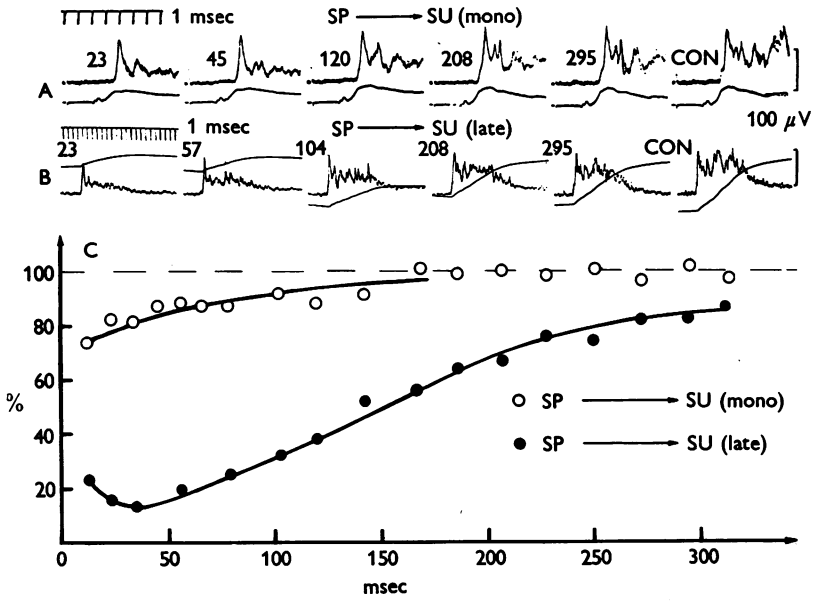

Fig. 3. Inhibition of discharges recorded monophasically from the ipsilateral cutaneous tract. The action potentials were evoked by a single SU stimulus (4 times threshold) and were conditioned by another single stimulus (4 times threshold) in SP. The specimen records in A show in the upper line the early tract discharges, in the lower line the cord dorsum potentials. Each record consists of 3 superimposed sweeps. The numbers indicate the interval (msec) between the two volleys, and CON is the control record. B shows a similar series recorded with a slower sweep speed, and with integrated traces so that the amplitude of the late discharges can be measured. Potential scales are for the monophasic records only. In C (○) the depression of the monosynaptic discharge (i.e. the amplitude of the first spike in A) is plotted as percentage of the mean control value, against the interval (msec) between the two volleys. There is plotted as (●) the depression of the late discharges as given by the integrated records of B. These were measured after the time of the monophasic spike in order to reject its contribution to the integrated response, i.e. the measurements were made between the levels of the integrated curves at from 1·3 msec to 19 msec after the onset of the monophasic discharge.

of the anaesthesia would make the monosynaptic discharges more vulnerable to depression. However, it would be expected that, as in Fig. 3, only the deeper phase of the depression would be signalled by diminution of the monosynaptic discharge, and that diminution of the delayed discharges would signal a depression corresponding in time course with that observed for flexor reflexes, which likewise would be vulnerable to all grades of depression.

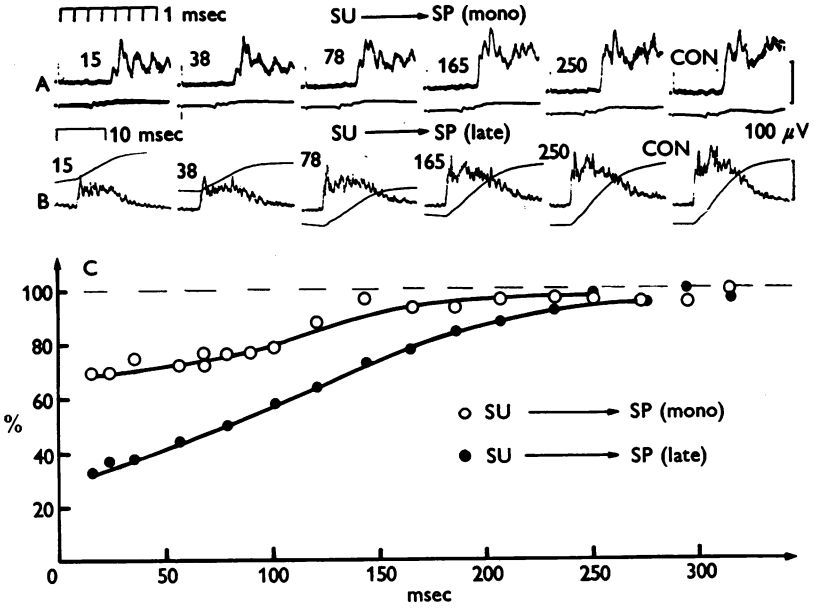

Fig. 4. Inhibition of the discharge of the ipsilateral cutaneous tract recorded and plotted as in Fig. 3. The discharges were evoked by SP and conditioned by SU. All stimuli were at 4 times threshold. Figure 4 gives interaction of the same nerve pair as in Fig. 3, but with the reverse sequence.

Figure 5 shows that Group I muscle volleys are effective in inhibiting both the monosynaptic and the later components of the ipsilateral discharge. At the optimal interval in B and C the monosynaptic discharge was reduced almost to 80 % of the control by 4 Group I PBST volleys, and the inhibition was detectable at intervals beyond 200 msec. This is a remarkable effect for Group I muscle volleys against such a powerful test response. However, in Fig. 5A and C a cutaneous volley was much more effective against the same test response. In another experiment (Fig. 5D) 4 PDP Group I volleys were nearly as effective as a combined cutaneous volley in depressing the monosynaptic discharge, but in Fig. 5E the cutaneous volleys were much more effective in depressing the late discharges.

In summary, it can be stated that in every respect testing for inhibition by the tract discharges has given results comparable with those obtained when employing flexor reflexes as the test response. The agreement was particularly close for the late tract discharges, which is not surprising because these may be presumed to be caused largely by polysynaptic excitatory action, just as occurs with the flexor reflex. Usually the inhibition of the monosynaptic tract discharge was much less in degree and also briefer in duration. Group I volleys from PDP or PBST nerves have approximately the same efficacy relative to cutaneous volleys when tested

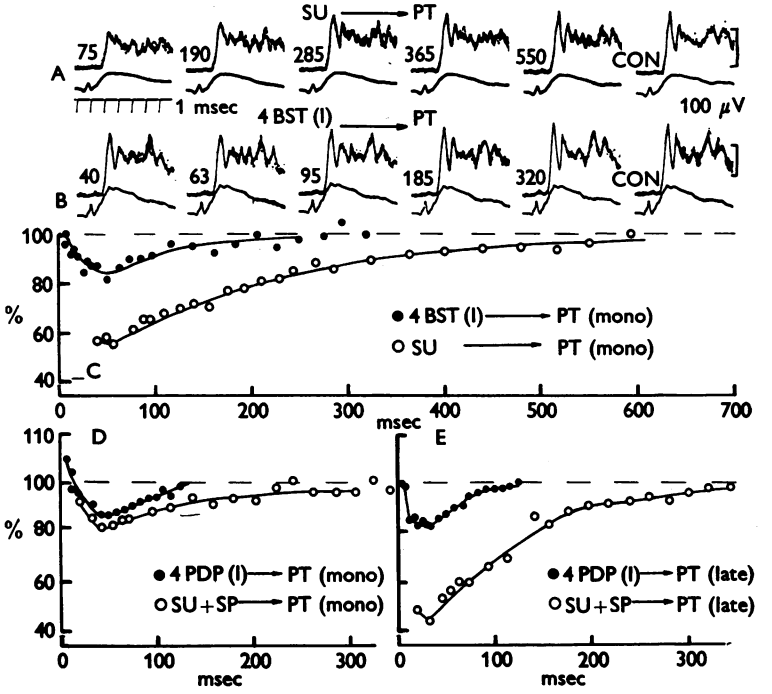

Fig. 5. Inhibition of the monophasic discharge of the ipsilateral cutaneous tract recorded and plotted as in Fig. 3. A and the open circles in C show the influence of a conditioning volley in SU on the monosynaptic spike evoked by a single volley in PT. B and the filled circles in C show the inhibition of the same monosynaptic discharge by 4 Group I volleys (at 300/sec) in PBST nerve. D and E are taken from another experiment. In D the monosynaptic tract discharge evoked by a single PT volley was conditioned either by 4 Group I volleys (300/sec) in PDP nerve (●) or by a single cutaneous volley in SU plus SP (○). In E the influence of the same conditioning volleys in PDP (●) and SU+SP (○) on the late part of the same tract discharge can be seen, the measurements being made from the integrated records as in Fig. 3. All cutaneous nerves have been stimulated with 4 times threshold strength. Voltage calibration of 100 μV in A and B is for tract discharges only.

against tract discharges and flexor reflexes. In both cases the duration of the inhibition tends to be less than that produced by cutaneous volleys.

These investigations on the ipsilateral cutaneous tract have certainly established that the inhibition is exerted on the first synaptic relay made by the primary afferent fibres of the cutaneous nerves. Furthermore, these primary afferent fibres exhibit a depolarization that appears as a dorsal root potential which in general parallels the observed inhibition for the different kinds of afferent volley; hence, it would appear that the inhibition of flexor reflexes and of tract responses is demonstrated to be another example of presynaptic inhibition. However, the identification of an inhibitory action as presynaptic rather than post-synaptic eventually does depend on the precise information that is provided by intracellular recording from the inhibited neurones, as described in the next section.

Inhibition of interneurones and tract neurones

Neurones monosynaptically excited by cutaneous nerve volleys (C type neurones). Altogether 18 C type neurones have been tested for the inhibitory action of volleys in the FRA, but only in eight of these neurones was the recording micro-electrode in an intracellular position so that it could record the EPSP produced by the testing volley. In the other neurones the inhibition could be studied by the spike discharges recorded extracellularly, there being a lengthening of latency, a diminution in number of spikes or even a complete suppression. By these various criteria it was shown that every one of the 18 C type neurones was inhibited by FRA volleys, the duration of the inhibition being never less than 100 msec and sometimes up to 300 msec.

The most reliable experiment is illustrated in Fig. 6, where both the testing and conditioning volleys produced EPSPs without any superimposed spikes, though there was a little polysynaptic excitatory action just after the summit and on the declining phase of the monosynaptic EPSPs. In Fig. 6A the EPSPs produced by the testing volley in the SP nerve are displayed at a fast sweep speed so that the time courses of the EPSPs can be observed in detail. Measurements for the whole series that is partly illustrated in Fig. 6A, B are plotted in Fig. 6C. The depression of the EPSP is maximal at brief testing intervals, there being rapid recovery beyond 20 msec, but there appears still to be a little depression at the longest testing intervals. The control EPSP seems to differ only on account of the polysynaptic EPSPs superimposed on its declining phase. It can be concluded that the EPSP depression in Fig. 6 corresponds closely to that observed with the monosynaptic EPSPs of motoneurones (Eccles, Eccles & Magni, 1961). Since it has a time course comparable with the presynaptic

depolarization observed by intracellular recording (Eccles & Krnjević, 1959), it can be concluded that the EPSP depression of Fig. 6 is an example of presynaptic inhibition in which the synaptic excitatory action is diminished on account of the presynaptic depolarization.

An EPSP depression having the long time course of the inhibitory action produced by FRA volleys has been observed with the other seven C type

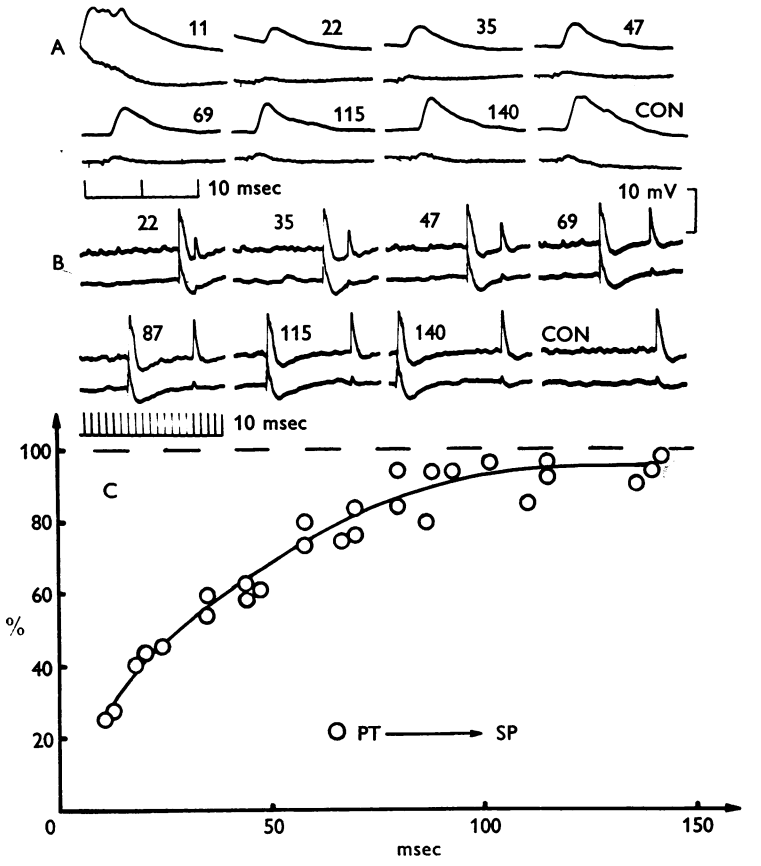

Fig. 6. Depression of excitatory post-synaptic potential (EPSP) of a C type interneurone (depth 2·3 mm). B shows in the upper trace intracellularly recorded EPSPs that were evoked monosynaptically by a single volley in SP nerve and conditioned by another single volley in PT nerve. In A are faster recordings of the EPSPs evoked by the testing volley. The numbers in A and B indicate the intervals (msec) between the two volleys. The lower traces in A and B are the cord dorsum surface potentials at L 7 segmental level. In A and B CON is the control EPSP. Same voltage calibration for all upper traces in A and B. Amplifier time constant for upper traces in A is 200 msec and in B is 20 msec. In C the sizes of the conditioned EPSPs are plotted (as percentages of the mean control value) against the testing intervals for the series partly illustrated in A and B.

neurones in which EPSPs could be recognized. In the remaining C type neurones inhibitory action was exhibited by the spike discharges; and, as illustrated in Fig. 7, there was lengthening of the latency of discharge and reduction in the number of discharges, effects which were observed over long test intervals—even up to 300 msec. On the few occasions where conditioning was effected by afferent volleys from muscle, there was likewise an inhibition of spike discharges from a C type neurone, but these volleys included Group II and III impulses; Group I volleys alone have not yet been employed for conditioning.

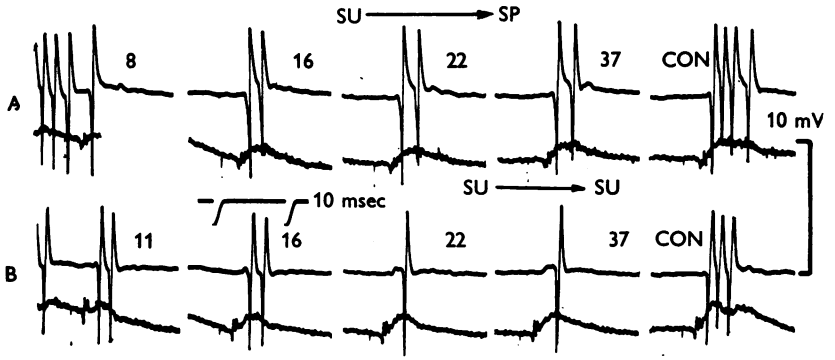

Fig. 7. Reduction in number of discharges and lengthening of latency of a C type interneurone (depth 2 mm). Upper traces are the extracellular recordings, lower traces are the cord dorsum surface potentials recorded from L7 segmental level. In A the spikes were evoked by a single volley in SP nerve and conditioned by a single volley in SU nerve. In B a conditioning volley in SU preceded a test volley in the same nerve. The interval (msec) between the conditioning and the testing volley is indicated for each record, CON being the controls. At the shortest intervals part of the spikes evoked by the conditioning volleys can also be seen. Voltage calibration is for extracellular recording only.

These investigations on type C neurones with micro-electrode recording have thus shown that the monosynaptic activation by cutaneous volleys is depressed by FRA volleys in just the same way as monosynaptic activation of motoneurones is depressed by Group I volleys in the nerves to flexor muscles but not by other muscle volleys or by cutaneous volleys (Eccles, Eccles & Magni, 1961). It can be concluded that the depression of the various responses produced by FRA volleys, as illustrated in Figs. 1–7, is likewise due to a presynaptic inhibitory mechanism. If, as seems likely, this presynaptic inhibition is exerted on all the cutaneous afferent fibres, the actual neuronal mechanism concerned in the production of presynaptic inhibition must itself also be subjected to this inhibition. This effect can be most easily demonstrated by recording the presynaptic depolarization in the DR fibres, as in the next section. Meanwhile, additional evidence can be obtained by observing the responses of D type cells, some of which are

assumed to be interneurones on the neuronal pathway responsible for producing presynaptic inhibition (Eccles, Kostyuk & Schmidt, 1962).

D type cells. The inhibitory action of a preceding afferent volley has been investigated with only 7 D-type cells, and all have exhibited a depression with the time course characteristic of presynaptic inhibition. In the absence of intracellular recording the depression has been shown both by a diminution in the number of impulses evoked by the testing volley, and by a lengthening of their central latency. For example, the testing volley in SP nerve alone in Fig. 8 evoked a discharge of 4 impulses with a central latency of 1·7 msec; and, at intervals of 22–55 msec after the conditioning

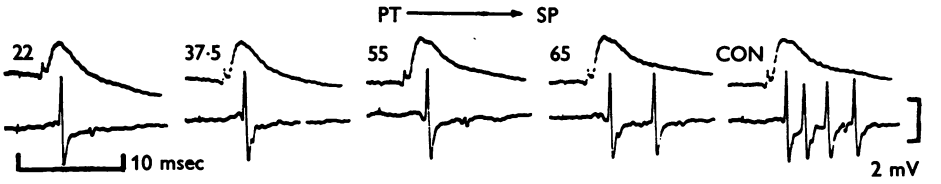

Fig. 8. Reduction in number of discharges of a D type interneurone (depth 1·75 mm). The spikes were evoked by a single volley in SP nerve and conditioned by another volley in PT nerve. Lower traces are the extracellular recordings from the interneurone, upper traces the cord dorsum potentials at L7 segmental level. The intervals (msec) between conditioning and testing volleys are given for each record. Voltage calibration is for extracellular recording only.

volley in PT nerve, the testing response was reduced to only one impulse with a latency about 0·2 msec longer. Some recovery had occurred at the longest testing interval of 65 msec in Fig. 8, but evidently the recovery was running the slow time course characteristic of presynaptic inhibition. This prolonged depression of D type cells, activated as in Fig. 8 disynaptically from cutaneous afferents, is of course to be expected, because it must be assumed that these cells are activated secondarily to C type cells, which themselves have all exhibited the presynaptic inhibition.

Inhibition of the dorsal root potentials

The initial investigations on the dorsal root potential (DRP) revealed that a second volley in the same or a different afferent produced a diminished DRP even when the testing interval was several hundred milliseconds (Barron & Matthews, 1938; Bonnet & Bremer, 1939; Bremer & Bonnet, 1942; Eccles & Malcolm, 1946); and this was also observed with contralateral conditioning (Mamonets, 1960, 1961). Despite the frequent confirmation of these original findings there has been no satisfactory explanation of this prolonged depression, which has been referred to by such non-committal terms as occlusion or fatigue; but now it is necessary to enquire whether the depression is attributable to presynaptic inhibition.

There is much evidence in support of the postulate that afferent volleys generate the DRP by exciting interneuronal pathways which eventually end in synapses on the central terminals of primary afferent fibres (Eccles, Kostyuk & Schmidt, 1962). Furthermore, it has been shown above that a conditioning FRA volley produces presynaptic inhibition of three different kinds of responses evoked by a testing FRA volley: the responses of interneurones; the monosynaptic and polysynaptic tract discharges; and the flexor reflex. If depression of the testing DRP is a further example of presynaptic inhibition, it would be expected to exhibit a similar time course, the depression being maximal at short testing intervals and having a total duration of about 300 msec.

In the specimen records of Fig. 9A there is seen to be a large depression of the DRP evoked by a SP volley when it is preceded by a SU volley.

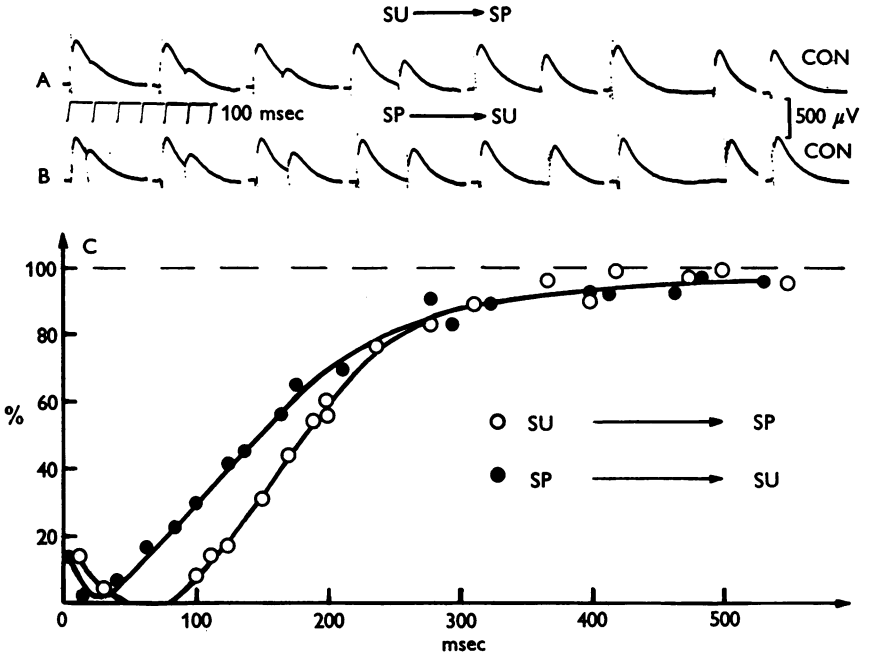

Fig. 9. Interaction of cutaneous volleys as revealed by the dorsal root potentials (DRP). The rootlet was taken from the caudal part of L6 dorsal root. A shows the control dorsal root potential (CON) generated by a SP volley and its inhibition by a preceding volley in SU at intervals given by the time scale. In B the DRP evoked by the SU volley was conditioned by a SP volley. In C are the plotted points of the series partly illustrated in A (○) and in B (●). The ordinates are the sizes of the DRP expressed as percentages of the mean control values and measured as the addition to the conditioning DRP. The stimulus strength for the nerves was adjusted to give about the same DRP size for SU and SP in the rootlet under observation.

When the DRP produced by the SP volley at each testing interval is calculated as the potential added to the conditioning DRP and plotted against the testing interval (Fig. 9C, open circles), it is seen that the very deep depression at brief intervals recovered along a curve resembling the recovery from the presynaptic inhibition of other responses to a testing cutaneous volley (Figs. 1, 3, 4, 5, 6); and it was still incomplete after 300 msec. A similar prolonged recovery is exhibited in Fig. 9B and C (filled circles) when the conditioning and testing volleys were reversed.

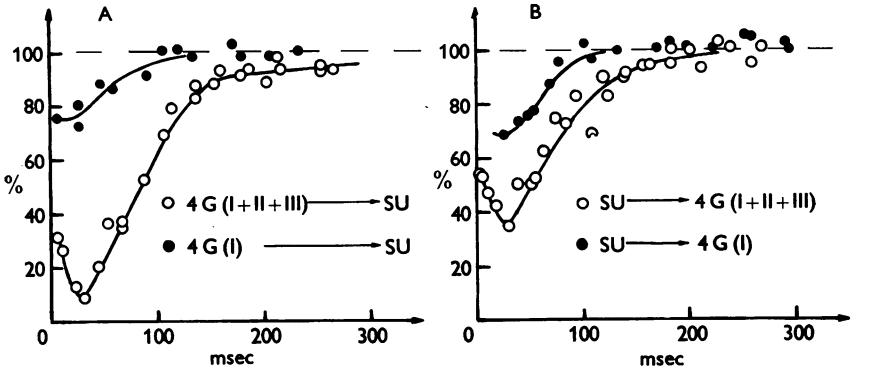

Fig. 10. Dorsal root potential (DRP) interaction recorded and plotted as in Fig. 9, but taken from another experiment. In A a DRP produced in a rootlet from L7 DR by a single volley in SU was conditioned by 4 volleys (300/sec) in GS that were evoked by stimuli of Group I strength (●) or Group III strength (○). B shows the reversed interaction: the same SU volley preceded a dorsal root potential generated by 4 volleys in GS of either Group I (●) or Group III (○) stimulus strength. The stimulation strength for SU was kept constant in A and B at about 4 times threshold. The amplitude of the unconditioned DRP produced by 4 Group I volleys in GS was 320 μV, that of the 4 Group I + II + III volleys was 480 μV, and that of the SU volley was 455 μV.

Figure 10A closely resembles Fig. 2B. In both a Group I GS volley caused a small and brief depression of the testing response evoked by a cutaneous volley (flexor reflex or DRP), while a Group I+II+III GS volley produced a much larger and longer depression, the test response being reduced to about 10 % in each case. The reverse sequence in Fig. 10B discloses that the cutaneous volley also depressed the DRP produced by the GS Group I+II+III volley much more than that of the Group I GS volley. Evidently there is a much more effective interaction between the afferent fibres that belong to the FRA system, the cutaneous and the Group II and III muscle impulses in this case. It has been regularly observed that the DRP evoked by a cutaneous volley was depressed by the muscle FRA volleys with about the same effectiveness as by a cutaneous volley giving a DRP of comparable size, and similarly with the reverse

sequence of conditioning and testing volleys. This is precisely the pattern of action that would be predicted according to the concept that all FRA volleys act through the same system of interneurones (Eccles & Lundberg, 1959*b*; Holmqvist, Lundberg & Oscarsson, 1960; Holmqvist & Lundberg, 1961).

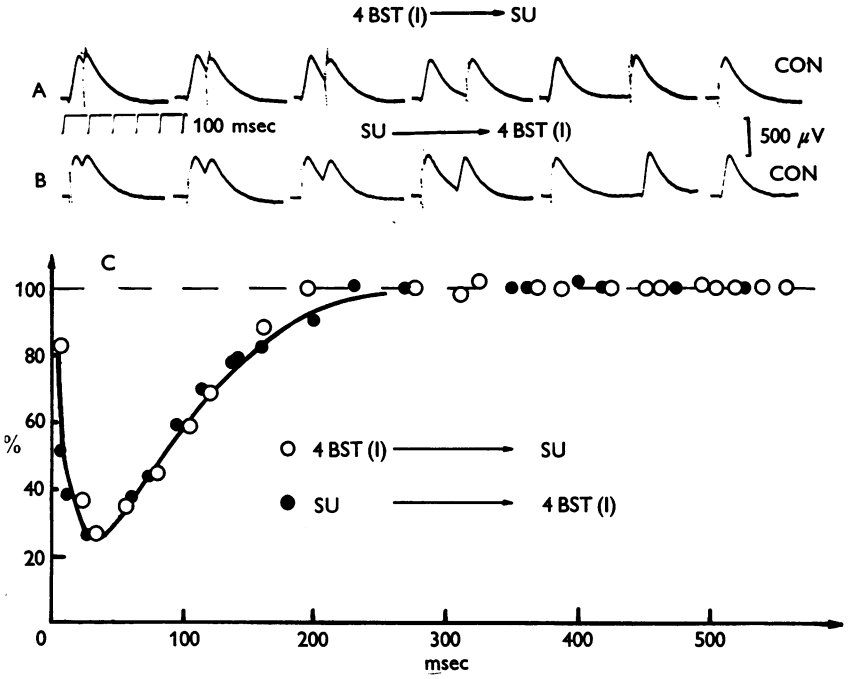

Fig. 11. Dorsal root potential interaction recorded from the same rootlet as in Fig. 9 and plotted similarly. In A the DRP generated by a SU volley was conditioned by 4 volleys (300/sec) of Group I strength in PBST. In B there was the reverse sequence. In C are plotted points from the series partly illustrated in A (○) and B (●). The stimulus strength for SU was adjusted to give about the same size of DRP as the 4 PBST volleys of Group I strength.

However, as is illustrated in Fig. 11, a very large depressant action is exerted by PBST Group I volleys on the DRP produced by a cutaneous volley and vice versa; yet these two types of volleys must in large part activate separate systems of interneurones (Eccles, Kostyuk & Schmidt, 1962). The maximal depression of over 70 % in Fig. 11 is unusually large, but depressions of about 50 % have been regularly observed in the interaction between the large DRPs produced by cutaneous volleys and by 4 Group I PDP or PBST volleys. Such depressions are certainly less than the depressions of about 100 % regularly observed in the interaction of two cutaneous volleys. They are also briefer. The time course of recovery from the depression was, for example, much slower in Fig. 9C than in Fig. 11C.

DISCUSSION

By four independent types of investigation it has been shown that a conditioning FRA volley produces a depression of the responses to a testing FRA volley which has a time course even longer than the depolarization that the conditioning volley produces in the primary afferent fibres, i.e. the dorsal root potential. This depression was exerted on the monosynaptic discharge which alpha cutaneous impulses produce in the fibres of the dorsolateral funiculus of the same side. By intracellular recording from neurones monosynaptically excited by cutaneous impulses this depression was found to be exerted on the monosynaptic EPSP. There is such a close parallelism with the presynaptic inhibition of the Group I system that undoubtedly the above four types of FRA depression must be regarded as examples of presynaptic inhibition. Thus the primary afferent depolarization that appears as the DRP of the FRA fibres depresses the synaptic excitatory action of these fibres, presumably by diminishing the output of transmitter (Hagiwara & Tasaki, 1958; Eccles, Kostyuk & Schmidt, unpublished observations).

This presynaptic inhibition of the FRA system is remarkable both for its power and for its duration. Furthermore, each cutaneous afferent fibre is actively depolarized (Koketsu, 1956; Eccles & Krnjević, 1959) and the inhibition is not an effect depending on synchronization of afferent input into the spinal cord. The random asynchronous discharge produced by receptor organs would be effective in activating interneurones, which through 'feed-back' pathways (cf. Eccles, Kostyuk & Schmidt, 1962, Fig. 9) would depolarize the presynaptic terminals of the FRA fibres and hence depress their synaptic excitatory power. Thus the FRA presynaptic inhibition possesses the essential features of a negative feed-back system. It should be mentioned in parentheses that, in contrast to presynaptic inhibition, the generation of DRRs does require the approximate synchronization of a large afferent input, such as occurs when a whole cutaneous nerve is stimulated electrically. It is therefore unlikely that such reflexes occur to any appreciable extent under physiological conditions.

Intracellular recording from cutaneous fibres in the spinal cord showed that Group I afferent volleys from muscle sometimes produced a small depolarization (Eccles & Krnjević, 1959); single cutaneous volleys gave a much larger depolarization. In these earlier investigations only single volleys were used. In all presynaptic inhibitory actions brief repetitive muscle volleys are much more effective (Eccles, Eccles & Magni, 1961; Eccles, Magni & Willis, 1962). In unpublished investigations (Eccles, Schmidt & Willis) it has now been found that brief repetitive volleys in the PBST or PDP nerves produce quite large depolarizations of cutaneous

fibres. Hence there has been direct confirmation of the inferences from the present investigation that Group I volleys from muscle depolarize FRA fibres and hence depress the various responses produced by FRA volleys.

However, it has invariably been observed that the presynaptic inhibition produced by Group I volleys runs a briefer time course than that produced by FRA volleys. Furthermore, some of the depressions produced by FRA volleys have a very prolonged tail (see Fig. 1) that persists even beyond 1000 msec. Such prolonged depressions are always observed when two volleys traverse the same monosynaptic pathway (Lloyd, 1957; Curtis & Eccles, 1960), and have been attributed both to depletion of transmitter and to desensitization of the post-synaptic receptor sites. With the polysynaptic pathways involved in the flexor reflex or in the production of the DRP there is likely to be convergence of two FRA volleys on to the same interneurones, even though initially in separate nerves. Such convergence is readily observed when recording from interneurones (see Eccles, Kostyuk & Schmidt, 1962, Fig. 6); hence it can be assumed that, even when the conditioning and testing FRA volleys are in different nerves, there is likely to be depression because convergence on to a common path is likely. The depressant action arising from repetitive activation of synapses is thus prolonged beyond the duration of the presynaptic inhibitory action. However, when the conditioning volley is in Group I muscle afferents, there is little convergence on to interneurones, hence the depressed FRA responses would be almost entirely due to presynaptic inhibition. The Group I pathway must be distinct from the FRA pathway, at least in the presynaptic depolarization of Group I muscle fibres, and convergence on to the same interneurones seems to be uncommon; hence the simplest postulate is that FRAs and Group I muscle afferents converge by independent pathways on to the FRA fibres, which they depolarize by separate synapses.

When attempting to understand the physiological significance of the negative feed-back provided by presynaptic inhibition, it is helpful to consider the operational conditions that normally obtain with all the diversity of afferent input into the spinal cord. Hitherto it has been assumed that all this sensory information is processed in the spinal cord during transmission through interneuronal pathways which offer opportunities for inhibitory action at each synaptic relay. This inhibition would be exerted by a specific post-synaptic process generating currents that antagonized the post-synaptic depolarizing action of the excitatory synapses. Presynaptic inhibition, on the other hand, provides a mechanism for suppressing the sensory input before it can exert any synaptic action. In this way a powerful presynaptic input through FRA channels can suppress all trivial inputs before they have an effective action on the

central nervous system, which, as a consequence, is 'cleared' for the 'urgent' actions set in train by the powerful input. It will be objected that the principal input will also itself be subjected to the diffuse depressant action of the presynaptic inhibition which it generates; but if it is sufficiently powerful the depression will be negligible, as is illustrated, for example, with the monosynaptic tract discharges in Figs. 3, 4, 5. In general terms it can be stated that presynaptic inhibition provides the first stage in what we may term 'perceptual attention', whereby powerful sensory inputs with an implication of urgency can suppress all concurrent trivial inputs into the central nervous system.

The general thesis of this paper and of other recent investigations on presynaptic inhibition (Eccles, Kozak & Magni, 1961; Eccles, Eccles & Magni, 1961; Eccles, Magni & Willis, 1962; Eccles, Kostyuk & Schmidt, 1962; Eccles, Schmidt & Willis, 1962) is that there are in the spinal cord two systems that operate in producing presynaptic inhibition. One system is virtually restricted to Group I muscle afferents, being produced very largely by Group I fibres of flexor muscles. The other system probably includes all the FRA group on the receiving side, and is activated even more widely because the Group I muscle afferents contribute in addition. The operational relationships of the two systems may thus be represented with arrows showing directions of the depolarizing actions:

$$\boxed{\text{Group I fibres}} \leftarrow \underset{\text{flexor muscles}}{\text{Group I volleys}} \rightarrow \boxed{\text{FRA fibres}} \leftarrow \text{FRA volleys.}$$

These two systems correspond roughly to two different modes of sensory input into the lumbar region of the spinal cord. There is first the input from limbs functioning as passive receptors, e.g. hair movement, touch and pressure on skin and pressure on muscle; secondly there is the Group I input, which is largely concerned with control of movement and which is activated largely in response to the alpha and gamma motoneuronal discharges to muscle in combination with limb movements and external forces producing muscle tension.

The recognition of the presynaptic inhibitory action of FRAs enables explanations to be given for the earlier experiments of Gasser (1937) and Bremer and their colleagues in which there appeared to be a correlation between the P wave which an afferent volley sets up in the cord dorsum and the inhibitory action of that volley. But presynaptic inhibition also provides explanations for many otherwise perplexing findings. For example, Kuno & Perl (1960) observed that a SU volley 45 msec before a conditioning medial gastrocnemius volley (Group I+II+III) suppressed the facilitation which this latter volley, by itself, exerted on a later testing monosynaptic reflex to the biceps semitendinosus muscle. It seems likely

that this is an example of presynaptic inhibition within the FRA system: SU inhibiting the action of Groups II and III of muscle. Another instance is provided by several observations on sensory phenomena in man (Wall & Cronly-Dillon, 1960). Various types of skin stimulation were observed to depress the sensation aroused by a test stimulus applied to an adjacent skin area. Analogous responses were also observed in the responses of cells in the cat spinal cord. It seems likely that presynaptic inhibition within the FRA system could explain most of these observations.

As a final comment it can be suggested that presynaptic inhibition may occur on afferent pathways at sites remote from the zone of entry into the cord. For example, inhibition with the prolonged time course of presynaptic inhibition occurs with the synaptic relay of Group Ia fibres on the DSCT cells in Clarke's column (Eccles, Oscarsson & Willis, 1961). Furthermore, Wall (1958) showed that, after a conditioning volley in the S1 dorsal root, the presynaptic terminals of primary afferent fibres in the nucleus gracilis in the upper cervical region displayed an increased excitability that had a time course comparable to that observed in the lumbar enlargement. It can be presumed likewise that this increased excitability arises from a synaptic depolarization; hence the conditioning volley would have a presynaptic inhibitory action in the nucleus gracilis.

SUMMARY

1. This investigation relates particularly to the presynaptic inhibitory action produced by volleys in those afferent fibres that evoke flexor reflexes; the cutaneous and the high-threshold muscle afferent fibres.

2. A single cutaneous volley causes a prolonged depression of the test response evoked by a volley in another cutaneous nerve, the same prolonged depression (usually in excess of 300 msec) being exhibited by the following test responses: flexor reflexes, monosynaptic and delayed discharges in the dorsolateral funiculus of the same side; dorsal root potentials.

3. In general, this conditioning with a single cutaneous volley was more effective, both in the amount and the duration of the depression, than brief tetani (4 volleys of Group I + II + III) in muscle nerves; but brief tetani of Group I volleys from flexor muscles were surprisingly effective, though the depression was distinctly less prolonged.

4. The size of the monosynaptic EPSPs evoked by cutaneous volleys in interneurones of the dorsal horn is depressed by conditioning volleys with a time course which corresponds to the prolonged inhibitory actions. The post-synaptic membrane seems not to be changed during this depression.

5. It is concluded that these inhibitions occur mainly on account of depolarization of the presynaptic cutaneous fibres, i.e. that they are

examples of presynaptic inhibition; furthermore, that this presynaptic inhibition of cutaneous fibres is produced by two virtually independent pathways through interneurones, one from the Group I fibres from flexor muscles, the other for all the FRA group of fibres.

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