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CENTRAL PATHWAYS RESPONSIBLE FOR DEPOLARIZATION OF PRIMARY AFFERENT FIBRES

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In the first electrophysiological observations on the central nervous system Gotch & Horsley (1891) recorded from the surface of the spinal cord electrical potential changes which were associated with reflex activity. The subsequent investigation of this phenomenon began with a systematic examination of the various components of the cord potential produced by an afferent volley in a dorsal root, and the attempt to correlate these components with the reflex contractions of muscles (Gasser & Graham, 1933; Hughes & Gasser, 1934*a*, *b*). In the initial investigation (Gasser & Graham, 1933) evidence was presented that the prolonged (about 200 msec) positive wave of the dorsum of the cord (the P wave) was associated with a depression of the initial negative potential wave (the N wave) evoked by a second dorsal root volley, whether in the same or in a different ipsilateral root. It was suggested that the P wave was due to the flow of current in structures which were oriented dorso-ventrally and depolarized at their ventral ends, and that these structures were interneurones.

The recording of potentials electrotonically propagated along the primary afferent fibres and so into the dorsal root was introduced by Barron & Matthews (1935, 1938) and has the great advantage over the cord dorsum leads in that it appears to give a selective lead from the mechanism generating current flow within the spinal cord. It was remarkable that in response to all varieties of afferent input the dorsal root potentials (DRPs) were uniformly in the depolarizing direction. It was concluded that the DRP and the P wave of the cord dorsum are produced by the same potential generator in the spinal cord, and this identification has been accepted by all subsequent investigators (see Bremer & Bonnet, 1942; Bernhard, 1952, 1953*a*; Koketsu, 1956*a*, *b*; Eccles, Magni & Willis, 1962).

Subsequently there have been many experimental investigations both of the cord dorsum potentials (Bernhard, 1952, 1953*a*, *b*; Bernhard &

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Widén, 1953; Austin & McCouch, 1955) and of the depolarization of primary afferent fibres which has been recorded either from the isolated root (Bonnet & Bremer, 1938, 1952; Fessard & Matthews, 1939; Dun, 1941; Bremer & Bonnet, 1942, 1949; Eccles & Malcolm, 1946; Beritoff & Roitbak, 1947; Lloyd & McIntyre, 1949; Woronozov, 1952; Lloyd, 1952; Brooks & Fuortes, 1952; Eisenman & Rudin, 1954) or by an intracellular micro-electrode in the primary afferent fibres, usually in the dorsal region of the cord (Koketsu, 1956*a*, *b*; Eccles & Krnjević, 1959*a*; Eccles, Magni & Willis, 1962). There is general agreement that cutaneous afferent volleys are very effective in depolarizing primary afferent fibres, so generating DRPs; though a considerable action by muscle afferent volleys has been reported by some investigators (Brooks & Fuortes, 1952; Eccles & Krnjević, 1959*a*; Eccles, Magni & Willis, 1962), but not by others (Fessard & Matthews, 1939; Koketsu, 1956*b*; Wall, 1958).

However, there is much diversity in the attempts to explain the manner in which DRPs are produced. Barron & Matthews (1938), Dun (1941), and Brooks & Fuortes (1952) suggest that DRPs arise primarily in dorsal root fibres by ionic changes external to their central terminals 'and by a mechanism analogous to that responsible for the after-potentials in nerve'. According to Bonnet & Bremer (1938, 1952), Eccles (1939), Bremer & Bonnet (1942, 1949), Eccles & Malcolm (1946), Lloyd & McIntyre (1949) and Kostyuk (1956) the primary afferent fibres do not act directly on each other, but interneurones are the primary generators of the DRP, there being assumed to be some unspecified mechanism of electrical transmission from them to the terminals of the primary afferent fibres that are in close apposition. It seemed impossible otherwise to explain the very wide segmental distribution of the depolarization, and particularly the potentials in the contralateral dorsal roots. A further argument against the direct interaction of primary afferent terminals was based on the observation that impulses in a particular afferent fibre had no specific action in depolarizing that fibre (Koketsu, 1956*a*, *b*; Eccles & Krnjević, 1959*a*). Nor is the process noticeably selective within an assemblage of afferent fibres; for example, a volley in one dorsal root produces in that root a DRP that is about the same size as the DRP produced by an adjacent root (Barron & Matthews, 1938; Eccles & Malcolm, 1946; Lloyd & McIntyre, 1949).

The present paper gives an account of investigations relating particularly to the organization of the central pathways concerned in depolarization of the central terminals of afferent fibres. The following paper (Eccles, Kostyuk & Schmidt, 1962) will show how this presynaptic depolarization of cutaneous fibres accounts for a wide variety of inhibitory actions.

METHODS

Throughout the whole experiment the animal (cat) was lightly anaesthetized with pentobarbital sodium. The spinal cord preparation and general experimental arrangements have been described previously (Eccles, Magni & Willis, 1962). For example, the DRPs were recorded as there described from a small rootlet that was usually dissected out of the middle of the L7 dorsal root, but was sometimes the most caudal rootlet of L6; and the same techniques were employed for the potential recorded from the dorsal surface of the cord and the field potentials within the cord. When recording the potentials on or within the spinal cord, or from the isolated dorsal root, the time constant of the amplifier was 1 sec except in a few experiments where a DC differential amplifier was employed. All these potentials were elicited at a very slow repetition rate, usually 0·5/sec, but sometimes even slower in order to avoid the depression that can be detected for at least 1 sec in some of these responses. The technique of investigating the responses of interneurones has also been described previously (Eccles, Eccles & Lundberg, 1960).

The following cutaneous nerves have been prepared and mounted on platinum electrodes for stimulating, and their identification symbols are also given: sural (SU) which included both branches that arise from the sciatic nerve in the middle of the thigh; superficial peroneal (SP), from which the associated nerves to peroneous brevis and tertius muscles were removed; posterior tibial (PT) prepared mid-way between knee and ankle, but including the innervation also of flexor digitorum brevis and the foot muscles; saphenous (SA) prepared at the proximal part of the thigh and mounted on a buried electrode. In addition the following muscle nerves were prepared: posterior biceps plus semitendinosus (PBST); semimembranosus plus anterior biceps (SMAB); gastrocnemius-soleus (GS); flexor digitorum longus plus flexor hallucis longus (FDHL); plantaris (PL); the whole of the muscle branches of deep peroneal with the exception of the branch to extensor digitorum brevis, but including the nerves to the three peroneal muscles (PDP). In almost all experiments it was possible to remove the small interosseus nerve lying between the two branches of the FDHL nerve (see Hunt & McIntyre, 1960*a*). Other names with abbreviations commonly used in the text are as follows: PAD (primary afferent depolarization) as defined by Eccles, Magni & Willis (1962); DRP (dorsal root potential) as measured from the isolated dorsal root; DRR (dorsal root reflex), impulses discharged outwards along dorsal root fibres in response to an afferent volley (Toennies, 1938, 1939); Groups I, II and III afferent fibres from muscle, as defined by Lloyd & Chang (1948) and by Hunt & Perl (1960); A, B and C types of interneurones, as identified by their monosynaptic activation (Eccles *et al.* 1960). EPSP is the abbreviation for the excitatory post-synaptic potential (see Eccles, 1957).

RESULTS

Dorsal root potentials evoked by various types of afferent impulses

The simplest method of investigating depolarizations produced in the central terminals of primary afferent fibres is to record them after electrotonic propagation outwards along these afferent fibres and so into a dorsal root or rootlet that is isolated except for its entry into the spinal cord and mounted on electrodes, one close to its cord entry and the other on the distal cut end (see Barron & Matthews, 1935, 1938; Bonnet & Bremer, 1938). Hitherto, in most investigations such DRPs have been evoked by afferent volleys set up by stimulation of the dorsal roots or mixed (cutaneous and muscle) afferent nerves, but there have been isolated attempts

to relate the production of DRPs to specific types of afferent fibre. The original investigations of Toennies (1938, 1939) on the dorsal root reflexes (DRRs) demonstrated unequivocally that they are very effectively produced in cutaneous afferent fibres by cutaneous afferent impulses; and DRRs are generally recognized as being generated by the DRPs (see Eccles, 1939; Brooks & Koizumi, 1953). Brooks & Fuortes (1952) showed that DRPs of comparable time course are produced by afferent volleys from both cutaneous and muscle nerves, and this has been fully confirmed (Eccles & Krnjević, 1959*a*; Eccles, Magni & Willis, 1962). However, there has as yet been no systematic study of the DRPs produced both by cutaneous afferent volleys set up by all grades of stimulus strength, and by the higher threshold components (Groups II and III) of muscle afferents.

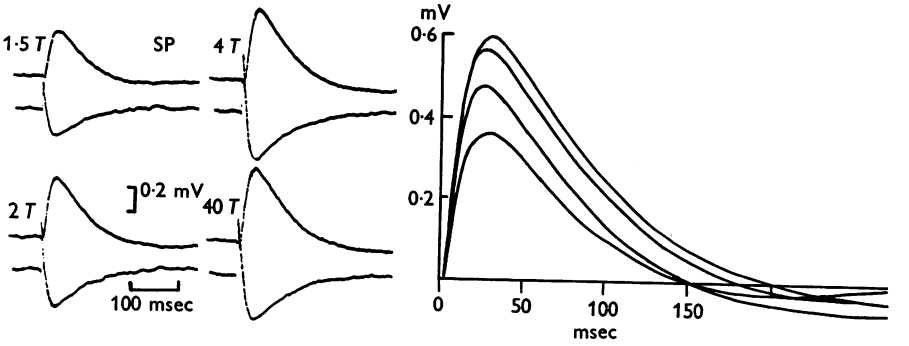

Fig. 1. Dorsal root potentials (DRP, upper traces of specimen records) evoked by afferent volleys of increasing strength in SP nerve. The rootlet was the most caudal in the L6 dorsal root. The lower traces are cord dorsum surface potentials recorded by an electrode slightly more caudal than the level of the dorsal rootlet. Stimulus strength is indicated relative to threshold strength (*T*). In the right-hand diagram the four DRPs are enlarged and superimposed to illustrate the change in amplitude and time course. The amplifiers had a time constant of 1 sec. There was no appreciable change in the time course of the DRP observed with DC amplification. The undershoot after 150–200 msec was an invariable feature. Negativity is upwards with respect to the indifferent electrode, in these and subsequent records.

In Fig. 1 it is seen that, when the strength of stimulation applied to a cutaneous nerve is progressively increased, the DRP likewise increases for strengths up to about four times threshold, but does not appreciably alter in time course. Stronger stimulation (increase from 4 to 40*T* in Fig. 1) effects little if any change in the rising phase, but results in a small late addition to the summit and declining phase. These observations correspond with those of Toennies (1938, 1939) on the dorsal root reflex, which was evoked mainly by the low-threshold cutaneous fibres. The DRP produced by the high-threshold cutaneous fibres is given by the difference between the DRPs with stimuli of 4*T* and 40*T* in Fig. 1. Its late onset is at least

partly explained by the much longer conduction time of the high-threshold impulses. Figure 1 further shows that after 150–200 msec the DRP reverses to a low positivity, which has been designated DR_{VI} by Lloyd (1952).

By investigating the adequate stimulation proper for cutaneous afferent fibres Hunt & McIntyre (1960*b*) showed that the so-called alpha group of cutaneous fibres (alpha-beta group of other authors) with conduction velocities ranging from 100 m/sec down to 36 m/sec belonged to three distinct functional groups, which were concerned with hair movement, touch and pressure, and which were each distributed throughout this large range of fibre diameter (17–6μ). A stimulus of almost four times threshold strength (4T) would be required to set up a maximal alpha volley and this corresponds to the observation that a stimulus strength of about 4T was usually required to evoke a maximal DRP. There is as yet no evidence concerning the relationship of modality of alpha fibre to the generation of the DRP. All that can be stated is that fibres with a size range covering the whole alpha group are concerned in the production of the DRP and that the smaller delta group of cutaneous fibres is much less effective. A similar relationship also holds for the production of the flexor reflex by cutaneous volleys (Mark & Steiner, 1958).

It has already been shown that, with a wide variety of muscle nerves, both Group I and Group II afferent volleys produce DRPs (Brooks & Fuortes, 1952; Eccles, Magni & Willis, 1962). Figure 2 illustrates a more discriminative investigation in which the nerve stimulation was increased up to the maximum for Group III. With most muscle nerves strengthening of the stimulation above Group I maximum resulted in a large increase in the DRPs. For example, in Fig. 2A and B a maximal Group I GS volley (stimulus strength 2·1 times threshold) evoked a very small DRP. The DRP was approximately doubled when the stimulus was maximal for Group II (8·4T strength), and was greatly increased for a maximal Group III volley (42T strength). With the PBST nerve (Fig. 2C, D) Group I volleys were relatively more effective and Group III relatively less. In general, Group I afferent volleys from flexor muscles produced larger DRPs than those from extensor muscles (see Eccles, Magni & Willis, 1962), but Group III volleys from extensor muscles were particularly effective. The summits of the DRPs evoked by Group III volleys were later than the Group I and II DRPs.

It will be appreciated that the investigations on the DRPs give no information as to the types of afferent fibre whose depolarization is responsible for the DRP. The DRRs recorded from cutaneous nerves certainly show that cutaneous afferent fibres are largely depolarized in the DRPs evoked by cutaneous volleys (Toennies, 1938, 1939; Brooks & Koizumi, 1956; Eccles, Kozak & Magni, 1961); and intracellular recording

from afferent fibres has demonstrated this specific incidence of the depolarization (Koketsu, 1956*a*, *b*; Eccles & Krnjević, 1959*a*, *b*). Furthermore, studies both of the DRR (Eccles, Kozak & Magni, 1961) and of the intracellular potentials of muscle afferent fibres (Eccles, Magni & Willis, 1962) have shown that both cutaneous volleys and volleys in Group II and III fibres from muscle produce little or no depolarization of Group I muscle afferents. But it is not yet known if Group II and III muscle afferents are depolarized by cutaneous afferent volleys or by volleys in any type of muscle afferent; nor is there yet good evidence relating to the effectiveness of Group I, II and III muscle afferents in depolarizing

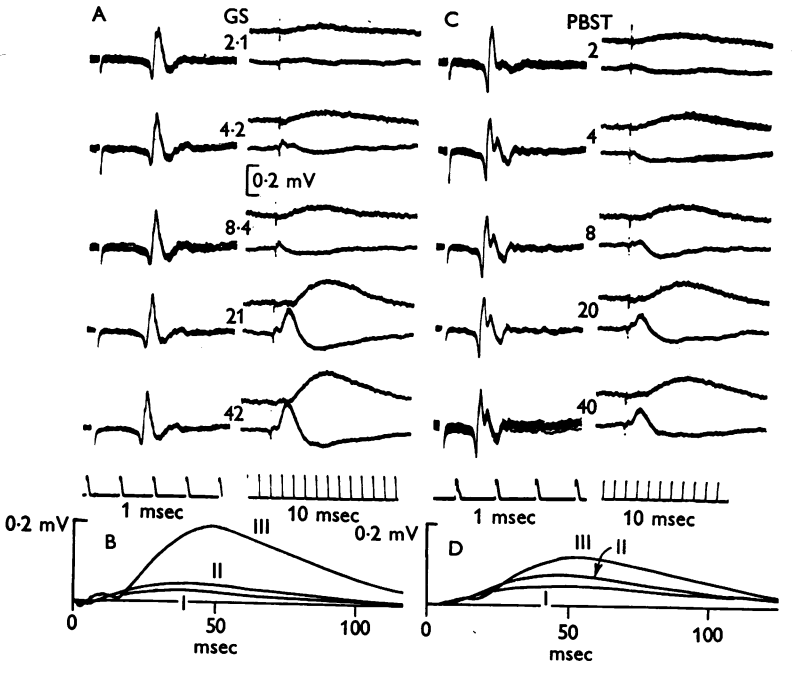

Fig. 2. Dorsal root potentials generated by single afferent volleys of increasing strength in muscle afferents. In A the right-hand column shows in the upper trace the DRP recorded from the most caudal rootlet of L 6 dorsal root and in the lower trace the cord dorsum surface potential recorded in the vicinity of this rootlet. The left-hand column shows the same surface potential taken with a much faster sweep in order to display spike potentials of the afferent volleys. From above downwards the numbers indicate strengths of stimulation relative to threshold strength. In B are superimposed enlarged traces of the DRPs generated by stimuli maximal for Group I, Group II and Group III (2·1, 8·4 and 42 times threshold respectively) in order to allow comparison of amplitude and time course. C and D correspond to A and B using PBST instead of GS. The voltage calibration in A is for the DRP traces in A and C only. Time constant of the amplifiers was 1 sec for all slow recordings and 20 msec for the fast surface traces.

cutaneous afferents. However, the interaction experiments described in the following paper indicate that in producing the DRP there is an appreciable convergence of cutaneous impulses and of Groups I, II and III muscle afferent impulses on to the same primary afferent fibres, which presumably are largely cutaneous fibres.

Slow potentials generated in the spinal cord by afferent volleys

There has been frequent confirmation of the original observations of Gasser & Graham (1933) that an afferent volley in a dorsal root produces first a negative potential (N wave) of the cord dorsum (with respect to an indifferent lead) and a later positive potential (P wave). It has further been shown that cutaneous afferent volleys are particularly effective in generating these N and P waves (Brooks & Fuortes, 1952; Bernhard, 1952, 1953*a*, *b*; Bernhard & Widén, 1953; Austin & McCouch, 1955). However, there has been very little investigation of the potential fields within the spinal cord which correspond to the P waves, and which are of particular interest in this present investigation. Koketsu (1956*b*) illustrates a series of potentials recorded by a penetrating micro-electrode at various depths below the cord dorsum. The P wave is clearly seen at the surface; it decreases to zero by a depth of 1·4 mm; and there are traces of a reversed potential at depths of 2·1 mm and more. Coombs, Curtis & Landgren (1956) found that the P wave generated by a sural volley had a maximum at 0·8 mm depth, and that in the ventral horn there was a late negative wave having the same time course as the P wave. The depth at which reversal occurred was not specified.

Systematic investigation of the field potentials produced by cutaneous afferent volleys has shown that at a depth of about 1 mm below the cord dorsum the P wave reverses to a negative potential of comparable time course. In assessing the effect of depth on the P wave, it is necessary to measure it after the end of the N waves that are recorded from the dorsum of the cord, and which reverse to positive waves at depths of 2·2–3·2 mm (Coombs *et al.* 1956; Fernandez de Molina & Gray, 1957). As shown in the specimen records of Fig. 3, the slow negative potential reaches a maximum at a depth of about 1·2 to 1·6 mm. In order to construct a potential field diagram, records such as those of Fig. 3 have been made for a series of parallel tracks 0·25 mm apart. The amplitudes of the P waves (or of the reversed waves) have been measured at an interval of 40 msec after the afferent volley entered the cord so as to avoid interference by the initial waves. On the basis of these measurements the contour lines of a potential field diagram can be drawn as in Fig. 3, which has been related to the transverse section of the spinal cord by observing in a histological preparation the micro-electrode that was left in position in the most medial track.

It is seen that the maximal zones of positivity and negativity lie fairly close on each side of a zero-potential line that runs obliquely across the spinal cord, being more ventral medially than laterally. This reversal line lies approximately parallel to, but about 1 mm more dorsal than, the reversal line observed for the field potential which is generated by Group I afferent volleys from flexor muscles and which is attributed to the depolarization of Group I afferent fibres of all types of muscle (Eccles, Magni & Willis, 1962). The field potential generated by cutaneous volleys can be similarly accounted for by the flow of current produced when there is an active depolarization of the ventral ends of core-conductor elements that are oriented rather more obliquely than the electrode tracks in Fig. 3. The

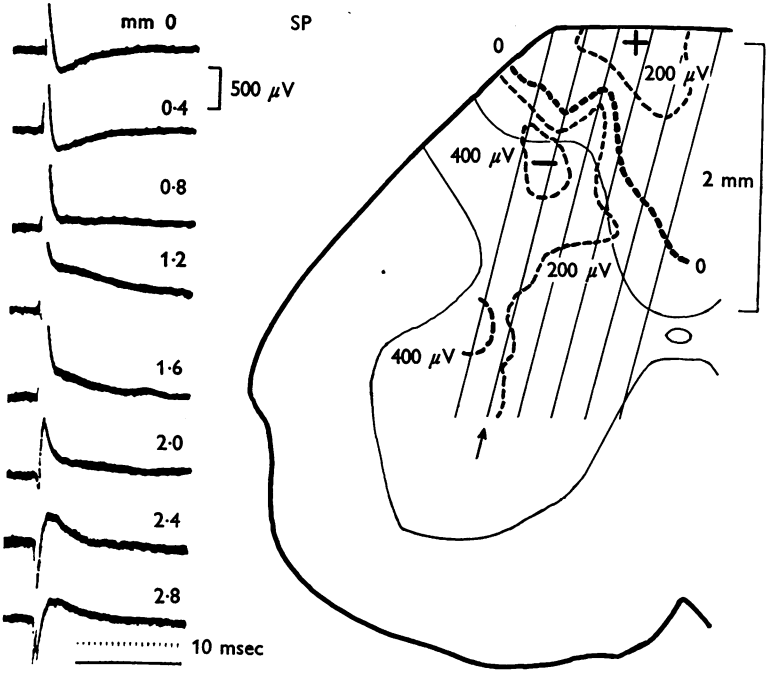

Fig. 3. Field potentials produced by single afferent volleys from SP nerve. The left-hand column shows specimen records of the field potentials generated by a stimulus to SP nerve of four times threshold strength at the indicated depths along the track marked by an arrow in the contour diagram. Records were made at each 0·2 mm, but only every second record is displayed. Upward deflexions signal negativity relative to the indifferent earth lead. The contour diagram is derived from measurements of a series of six tracks at 0·25 mm intervals, as shown by the oblique lines. The potentials were measured 40 msec after the volley in order to avoid distortion by focal synaptic potentials, but as a consequence the positive potentials in the cord dorsum were underestimated. After the last (most medial) track the micro-electrode was left in the spinal cord and its position was determined in the histological preparation.

only difference arises on account of the more dorsal site of the active depolarization produced by the cutaneous volleys. The required direction of the core conductors agrees closely with the direction of the collaterals of the cutaneous afferent fibres that enter the dorsal horn after branching from the parent fibres in the dorsal column (cf. Fig. 9). Preliminary investigations on the field potentials generated by high-threshold muscle afferent volleys show that their field potentials are comparable with those of Fig. 3.

The interneuronal pathways concerned in primary afferent depolarization

In the introduction an account has been given of the evidence leading to the postulate that the DRP is generated by the action of interneuronal pathways. However, very little is known about these postulated interneurones. Before attempting to identify such interneurones it is necessary to specify their expected properties. There is such diversity in the responses of the interneurones in the spinal cord that it is also necessary to attempt to arrange them into functional systems.

Investigations on the action of afferent volleys both indirectly on motoneurones via interneuronal pathways and on the cells of origin of ascending tracts have led to the conclusion that cutaneous and joint afferent fibres as well as Group II and III afferent fibres from muscles share in a diversity of central actions: actions through interneuronal pathways to evoke the discharge of impulses to flexor muscles, the flexor reflex (Lloyd, 1943; Eccles & Lundberg, 1959*a*, *b*); the discharge of impulses up several distinct pathways in the dorsolateral funiculus of the same side (Holmqvist, Lundberg & Oscarsson, 1956, 1960; Oscarsson, 1958; Lundberg & Oscarsson, 1960, 1961); the discharge of impulses up pathways in the ventrolateral funiculi of both sides (Oscarsson, 1958; Holmqvist *et al.* 1960); the inhibition of the ventral spinocerebellar tract cells of the same side (Oscarsson, 1957; Eccles, Hubbard & Oscarsson, 1961). Hence the generic term, flexor reflex afferents (FRA), has been applied to this diverse assortment of primary afferent fibres (Eccles & Lundberg, 1959*a*; Holmqvist *et al.* 1960; Holmqvist & Lundberg, 1961). It can be assumed that the FRA excite a specific interneuronal system. The flexor reflex is one of the manifestations of activation of this system. There is now much evidence (Eccles, Kostyuk & Schmidt, 1962; Eccles, Schmidt & Willis, unpublished observations) that depolarization of cutaneous afferent fibres also occurs when this system is activated (see, e.g. Figs. 1, 2).

By contrast the Group Ia and Ib afferent fibres from muscles form a distinct system when defined in terms of the depolarizing action on Group I afferent fibres of muscles, for this action is uniquely exerted by the Group I fibres from muscles, particularly from flexor muscles, the

aggregate depolarization produced by cutaneous volleys being only about 5% of that from muscle volleys (Eccles, Kozak & Magni, 1961; Eccles, Magni & Willis, 1962).

However, it is now known that the FRA system of primary afferent fibres is also very effectively depolarized by the Group I system from muscle (Eccles, Kostyuk & Schmidt, 1962; Eccles, Schmidt & Willis, unpublished observations), though probably via an independent interneuronal pathway. Thus it can be assumed provisionally that two distinct interneuronal systems are responsible for primary afferent depolarization. Group I muscle afferents are depolarized only from the system activated by Group I muscle impulses, while the cutaneous fibres and possibly the other fibres of the FRA system are depolarized by both systems of interneurones, the FRA system and the Group I muscle system.

In the following paper (Eccles, Kostyuk & Schmidt, 1962), evidence will be presented which suggests that these two systems are virtually independent and separately converge on to the FRA fibres. The aim of the present investigation is to search for interneurones that can be classified as belonging to the one or other system by virtue of the fields from which they receive their synaptic excitation.

Cells on the interneuronal pathway activated by FRA fibres. The first relay cells have already been extensively described and illustrated, belonging as they do to the type C of interneurones (Hunt & Kuno, 1959; Wall, 1959, 1960; Kostyuk, 1959, 1960; Eccles, Eccles & Lundberg, 1960; Armett, Gray & Palmer, 1961). In addition to monosynaptic activation by low-threshold cutaneous fibres it was also reported that type C neurones were often activated by high-threshold muscle afferents, but not by those of Group I. Possibly both the two subtypes, CT (the ipsilateral tract cells), and CN (the interneurones) could be the first relay cells of the FRA pathway giving primary afferent depolarization; the axons of the tract cells may give off collaterals, which have connexions similar to the CN cells. Both types of C cells are remarkable for their rapid repetitive responses to single cutaneous volleys. There have been 31 type C cells in the present series, which are additional to the 33 previously described (Eccles *et al.* 1960). Figure 4 shows responses of a C type cell to volleys produced by various strengths of stimulation of the superficial peroneal nerve. With stimuli of $1{\cdot}35T$ or stronger the spike responses were followed by small irregular EPSPs, which signal delayed excitatory synaptic actions (see Hunt & Kuno, 1959; Wall, 1959). With stimuli of several times threshold strength much of this delay is explicable by the longer conduction time of the high-threshold afferent fibres, but it seems likely that relay through interneuronal pathways also is a contributory factor. Possibly the very delayed responses of C type cells that are evoked by high-threshold muscle

afferents (see Eccles *et al.* 1960) are also due to interneuronal relays as well as to the long conduction time.

Since the central latency for the depolarization of cutaneous afferent fibres is usually 2–3 msec (Koketsu, 1956*b*; Eccles & Krnjević, 1959*a*) it would be expected that there would be at least two interneurones in serial order on the central pathway, i.e. that the C neurones would activate another set of interneurones which we may call D neurones, and that these in turn would cause the primary afferent depolarization (PAD). In an

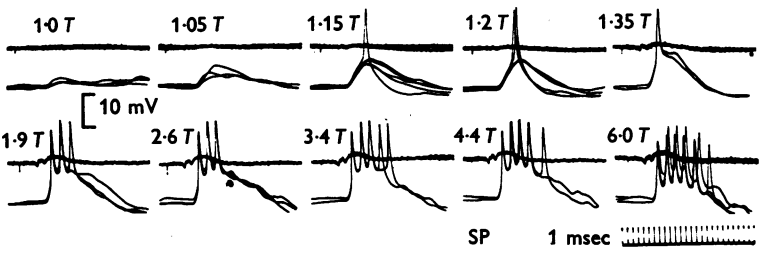

Fig. 4. Monosynaptic excitatory post-synaptic potentials (EPSPs) and spikes of a C type interneurone (depth 2·3 mm) produced by single volleys of increasing size in SP nerve. The lower traces show the intracellular records, the upper ones the cord dorsum potentials recorded at L 7 segmental level. Stimulus strength (relative to threshold as unity) is indicated for each record. Voltage calibration is for intracellular recording only. The resting potential was − 60 mV. Each record is formed by the superposition of several faint traces.

earlier investigation (Eccles *et al.* 1960) it was reported that almost 30 interneurones could not be classified into the A, B or C types because they were not monosynaptically activated by volleys in any of the muscle or cutaneous nerves prepared for stimulation. In the present series of almost 100 interneurones there have been 32 in this category. Seven of them exhibited properties that would be expected for the D neurones producing the PAD of cutaneous afferent fibres; they were strongly excited by volleys in all three cutaneous nerves (SU, PT and SP) and also by Group II and III impulses from several muscle nerves. Examples are given in Figs. 5 and 6.

The neurone illustrated in Fig. 5 gave repetitive discharges in response to each of the three cutaneous afferent volleys, but the central latencies were always too long for monosynaptic activation, 1·8 msec for the PT volley and 2·3 msec for both the SP and SU volleys. Furthermore, when stimulated at Group II strength every muscle nerve also produced a discharge with long latency, the briefest being 2 msec for gastrocnemius-soleus. It is evident that interneuronal discharges with the temporal characteristics of those in Fig. 5 would be ideally suited to produce a PAD having the observed latency of 2–3 msec and a time to summit

of 7–20 msec (Fig. 1; Koketsu, 1956*b*; Eccles & Krnjević, 1959*a*). The slow time course of decay requires further consideration.

Figure 6 gives another example of a D type cell with properties appropriate for the cutaneous PAD pathway. It is remarkable for the extremely high rate of discharge, up to 1250/sec, in response to single volleys from cutaneous nerves. Despite this very intense stimulation the central latency of the first discharge was never below 1·5 msec for the PT nerve and 2·0 msec for the SU and SP nerves, which is sufficiently long for disynaptic activation through such powerful pathways. The cell of Fig. 6

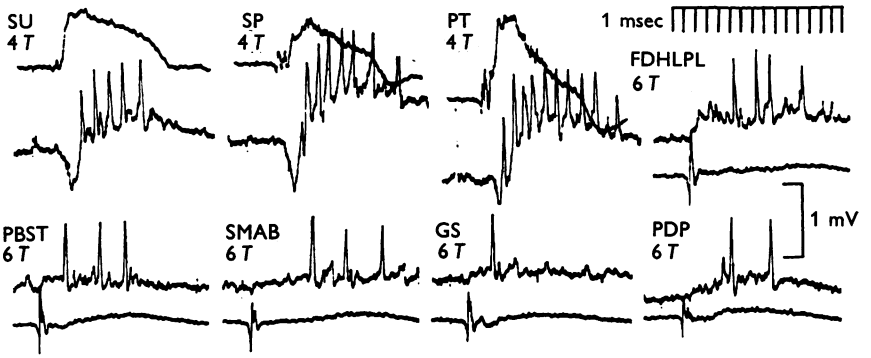

Fig. 5. Extracellular recording from a D type interneurone (depth 2·5 mm) activated by single afferent volleys in cutaneous and muscle nerves. The upper traces in the first three records (SU, SP and PT) and the lower traces in the other records are the cord dorsum potentials recorded at L 7 segmental level. The nerve stimulated and the stimulus strength relative to threshold strength is given for each record. Voltage calibration is for micro-electrode recordings only.

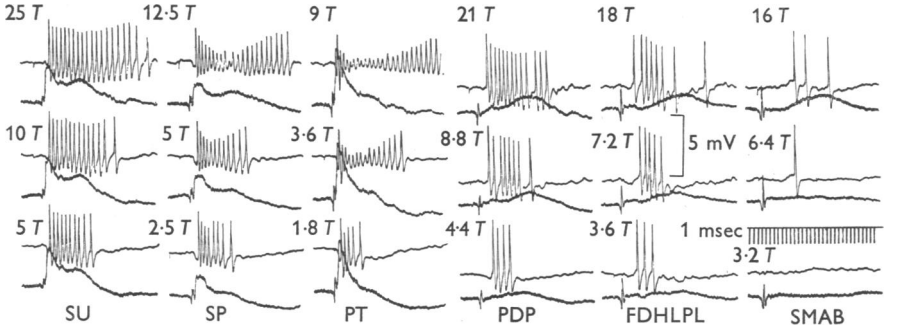

Fig. 6. Extracellular recording (upper traces) from a D type interneurone (depth 2·5 mm) activated by single afferent volleys in cutaneous and muscle nerves. The lower traces are the cord dorsum potentials recorded at L 7 segmental level. The nerve stimulated is indicated below each column, the stimulus strength relative to threshold strength is given for each record, there being increasing strength from below upwards. Voltage calibration is for upper traces only.

was also remarkable for the intensity of activation from Group II and III volleys from several muscle nerves, particularly from PDP and FDHL-PL. There was no activation from any of the Group I muscle afferent volleys; and even a Group II volley from SMAB nerve evoked only a single discharge, while a GS Group II volley was ineffective.

Six of these seven D cells were at the same region in the base of the dorsal horn at a depth of 1·65–2·5 mm from the dorsal surface. The remaining one was at 3·15 mm, which is probably too deep for interneurones acting on the terminals of cutaneous afferent fibres. No interneurone or tract cell that was monosynaptically activated by cutaneous afferent fibres was deeper than 2·8 mm in the total of 64 (Eccles *et al.* 1960; and the present paper), and only two were deeper than 2·5 mm. There is good agreement with Armett *et al.* (1961), who found that the deepest C type cell in a total of over 30 was at 2·5 mm, at the L6 level. A similar location has been observed by Wall (1960) for 45 C type cells in the lumbar enlargement. From these observations it can be concluded that the deepest penetration of the central terminals of cutaneous fibres is at 2·5 mm below the cord dorsum at the L6 and L7 segmental levels.

Cells on the interneuronal pathway activated by Group I muscle afferents. It has been shown that this depolarizing action is preponderatingly exerted by Group I afferent fibres from muscles, particularly from the physiological flexors of the knee, ankle and digits (Eccles, Magni & Willis, 1962). The central latency is compatible with at least two and possibly more interneurones on the pathway. Thus, when measured directly, the central latency for depolarization of Group I muscle afferents usually was as brief as 4 msec (Eccles, Magni & Willis, 1962). Correspondingly, the central latency of the DRR generated by this depolarization was never less than 4 msec, and usually was about 6 msec at normal body temperature (Eccles, Kozak & Magni, 1961).

Presumably the first synaptic relay would be from the Group I afferent fibres from muscle on to the A and B cells of the intermediate nucleus, for these are the only interneurones exhibiting monosynaptic excitation (Eccles, Fatt & Landgren, 1956; Eccles *et al.* 1960). As yet specialized categories of these cells have not been recognized, though it is postulated that some are purely inhibitory cells concerned in the inhibition of motoneurones and doubtless of other neurones. It would be expected that the first relay cells on the pathway for the PAD of Group I muscle afferents would be activated by Group I volleys from PBST and PDP nerves; and in the present series the 30 cells of type A or B included 8 that were monosynaptically activated only by the Group I fibres of the PBST or PDP nerves. Responses of such specifically activated interneurones have already been illustrated (Eccles *et al.* 1960, Figs. 5 and 7A–F).

Several criteria should be satisfied by interneurones before it becomes likely that they occupy the second or later places of the serial order in the polysynaptic PAD pathway of Group I muscle afferents. First, they must be specifically activated by the Group I volleys from flexor muscles (PDP or PBST) and not from extensor muscles, and the latent period of activation must be too long to be monosynaptic. Secondly, they must not be activated to any appreciable extent by Group II or III afferent impulses from muscles or by afferent volleys from cutaneous nerves. Thirdly, prolonged tetanization of the PBST or PDP nerves must evoke continued discharge of these interneurones, though not necessarily at the same frequency as at the onset. Five of the 32 type D interneurones satisfied these rather rigorous criteria, though in one there was an appreciable Group II excitatory action from PBST in addition to the Group I action. All five were at a depth of 2·0–2·4 mm.

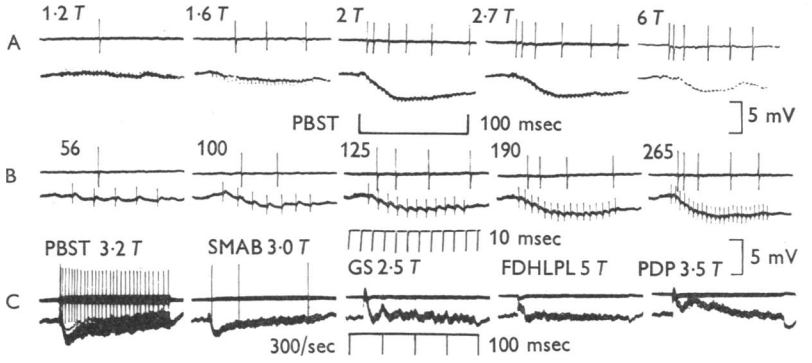

Fig. 7. Extracellular recording (upper traces) from a D type interneurone (depth 2·15 mm). The lower traces are the cord dorsum potentials at L 7 segmental level. A shows the response to tetanic stimulation (265/sec) of PBST nerve with stimulus strengths given relative to threshold. In B the stimulus strength to PBST was kept constant at 2·15 *T*, just maximal for Group I, and various tetanus frequencies were employed: numbers show frequencies in c/s. C shows the responses to tetanic stimulation (300/sec) of different muscle nerves at a much slower sweep speed. The nerve and the stimulus strength relative to threshold are indicated on each record. Upper voltage calibration is for upper trace in A; lower calibration is for upper traces in B and C.

The interneurone illustrated in Fig. 7 was excited polysynaptically only from PBST and to a very small extent from SMAB. With repetitive stimulation of the PBST nerve at 265/sec in Fig. 7A there was a single response at the low strength of 1·2 *T*, and with increasing stimulus strength there was an increase in the number of responses until the stimulus was maximal for Group I at 2·0 *T*. Further increase to a stimulus strength of 6 *T*. which would be almost maximal for Group II, caused virtually no

increase in the number or frequency of the responses. In Fig. 7 B increasing the frequency of stimulation at strengths supramaximal for Group I (2·15 *T*) gave an increase in the number of discharges which corresponded closely to the observed effect of frequency on the intensity of the EPSP depression that is attributable to the presynaptic depolarization (Eccles, Eccles & Magni, 1961, Fig. 8). It is further shown in Fig. 7 C that the interneurone discharged throughout a PBST tetanus at 300/sec for 0·34 sec, the discharge reaching a steady frequency of about 80/sec during the latter half of the stimulation, which corresponds to observations on the level of EPSP depression that is maintained during prolonged stimulation (Eccles, Eccles & Magni, 1961, Fig. 7). It is seen also in C that a few discharges were evoked by a SMAB tetanus, while prolonged tetanization of other muscle nerves did not evoke a single discharge.

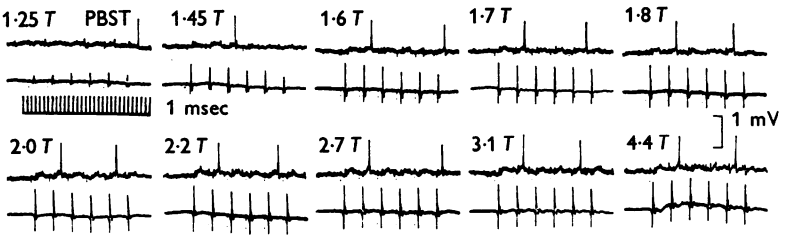

Fig. 8. Extracellular recording (upper traces) from a D type interneurone (depth 2·3 mm) activated by tetanic afferent volleys (220/sec) of increasing strength in the PBST nerve. The stimulus strengths relative to threshold are given for each record. The lower traces are the cord dorsum potentials recorded at L7 segmental level. Voltage calibration is for upper traces only.

It has frequently been observed that two PBST Group I volleys produced a PAD that was much larger than double that produced by a single volley (Eccles, Magni & Willis, 1962, Figs. 1, 8, 9, 14). Correspondingly, D type cells activated by PBST volleys may be expected to exhibit temporal facilitation. This property is shown in Fig. 8, where there was progressive increase in the strength of repetitive stimulation at 220/sec. When the stimulation was at strength 1·6 *T*, the second volley excited a discharge with a latency as brief as 1·5 msec, but the first volley failed even with the strongest stimulation (4·4 *T*). At this strength most of the Group II fibres would be excited, yet the two discharges corresponded exactly to those evoked by a stimulus just maximal for Group I (1·8 *T*). With stimuli of 1·25 and 1·45 *T* it is seen that summation of more than two volleys is required to produce a discharge.

DISCUSSION

Figure 9 gives diagrammatically the postulated interneuronal pathway concerned in the depolarization of cutaneous afferent fibres by volleys in two types of FRA afferents, the alpha cutaneous fibres and Group II afferent fibres from muscle. The cutaneous afferent volley excites type C interneurones at the base of the dorsal horn, and these in turn activate D type interneurones that make synaptic connexions with the central terminals of primary afferent fibres. The foci of active depolarization so

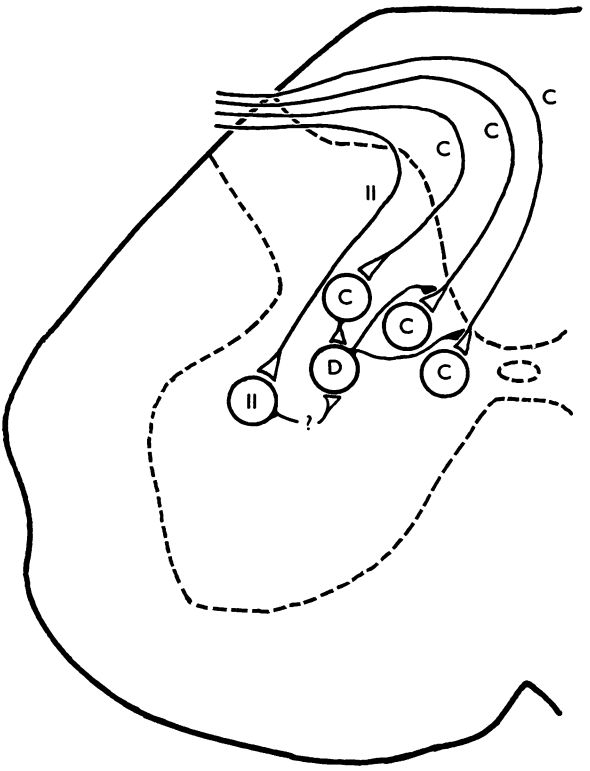

Fig. 9. Schematic diagram illustrating the suggested pathway for presynaptic inhibitory action on a cutaneous primary afferent fibre. Three cutaneous afferent fibres (C) and one muscle afferent fibre Group II (II) with their monosynaptic endings on interneurones are shown. D symbolizes the interneurone which has presynaptic connexions on cutaneous primary afferent fibres. For further explanation see text.

produced on cutaneous fibres at a depth of about 2 mm would cause the flow of current giving the potential field and line of reversal illustrated in Fig. 3. Doubtless the C and D type interneurones have also more complex paths of activation than the simplest possible pathways in the diagram.

The central connexions of a Group II afferent fibre from muscle are also partly shown in Fig. 9, but the path to the D cell is interrupted by a '?' in order to indicate the uncertainty. So far only a very few cells have been identified as being monosynaptically activated by Group II volleys. A similar uncertainty obtains for the Group III pathway, but again it has been shown to activate the same D cells that are activated by Group II and cutaneous impulses (Fig. 6). Though in Fig. 9 synaptic endings are shown on the collaterals of primary afferent fibres near their terminations in the base of the dorsal horn, no histological evidence can be adduced in respect either of the location of these synapses, or indeed for their very existence.

Figure 10 likewise gives diagrammatically the postulated interneuronal pathway concerned in the depolarization of Group I afferent fibres from muscle. In the diagram there are two Group Ia fibres and one Group Ib. The Group Ib and one Group Ia fibre are shown making synaptic contacts with a B cell and an A cell, respectively, in the intermediate nucleus, which in turn have synapses on a D cell that sends branches to establish synaptic contacts on the central terminals of the other Ia fibre in the motoneuronal nucleus. Active depolarization at this zone is indicated by the field potential (Eccles, Magni & Willis, 1962, Fig. 7B). As in Fig. 9, the connexions illustrated in Fig. 10 are the simplest possible. In fact the D cell would have synaptic endings on Ib afferent fibres, and on primary afferent fibres of cutaneous nerves and possibly on the other FRA fibres.

The D type interneurones that have properties appropriate for interneurones on the pathway activated by Group I fibres from muscle (Figs. 7, 8) appear to be very different from those that are likely to be D type cells on the pathway from the FRA afferents (Figs. 5, 6). However, much more investigation is required before any conclusions can be reached on the properties and on the locations of the interneurones of the two systems that are concerned in producing PADs of cutaneous fibres and Group I fibres from muscle. At least it has been shown that there are in the spinal cord interneurones with properties that would be expected for interneurones of these two systems. Both systems are concerned with presynaptic inhibition. The presynaptic inhibitory action of the Group I system on Group I primary afferents has already been reported (Frank & Fuortes, 1957; Frank, 1959; Eccles, Eccles & Magni, 1961). The presynaptic inhibitory action on the primary afferents of the FRA system will be described in the following paper (Eccles, Kostyuk & Schmidt, 1962).

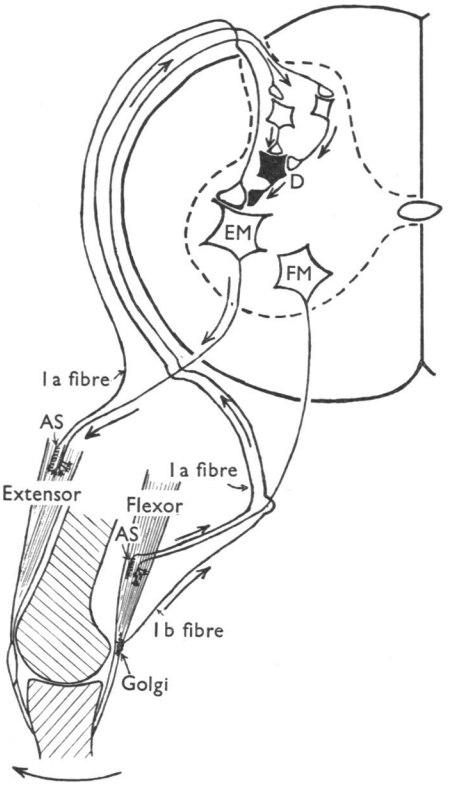

Fig. 10. Schematic diagram illustrating the suggested pathways for presynaptic inhibitory action on a primary afferent fibre (Ia fibre) of an extensor muscle by afferent volleys in Ia (from annulospiral (AS) endings on muscle spindles) and Ib (from Golgi tendon organs) afferent fibres of a flexor muscle. EM and FM symbolize extensor and flexor motoneurones, while D is the interneurone that has presynaptic connexions on primary muscle afferent fibres. For further explanation see text.

SUMMARY

1. An investigation has been made into the pathways that produce depolarization of primary afferent fibres in the lumbosacral region of the cat spinal cord.

2. Tests by graded stimulation of peripheral nerves have shown that the dorsal root potentials (DRPs) produced by cutaneous volleys are largely due to the alpha group, the contribution from the delta group being small and late. With most muscles Group II and III afferent volleys were particularly effective in generating DRPs, but Group I volleys from flexor muscles were also effective.

3. Corresponding to the DRP there are prolonged potential waves in the spinal cord, positive dorsally, negative ventrally. The contour diagram conforms with a field potential produced by an active depolarization of the cutaneous fibres in the spinal cord at a depth of 1·2 to 2·0 mm.

4. In addition to the interneurones monosynaptically excited by one or other type of afferent volley, there are interneurones (D type interneurones) in the dorsal horn which are exclusively excited through one or more interneurones by cutaneous volleys and high-threshold muscle volleys. Their properties fit the requirements expected for interneurones lying on the pathways producing depolarization of cutaneous afferent fibres.

5. A second group of D type interneurones has been found which are specifically activated by Group I volleys from flexor muscles, and not by cutaneous or high-threshold muscle volleys. In every respect these interneurones have properties which indicate that they occupy second or later places in the pathway by which Group I afferent volleys from muscle depolarize primary afferent fibres.

6. These findings support the postulate that two separate pathways are concerned in producing depolarization of primary afferent fibres.

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