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ANTINOCICEPTIVE EFFECTS OF DORSAL COLUMN STIMULATION IN THE RAT: INVOLVEMENT OF THE ANTERIOR PRETECTAL NUCLEUS

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SUMMARY

1. The effects of stimulating A fibres in the dorsal columns on the responses of dorsal horn neurones to intense cutaneous stimuli were studied in the rat anaesthetized with urethane.

2. Multireceptive cells deep in the lumbar dorsal horn were excited for 5–10 ms by dorsal column stimulation and subsequently responses to noxiously hot water placed on the cutaneous receptive field were reduced for the following 4–5 min. Seven of the cells studied projected to the brain via the contralateral anterolateral funiculus.

3. If the discharge of the multireceptive neurones was raised by ionophoretic application of DL-homocysteic acid, a brief period of inhibition lasting for 100–150 ms was seen following a single stimulus to the dorsal columns. Studies were conducted to determine if this brief inhibition could account for the long-lasting inhibition of responses to high-threshold stimuli.

4. Dorsal columns were transected at cervical levels. Stimulation caudal to the transection evoked only the brief excitation and subsequent inhibition for 100–150 ms. No long-lasting inhibition of high-threshold cutaneous afferent input was seen.

5. Stimulation of the dorsal columns rostral to transection did not evoke the brief excitation or inhibition of multireceptive dorsal horn neurones. However, the 4–5 min inhibition of responses to high-threshold cutaneous stimuli was present.

6. The long-lasting inhibition of responses to high-threshold stimuli by dorsal column stimulation was blocked by microinjection of γ-aminobutyric acid into the anterior pretectal nucleus (APTN) but not by microinjections into adjacent areas of the brain.

7. Ipsilateral lesions of the dorsolateral funiculus at the cervical level also blocked the long-lasting inhibitory effects of dorsal column stimulation.

8. It is concluded that the brief excitation and inhibition of multireceptive dorsal horn neurones is due to antidromic action potentials passing caudally in the dorsal columns to activate spinal segmental mechanisms. The longer-lasting inhibition of responses to high-threshold cutaneous stimuli is due to action potentials ascending in the dorsal columns to activate cells in the APTN which in turn activate a descending inhibition mediated by the dorsolateral funiculus.

INTRODUCTION

Activation of A fibres in the dorsal columns causes antinociception in rats (Saade, Tabet, Soueidan, Bitar, Atweh & Jabbur, 1986), cats (Lindblom, Tapper & Wiesenfeld, 1977) and primates (Foreman, Beall, Applebaum, Coulter & Willis, 1976), and analgesia in man (Shealy, Mortimer & Reswick, 1967; Nashold & Friedman, 1972). The physiological effects of dorsal column stimulation and the anatomy of the pathways activated are still a matter for speculation. It is known that dorsal column stimulation sets up antidromic action potentials which descend to the spinal cord (Foreman *et al.* 1976; Lindblom *et al.* 1977) but it has become apparent that many of the effects of dorsal column stimulation, including perhaps the clinically most useful, are due to an ascending influence on the brain (Lindblom *et al.* 1977; Saade, Tabet, Banna, Atweh & Jabbur, 1985).

The anterior pretectal nuclei (APTNs) are bilateral structures on the diencephalic–mesencephalic border. The APTNs receive a crossed excitatory input from the gracile nuclei (Rees & Roberts, 1989*a*). Electrical stimulation of the APTN and microinjection of the excitatory amino acid DL-homocysteic acid (DLH) into the APTN both cause antinociception in rats (Roberts & Rees, 1986; Rees, Roberts & Sherwood, 1987). Stimulation of the contralateral gracile fasciculus of the dorsal columns drives cells in the APTN (Rees & Roberts, 1989*a*). These observations raise the possibility that the ascending effects of dorsal column stimulation may be relayed via the APTN. This possibility has been investigated. Preliminary accounts of these data have been reported to the Physiological Society (Rees & Roberts, 1989*b*).

METHODS

Experiments were conducted upon male Wistar rats (270–290 g) which were anaesthetized with urethane (1·2 g/kg I.P.). Tracheal and carotid cannulae were inserted and the animals placed into a stereotaxic frame. Blood pressure and rectal temperature were recorded throughout the experiment and maintained within physiological limits. The cervical cord was exposed by laminectomy between C2 and C4 and the dura reflected and pinned. The arachnoid was removed with a glass probe and the cord covered with warm mineral oil. The spinal vertebrae were clamped at the lumbar enlargement and laminectomy performed between L2 and S1. The lumbar cord was exposed as described for the cervical cord.

Three-barrelled microelectrodes with a tip diameter of less than 3 μm were used to record extracellularly the activity of neurones in the dorsal horn of the lumbar spinal cord. The barrels were filled with 4 M-NaCl, a 2% (w/v) solution of Pontamine Sky Blue dye in 0·5 M-sodium acetate and 0·2 M-DL-homocysteic acid. The electrical resistance of the recording barrel was 2–4 MΩ. Recordings of a neurone were displayed on oscilloscopes and at regular intervals permanent records of the action potentials were made. Studies were abandoned if there were any change in the amplitude, signal-to-noise ratio or shape of the action potential. The rate of discharge of the cell was recorded on a curvilinear pen-writing oscillograph.

During each experiment the dorsal columns were transected on the ipsilateral side at the level of C3. This was done using radio frequency diathermy with a very fine needle. The extent of each lesion was later determined histologically.

Recordings were made of dorsal horn neurones that responded to noxious hot water (54 °C) pumped onto the foot. These cells were all shown subsequently to be located deep in the spinal cord (laminae IV–VI) except for two cells which lay very superficially in the dorsal horn. All of the deep cells were multireceptive neurones responding to brush touch and light pressure as well as intense cutaneous stimuli. Only cells showing consistent and reproducible responses were studied. Bipolar silver-ball stimulating electrodes, with a ball diameter of 150 μm, were placed on the ipsilateral

cervical dorsal columns under microscopic control. Square-wave stimuli for 0·1 ms at 2 times A fibre threshold were applied at a frequency of 50 Hz for a period of 30 s. The effects of this stimulation were studied on the responses to intense cutaneous stimuli. The contralateral dorsal columns were then sectioned and the effects of stimulating both above and below a lesion were re-examined.

During each experiment a fine bipolar (200 μm) electrode was placed on the surface of the cervical cord in the region of the contralateral anterolateral funiculus (ALF). Attempts were then made to drive dorsal horn neurones antidromically to determine if the recorded cells projected to supraspinal sites via the ALF. Cells were identified as projection neurones if there was a constant latency between stimulus and recorded spike, if the recorded spike followed high-frequency stimulation (> 330 Hz), and if collision between antidromic and orthodromic spikes occurred. Multireceptive dorsal horn neurones projecting to the brain in the ALF are believing to be important to the perception of noxious stimuli (Mehler, 1974; Willis, Trevino, Coulter & Maunz, 1974).

In ten experiments a hole was drilled in the skull above the APTN, at stereotaxic co-ordinates: AP −4·5 and L +1·8 using the reference planes and incisor bar orientation of Paxinos & Watson (1982). A fine glass microinjection needle o.d. 70–90 μm (Azami, Llewelyn & Roberts, 1980) was then lowered into the APTN. The possibility that the APTN forms part of a supraspinal pathway which relays the antinociceptive effects of dorsal column stimulation was then examined. Stimulation was applied to the dorsal columns above the point of their transection. γ-Aminobutyric acid (GABA) was microinjected into the APTN to determine if this reduced the effectiveness of dorsal column stimulation; 0·5 μg GABA was microinjected over a 3 min period in a volume of 0·5 μl. At the end of these studies 0·5 μl Pontamine Sky Blue dye was microinjected into the APTN to allow histological verification of the injection site and to give some indication of the maximal extent of the affected tissue.

At the end of each experiment Pontamine Sky Blue was ejected ionophoretically from the recording electrode with 10 μA for 10 min and the animal was perfused with formal saline. The cord and/or the brain was removed and stored in formal saline. Later, 50 μm sections were cut and stained with Neutral Red for histological verification of the location of the dye spots.

RESULTS

Responses of multireceptive spinal neurones to dorsal column stimulation

The activity of multireceptive dorsal horn neurones was recorded with microelectrodes. These cells were identified by their distance from the dorsal surface of the spinal cord, by histological location of the Pontamine Sky Blue dye spot (which was determined after the experiments), and by the excitation of the cells by both high- and low-intensity cutaneous stimuli. Dorsal column stimulation usually resulted in excitation of these cells, the threshold stimulus intensity being very close to 0·2 V in all cases. It has been demonstrated (Rees & Roberts, 1989*a*) that this is the threshold voltage, with these electrodes in these preparations, for activation of A fibres. The latency to onset of multireceptive neurone discharge was 1–3 ms. In all subsequent studies, the dorsal column stimulus intensity was set at 2 times A fibre threshold.

Transient inhibition of multireceptive neurones by stimulation of the intact dorsal columns

Peristimulus time histograms (PSTHs) were used to analyse the response to single 0·1 ms square-wave pulses at 2 times A fibre threshold applied to the dorsal columns. At time 1–3 ms after the stimulus a single spike occurred. An example is shown in Fig. 1*A*. The time at which the stimulus was applied is marked by the arrow. The cumulative PSTH shows a brief period of excitation 2–3 ms following the stimuli.

The baseline firing rate of many of the multireceptive neurones recorded in the anaesthetized rat was low and it was difficult to identify brief periods of inhibition following dorsal column stimulation. To overcome this problem, the firing rate of the cell was raised by the ionophoretic application of the excitatory amino acid DL-homocysteic acid (DLH). Peristimulus time histograms obtained after the firing rate of the cell had been increased showed the excitation 1–3 ms following the stimulus. However, in these cells the excitation was followed by a period of inhibition lasting 100–150 ms. Examples are shown in Fig. 1*B–D*.

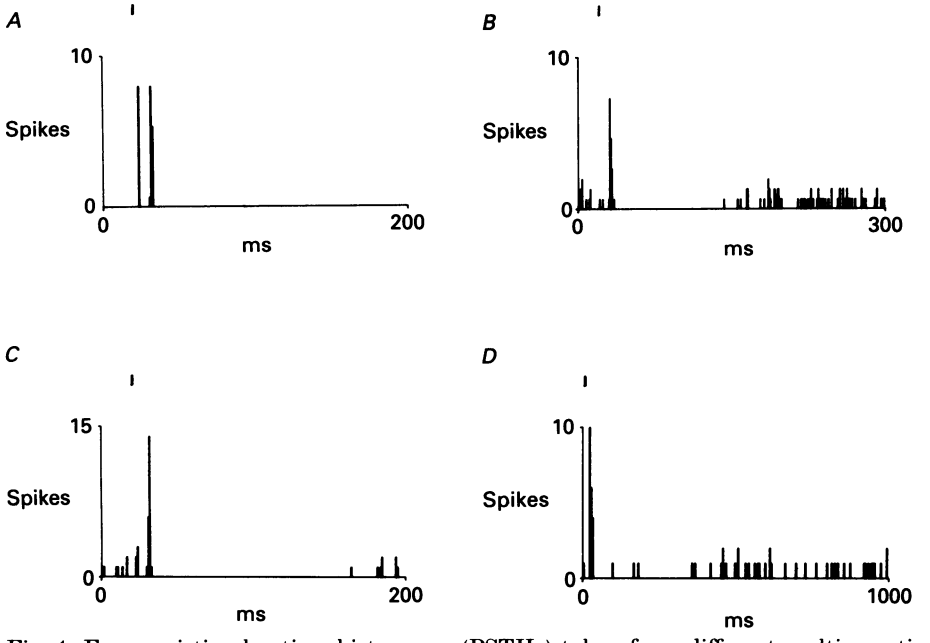

Fig. 1. Four peristimulus time histograms (PSTHs) taken from different multireceptive neurones. In each case the dorsal columns were stimulated at 20 ms with a single 0·1 ms pulse at 2 times A-fibre threshold. Each PSTH is the result of thirty trials. In *A* action potentials were recorded 2–3 ms post-stimulus. When the discharge rate of the recorded neurone was increased by ionophoretic application of DLH, as in *B–D*, a period of inhibition lasting 100–150 ms can be seen to follow the brief excitation.

Effects of stimulation of the intact dorsal columns on the responses of multireceptive neurones to intense cutaneous stimuli

Studies were made of thirty-four neurones in the deeper laminae of the dorsal horn (laminae IV, V and VI). With each cell, the greatest response was elicited by intense stimuli. The typical effect of stimulating the intact dorsal columns on the responses of multireceptive neurones to intense stimuli is illustrated in Fig. 2. Noxiously hot water applied to the foot reliably and reproducibly increased the firing rate of the multireceptive neurone. The discharge rate increased from 0 to 112 spikes s^{-1}. Following stimulation of the intact dorsal columns, at the point indicated by arrow 1, the noxious response was reduced by 51·8%. Subsequent responses were variable for the next 8 min. Inhibition of the response to intense cutaneous stimuli was

observed in each study (thirty-four) of a multireceptive neurone. The average inhibition was 46·3% and the average recovery time 4·6 min. Four of the cells were projection neurones with axons running in the contralateral ALF.

Effects of stimulating the intact dorsal columns on the responses of superficial dorsal horn neurones to intense stimuli

On two occasions recordings were made of neurones which were subsequently shown to be in the superficial dorsal horn. Both cells responded exclusively to intense

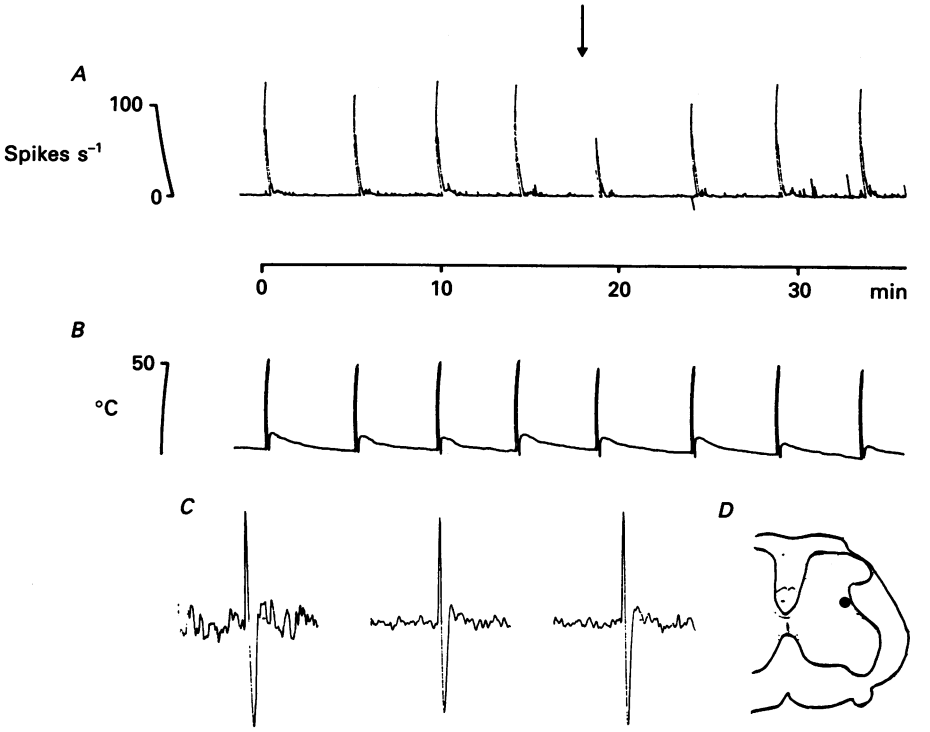

Fig. 2. The effect of electrical stimulation of the intact dorsal columns on the responses of a multireceptive dorsal horn neurone to noxious stimulation of the foot. *A* shows the discharge frequency of the cell: *B* shows the temperature of the receptive field recorded with a thermistor; *C* shows samples of the extracellularly recorded action potentials; *D* shows the deep location of the cell. At the arrow the dorsal columns were stimulated for 15 s. The responses to hot water were reduced to 50% for the next 8 min.

stimuli. Dorsal column stimulation did not excite these cells nor did it modify their responses to intense cutaneous stimuli. One example is illustrated in Fig. 3. The sample of recorded action potentials indicates that the signal-to-noise ratio was low, which probably reflects the relatively small size of superficial dorsal horn neurones. The lack of effect of dorsal column stimulation on these superficial cells in the dorsal horn is closely reminiscent of the lack of effects of APTN stimulation on these cells (Rees & Roberts, 1987).

It seemed unlikely that the transient inhibition of multireceptive neurones could account for the 4 min inhibition of the responses of these cells to intense cutaneous

stimuli. Attempts were made to determine whether these inhibitions were due to descending, spinal segmental effects of dorsal column stimulation or whether they resulted from ascending influences on supraspinal sites.

The effects of stimulating caudal to the site of a dorsal column transection

The dorsal columns were transected at the cervical level and stimulation applied below the lesion during the study of eight multireceptive neurones. Both transient

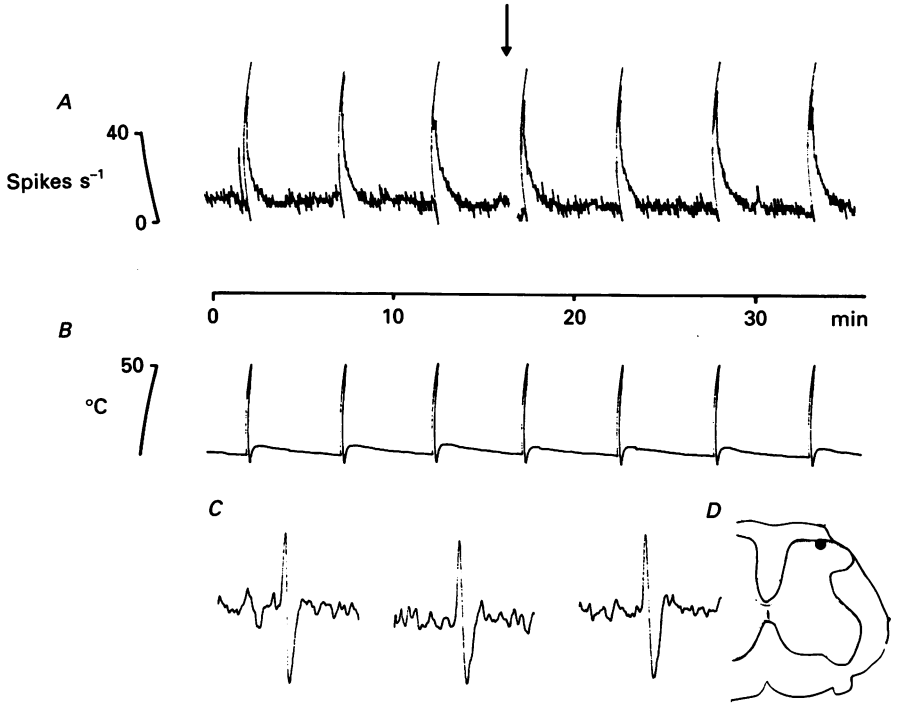

Fig. 3. The effect of electrical stimulation of the intact dorsal columns on the responses of a superficial dorsal horn neurone to noxious heating of the foot. *A* shows that the discharge rate of this neurone increased sharply when noxiously hot water was placed on the foot. At the arrow above the trace the dorsal columns were stimulated for 15 s without any effect on the response to noxious heat. *B*, *C* and *D* are as described in Fig. 2.

and longer-term effects of dorsal column stimulation were sought but only short-term inhibition was observed. Figure 4*A* illustrates the effects of a more prolonged period of stimulation of the dorsal columns on the DLH evoked firing of the cell. The box above the histogram indicates the time when the dorsal columns were stimulated, caudal to a dorsal column transection, at 2 times A fibre threshold for 30 s (0·1 ms square-wave pulses, 50 Hz). The discharge rate of the cell is clearly reduced throughout the period of stimulation. Recovery was seen rapidly when the stimulation was stopped. In the example illustrated the neuronal firing rate decreased from 30 to 18 spikes s^{-1}. The action potentials in Fig. 4*B* were recorded from the same cell during this study and show an increase in the extracellular spike amplitude during stimulation. This would be expected if the cell were hyperpolarized

during dorsal column stimulation. It is concluded that the transient inhibition of multireceptive neurones by dorsal column stimulation is due to spinal segmental mechanisms. The long-lasting inhibition of responses to intense cutaneous stimuli was not present during these studies and is therefore likely to be due to ascending influences on supraspinal sites. This possibility was examined by stimulating dorsal columns above the point of transection.

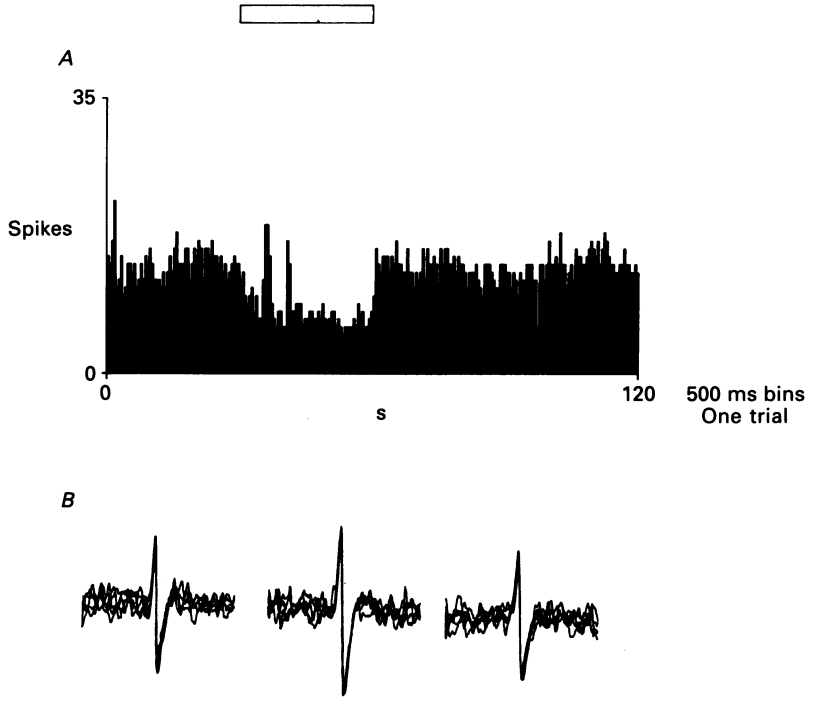

Fig. 4. The effect of electrical stimulation of the dorsal columns caudal to a dorsal column transection on the activity of a multireceptive dorsal horn neurone. *A* shows the discharge frequency of the cell which was increased by the sustained ionophoretic application of DLH. At the bar above the trace the dorsal columns were stimulated for 30 s. The discharge rate of the cell was reduced throughout the period of stimulation. *B* shows samples of extracellularly recorded action potentials taken before, during and after the period of stimulation. Each action potential is the result of five superimposed samples taken at random. The samples taken during stimulation show an increase in action potential amplitude.

Effects of stimulation rostral to the dorsal column transection

The effects of stimulating rostral to the dorsal column transection were studied on eight neurones. On each occasion stimulation resulted in inhibition of the response to noxiously hot water applied to the cutaneous receptive field. Responses evoked 30 s after the stimulation were inhibited by an average of 42·8%. Recovery of the response took up to 20 min. A typical example is shown in Fig. 5. Arrow 1 indicates a 15 s period of dorsal column stimulation below a dorsal column transection. The subsequent response to hot water was little affected. However, when the stimulating

electrode was placed rostral to the spinal transection it can be seen that the response shortly after stimulation was attenuated and that the response was variable for a period of 10 min. These results indicate that the long-lasting inhibition of the response to intense stimuli is due to activity in ascending dorsal column fibres which presumably activate supraspinal mechanisms.

As stimulation of the dorsal columns potently excites cells in the APTN (Rees & Roberts, 1989*a*) we have examined the possibility that the APTN is involved in the antinociceptive effects of dorsal column stimulation.

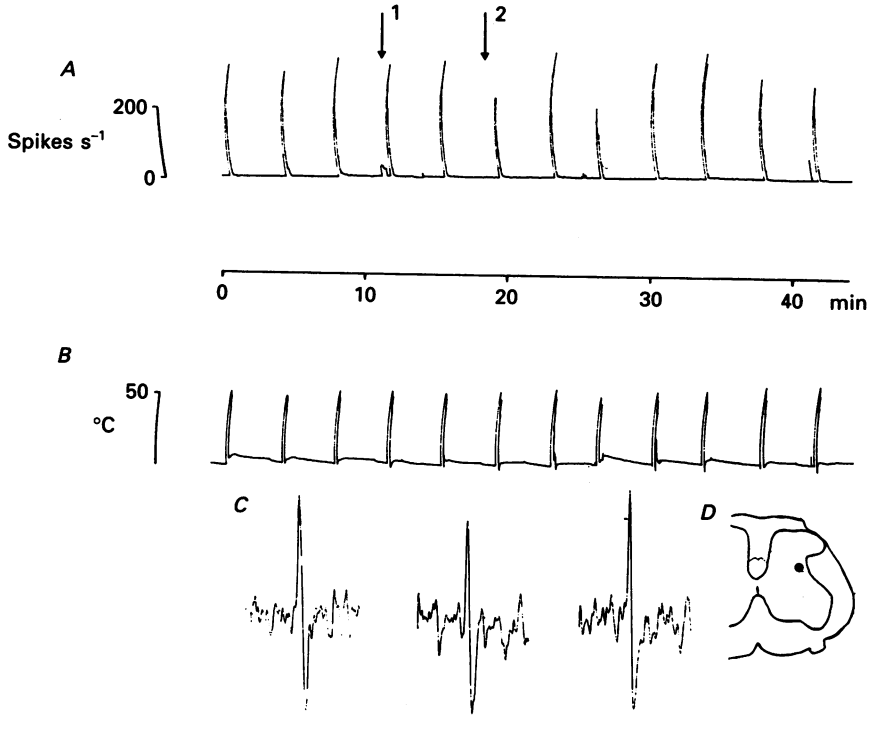

Fig. 5. The effects of stimulating the dorsal columns both below and above a dorsal column lesion on the high-threshold responses of a multireceptive neurone. *A* shows the discharge rate of the cell. *B*, *C* and *D* are as described in Fig. 2. At arrow 1 the dorsal columns were stimulated for 15 s below a dorsal column transection. The response to hot water was not affected by the stimulation. At arrow 2 the dorsal columns were stimulated above the dorsal column transection. The subsequent response to hot water was reduced to 60% and remained variable for the following 10 min.

The effects of microinjecting GABA into the APTN on the antinociceptive effects of stimulating ascending dorsal column fibres

Studies were made of ten multireceptive neurones in which responses to intense cutaneous stimuli were inhibited by stimulation of ascending dorsal column fibres. After 5 μg GABA was microinjected unilaterally in a volume of 0·5 μl into the contralateral APTN the effects of dorsal column stimulation were redetermined. In each of the six studies in which the injection was shown subsequently to have been

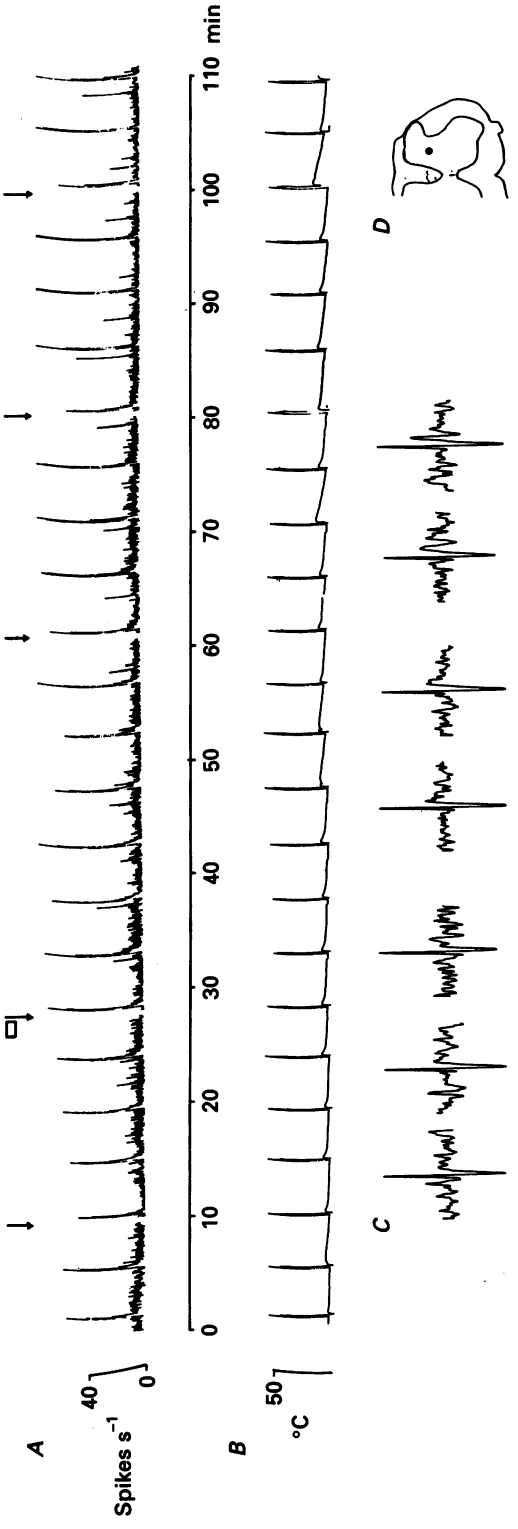

Fig. 6. The effects of dorsal column stimulation on the responses of a multireceptive neurone before and after microinjection of GABA into the APTN. The rate-meter trace *A* shows a regular discharge of the cell to hot water. The arrows above the trace indicate 15 s periods of dorsal column stimulation. The first period of dorsal column stimulation reduced the response to hot water. During the period indicated by the bar 0·5 μg GABA was microinjected into the APTN. The following two stimulations had little effect on the response of this neurone to hot water. After 50 min the inhibitory effects of the dorsal column stimulation had recovered. *B*, *C* and *D* are as described in Fig. 2.

made into the APTN, microinjection of GABA blocked the inhibitory effects of stimulating the dorsal columns. Tests were made every 20 min to determine if the inhibitory effects of dorsal column stimulation were recovered. The results are illustrated by Fig. 6 which is a continuous rate-meter record of a multireceptive

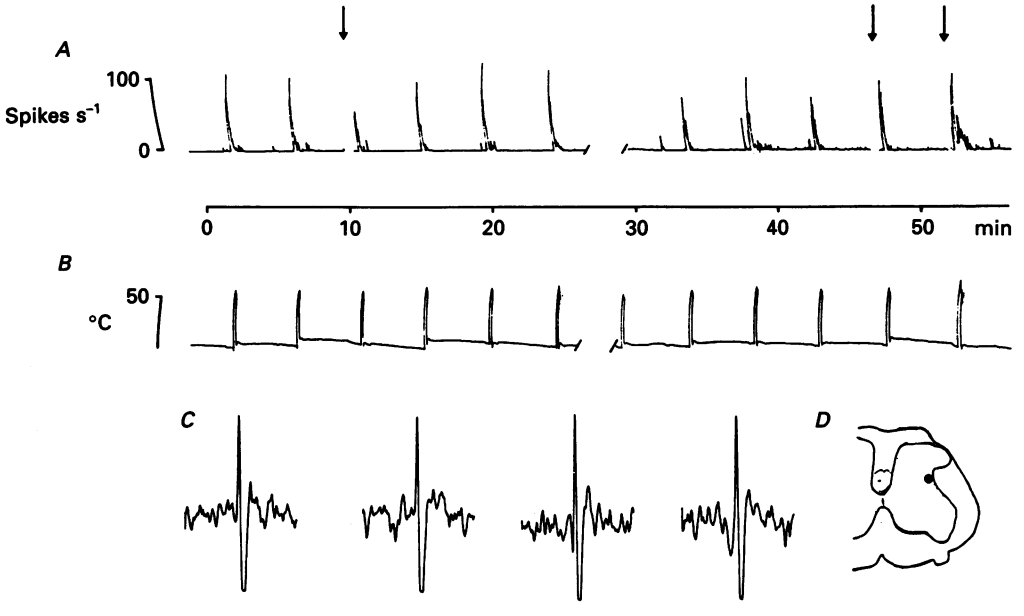

Fig. 7. The effect of stimulating the dorsal columns on the responses to hot water of a multireceptive neurone before and after section of DLF. *A* shows the discharge rate of the cell; *B*, *C* and *D* are as described in Fig. 2. The cell discharged briskly in response to noxiously hot water placed on the foot. At the first arrow the dorsal column was stimulated for 15 s. The response to hot water was reduced by 60%. At the break in the rate-meter record the DLF was lesioned with diathermy. Subsequent stimulations were without effect.

dorsal horn neurone, responding to noxiously hot water applied to the foot. At the time indicated by the first arrow the dorsal column fibres were stimulated above a dorsal column lesion. The subsequent response to hot water was reduced by 17·7%. During the period indicated by the bar, 0·5 μg GABA was microinjected into the APTN. The ascending dorsal column fibres were again stimulated at the second arrow but the subsequent response to hot water was unaffected. Stimulation of the dorsal columns 50 min after the GABA injection demonstrated the inhibition of the response to hot water had been recovered.

In four studies histological verification of the injection site revealed that the GABA had been injected more than 0·5 mm away from the APTN. Injections at these sites had little or no influence on the inhibitory affects of dorsal column stimulation.

Effects of lesions of the dorsolateral funiculus on the inhibition caused by stimulating the dorsal columns

The dorsolateral funiculus (DLF) contains descending inhibitory fibres from many brain stem and mid-brain areas including the a polysynaptic projection from APTN

(Rees & Roberts, 1987). If, as indicated by the previous experiment, the APTN is a central relay of the ascending effects of dorsal column stimulation, section of the DLF may abolish the effects without affecting the purely spinal segmental component. The DLF was sectioned unilaterally at the level C3 in five animals, showing that the lesions did not invade dorsal columns and only the longer-term effects of dorsal column stimulation were abolished. In each animal the transient inhibition, presumably due to segmental influences, was unaffected. Figure 7 illustrates the effects of a DLF lesion on the inhibition of a multireceptive neurone by dorsal column stimulation. At the first arrow above the rate-meter trace in Fig. 7 the dorsal column was stimulated for 15 s. The response of the cell to hot water placed on the foot was reduced for the subsequent 8 min. After a further 8 min the DLF was cut with a diathermy needle. Subsequent stimulation of the dorsal columns at the times indicated by the arrows caused no long-lasting inhibition of the response to hot water.

DISCUSSION

These experiments have examined some of the electrophysiological effects of stimulating the dorsal columns in the rat. A marked and prolonged inhibition was observed of the responses of spinal dorsal horn neurones to noxiously hot water placed on the foot. These observations are in agreement with previous studies (Foreman *et al.* 1976; Lindblom *et al.* 1977; Saade *et al.* 1985). A brief inhibition of the general excitability of multireceptive dorsal horn neurones was further observed which has also been described previously (Foreman *et al.* 1976). The present experiments demonstrate that these two effects of dorsal column stimulation (short-term and long-term inhibition) are the result of activating distinctly different mechanisms. Electrical stimulation of the dorsal columns below a transection causes a brief excitation followed by brief inhibition of multireceptive cells. Following a single stimulus an action potential was usually recorded 1–3 ms later. This is likely to result from antidromic activation of primary afferent collaterals in the dorsal fasciculi (Lindblom *et al.* 1977). The action potential was followed by brief inhibition lasting 100–150 ms. These observations are in agreement with previous reports of the segmental effects of dorsal column stimulation (Foreman *et al.* 1976). The inhibition was not due to excessive depolarization of the multireceptive neurone as the occasional spikes encountered during the depression were not reduced in amplitude but were bigger. This would be expected if the cell were inhibited postsynaptically. Furthermore, the period of inhibition was most clearly seen when the excitability of the cell was raised by electrophoretic application of DLH, which also suggests that the segmental inhibition is at least in part postsynaptic.

Similar conclusions may be drawn from the work of Foreman *et al.* (1976). They excited spinothalamic tract cells by stimulating the sciatic nerve and observed the inhibition of this response by dorsal column stimulation. The inhibition lasted for 100–150 ms. As they stimulated the peripheral nerve at C fibre intensity it must be assumed that the responses of these cells to both high- and low-threshold fibre activation were inhibited. These authors also recorded inhibitory postsynaptic potentials intracellularly which resulted from dorsal column stimulation and

concluded that much of the inhibition was postsynaptic. It is important to note that neither the results of Foreman *et al.* (1976) nor those reported here discount an additional presynaptic influence. In fact Foreman *et al.* (1976) noted that the time course of the IPSPs and the time course of the inhibition of sciatic nerve responses did not correlate and suggested that the differences may be due to presynaptic components of the inhibition. However, in both studies dorsal column stimulation inhibited the responses of multireceptive neurones to both high- and low-intensity stimuli, which implies a lack of specificity which may be expected from postsynaptic inhibition.

These effects of dorsal column stimulation are very unlikely to be due to the spread of stimulating current to structures other than the dorsal columns, as small movements of the stimulating electrode profoundly altered the effects of stimulation (Rees & Roberts, 1989*a*). The most likely fibre tract to be inadvertently stimulated is the dorsolateral fasciculus and the present experiments show that cutting this tract below the level of dorsal column stimulation had no effect on the short-term inhibition of multireceptive neurones. It is possible that the inhibition results from the antidromic activation of low-threshold primary afferent collaterals and the closing of a segmental, spinal gate as proposed by Melzack & Wall (1965). It does appear, however, that postsynaptic inhibition is involved and that the effects are less than totally selective for high-threshold primary afferent fibres. The dorsal columns contain many fibre types and it is also possible that the short-term inhibition of multireceptive spinal neurones results from antidromic activation of fibres descending from dorsal column nuclei (Burton & Loewy, 1977).

Whatever the detailed mechanism of the short-term inhibitions activated by stimulation of the dorsal columns below a transection, its characteristics, at least in rats anaesthetized with urethane, appear to be very different from the effects of dorsal column stimulation which are useful clinically. The inhibition of multireceptive spinal neurones lasts for only 100 ms or so beyond the period of stimulation and is not selective for intense stimuli. The same parameters of stimulation applied above the dorsal column transection, however, have effects which much more closely resemble those which are clinically useful. The responses of multireceptive neurones in the dorsal horn to intense cutaneous stimuli were selectively inhibited for periods of 5 min or more. This conclusion is similar to those of Lindblom *et al.* (1977) and Saade *et al.* (1985).

The implications of this observation have potential relevance to the clinical use of dorsal column stimulation. If it is assumed that the descending fibres of the dorsal columns are of primary importance to the pain-relieving effects of stimulation, then in patients with posterior quadrant lesions the dorsal column stimulation would be applied below the lesion. This would not seem likely from these experiments to effect a long-lasting pain relief. Nor should stimulation above the lesion be useful as the low-threshold primary afferent collaterals and postsynaptic dorsal column fibres would have degenerated. Stimulation of the gracile nucleus may be effective, however, if acceptable and technically feasible. Of course if the spinal lesion is sufficiently extensive to involve the DLF, then the present data show that a pain-relieving effect would not be expected.

Nothing was known of the pathways in the brain which mediate the ascending

effects of antinociceptive dorsal column stimulation. However, the APTN is known to receive a dense innervation from the dorsal column nuclei (Berkley, Budell, Blomqvist & Bull, 1986) and we have shown that this input is excitatory to APTN neurones (Rees & Roberts, 1989*b*). The APTN may be relevant to antinociception because electrical stimulation evokes a long-lasting inhibition of behavioural and multireceptive spinal neurone responses to intense cutaneous stimuli (Roberts & Rees, 1986; Rees & Roberts, 1987). This is due to activation of cell bodies in APTN rather than stimulation of fibres, because microinjection of DLH is antinociceptive (Rees *et al.* 1987). The present data show that inhibition of cells in the APTN by microinjection of GABA blocks the antinociceptive effects of dorsal column stimulation. This clearly implies that the APTN is a central relay of these effects. Of course there is an alternative explanation for the effects of GABA microinjection. The removal of an excitatory drive from APTN to some other part of the brain may disrupt the function of this unknown part of the brain which may contain the necessary relay. This is unlikely, however, in view of the known direct inputs to APTN from the dorsal column nuclei.

Antinociception from the APTN has been shown to be unaffected by lesions of the ventromedial rostral medulla (including nucleus raphe magnus) (Rees, H. & Roberts, M. H. T., unpublished data) and also is resistant to antagonists of 5-hydroxytryptamine (Rees, Prado, Rawlings & Roberts, 1987). In these respects the effects of APTN stimulation are significantly different from the effects of stimulating the periaqueductal gray (PAG). However, both PAG and APTN effects are potently reduced by α-adrenoceptor antagonists (Camarata & Yaksh, 1985; Rees *et al.* 1987) and by lesions of the DLF (Rees & Roberts, 1987; Basbaum & Fields, 1978). It is not possible at present to describe the descending limb of the neuronal pathway which mediates this inhibition of responses to intense cutaneous stimuli. This is being studied.

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