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THE SPREAD OF SENSITIZATION OF POLYMODAL NOCICEPTORS IN THE RABBIT FROM NEARBY INJURY AND BY ANTIDROMIC NERVE STIMULATION

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SUMMARY

1. Ninety-three polymodal nociceptor units with unmyelinated axons were isolated from rabbit sural nerves. Twenty-three were used for control data. These showed normal sensitization on repeated heating of their receptive fields, measured here as a drop in mean heat threshold.

2. Small injuries were made 5 (n = 15) or 10 (n = 12) mm outside the receptive fields of some polymodal nociceptors. This resulted in the development of spontaneous firing and lowered thresholds to heating of the receptive field.

3. Local anaesthetic previously injected into the site of injury blocked this spread of heat sensitization. Previous injection of saline had no effect.

4. Antidromic stimulation of the sural nerve, proximal to the recording site, also resulted in heat sensitization of polymodal nociceptors (n = 10).

5. Possible mechanisms for the spread of sensitization of polymodal nociceptors from nearby injury are discussed. Analogies are drawn between these results and those of Lewis (1935–36) on the spread of cutaneous hyperalgesia around a skin injury in man.

INTRODUCTION

Polymodal nociceptors, a group of high-threshold sensory receptors with unmyelinated (C) fibres, have been extensively studied and their properties are well established. They are found in large numbers in the cutaneous nerves of all mammals studied so far, including man (Iggo, 1959; Bessou & Perl, 1969; van Hees & Gybels, 1972; Kumuzawa & Perl, 1977). Cutaneous polymodal nociceptors are excited to maximal activity by mechanical and heat stimulation of noxious intensity and by irritant chemicals applied to the skin. A further striking property of these units is that severe heating of their receptive fields results in an enhanced responsiveness to further heating. This 'sensitization' is characterized by a lowered threshold, a higher frequency of firing at a given temperature and often the development of background firing (Bessou & Perl, 1969; Perl, Kumuzawa, Lynn & Kenins, 1974; Lynn, 1979). These properties have led to the suggestion that polymodal nociceptor activity could be responsible not only for pain at the time of injury but also for the hyperalgesia that follows skin injury in man (see Lynn, 1977).

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Besides the hyperalgesia at the site of an injury, an area of soreness also develops around it, on previously uninjured skin (Lewis, 1935–36), and it seemed possible that this too might be related to polymodal nociceptor sensitization.

The experiments described here were carried out to establish whether polymodal nociceptors could become sensitized by noxious stimulation outside their receptive fields. Perl *et al.* (1974) noted that extensive skin damage could result in spontaneous firing of polymodal nociceptors with receptive fields some distance from the site of injury but no quantitative measurements of sensitization were made.

In this study, single polymodal nociceptors were isolated from the rabbit sural nerve and small injuries were made outside their receptive fields. The results show that these injuries resulted in the development of spontaneous firing and the heat-sensitization of these units. The effect, on this spread of sensitization, of local anaesthetic injections into the site of injury was tested. Finally, the whole sural nerve was stimulated antidromically to see if that, too, resulted in polymodal nociceptor sensitization.

A preliminary report of these findings has been published (Fitzgerald, 1978).

METHODS

Preparation. The experiments were carried out on rabbits anaesthetized with urethane (1·8 g/kg) administered through the marginal ear vein. A tracheal cannula was inserted and the rectal temperature was monitored and maintained between 36·5 and 38·5 °C. The left leg was raised above the rest of the body and supported by a clamp at the toes and a pad under the knee. The sural nerve was exposed in the popliteal fossa for recording and electrical stimulation. In some experiments the nerve was cut proximal to the recording point but it was usually left intact. A short length of nerve was then desheathed and small filaments dissected from it under liquid paraffin. These were placed on a fine platinum wire recording electrode with an indifferent electrode on the whole nerve. A pair of platinum wire stimulating electrodes were placed under the nerve, 25–40 mm distal to the recording site. The small nerve filaments were split down until functionally single units could be identified. Single units were recognized by the consistent shape and size of their action potentials and by picking out the same all-or-none potentials on electrical stimulation of the whole nerve. Discharges from single afferent fibres were filtered, amplified and displayed on an oscilloscope and a U.V. recorder; they were also stored on magnetic tape along with the analogue signal of the skin temperature.

Heat stimulator. The receptive fields of polymodal nociceptors were heated with a radiant heat lamp previously described by Fitzgerald & Lynn (1977). An area of skin, about 1 cm^2, was heated by a small projector bulb with a built-in reflector. The skin temperature was monitored by a chromel–constantan thermocouple resting on the skin in the light beam and the signal from this was compared to a reference signal. The resultant error signal drove the power to the lamp. The control system allowed the skin to be heated to any pre-set temperature up to $65 \pm 0{\cdot}3$ °C at a steady $1{\cdot}0 \pm 0{\cdot}1$ °C/sec. The base-line temperature was always preset at 35 °C for a few seconds before the start of the stimulus.

Skin injuries. In some experiments the effect of an injury outside the receptive field was examined. After the receptive field had been carefully mapped with von Frey hairs, an injury was made in the adjacent skin 5 or 10 mm away by picking up a fold of skin with a pair of watchmakers' forceps and making a small cut with a pair of fine dissecting scissors. The resulting nick was about 2 mm long and less than 1 mm wide and went right through the dermis. No bleeding resulted from this cut. In most cases performing the injury did not result in firing of the recorded nerve ending 5 or 10 mm away, although sometimes this was unavoidable due to stretching of the skin.

In other experiments, the area to be injured was anaesthetized first by injecting a small volume (0·02–0·05 ml.) of 0·05% lignocaine hydrochloride subcutaneously with a 30 G needle. Alternatively, the same volume of 0·9% saline was injected.

Antidromic stimulation. In the experiments involving antidromic stimulation of the sural nerve, a second pair of platinum electrodes was placed under the nerve proximal to the recording point. Sometimes the nerve was cut centrally. Stimulation of 5–10 mA, 0·5 msec width at 1/sec for 6 min was applied. Recording through the distal pair of electrodes confirmed that this strength was sufficient to stimulate the C fibres. Because filaments were dissected away from the main nerve for recording single units, this antidromic stimulation did not directly invade the nerve endings of the polymodal nociceptor under investigation.

RESULTS

A total of ninety-three polymodal nociceptors were isolated from rabbit sural nerve These were identified by their conduction velocities, their responses to mechanical stimulation and also to heating of the skin.

The conduction velocities ranged from 0·56 to 1·28 m/sec, mean 0·89 ± 0·13 (± S.D.). The units had a wide range of mechanical sensitivity. Von Frey thresholds ranged from 25 mg to 5·3 g (or 2·5 to 22 g/mm^2) with a mean of 1·05 g ± 1·1 (± S.D.). However, they all responded maximally to strong pressure on the skin of the receptive field.

Receptive field size was carefully determined with von Frey hairs. With supra-threshold stimuli, the fields consisted of a single point $\leqslant$ 1 mm in diameter and the size did not seem to be influenced by the stimulus intensity. With just-threshold stimuli, the field was sometimes smaller, but this was not consistently observed.

Control units

Twenty-three of the ninety-three polymodal nociceptors were used for control data. The receptive fields were mapped and the mechanical thresholds found with von Frey hairs and then the radiant heat lamp was put into position. The skin temperature was held at 35 °C for a few seconds and then heat was applied at 1 °C/sec to a few degrees above threshold and then turned off. The first heat thresholds of the polymodal nociceptors varied between 44·0 and 65·0 °C, mean 55·5 ± 6·5 (S.D.) °C. This heating resulted in sensitization of the units. Low-frequency firing often developed (< 0·1–1·0 spike/sec) and a second, identical heat test, 4 min later, revealed that the mean threshold was 49·2 ± 6·3 °C (± S.D.) which is significantly lower than the first ($P < 0·01$). The mean drop in threshold was 4·3 ± 1·5 °C (± 5% confidence limits).

Fig. 1 shows an example of heat sensitization of a polymodal nociceptor.

The effect of injury outside the receptive field

Twenty-seven polymodal nociceptors were used to study the effect of an injury outside the receptive field. The field was carefully mapped with von Frey hairs and the mechanical threshold established; then the heat stimulator was put into position. Next, a small nick was made in the skin 5 or 10 mm outside the receptive field. The resultant injury was about 1 mm wide and performing it did not normally cause any firing of the polymodal nociceptor under investigation.

(i) *The development of spontaneous firing.* Following the injury, a pause was taken for 10–15 min. This time period was chosen because Lewis (1935–6) reported that the spread of hyperalgesia around an injury in man reached a maximum in 10–15 min. During this period, twelve out of fifteen polymodal nociceptors (80%) with an injury

5 mm away developed spontaneous activity. Before the injury was made, they had all been silent. The firing started about 30 sec after the injury was made and built up over the next 5 min. By the end of the 10–15 min period it had settled down to a steady, low level or had virtually stopped. The frequency of firing was low, never

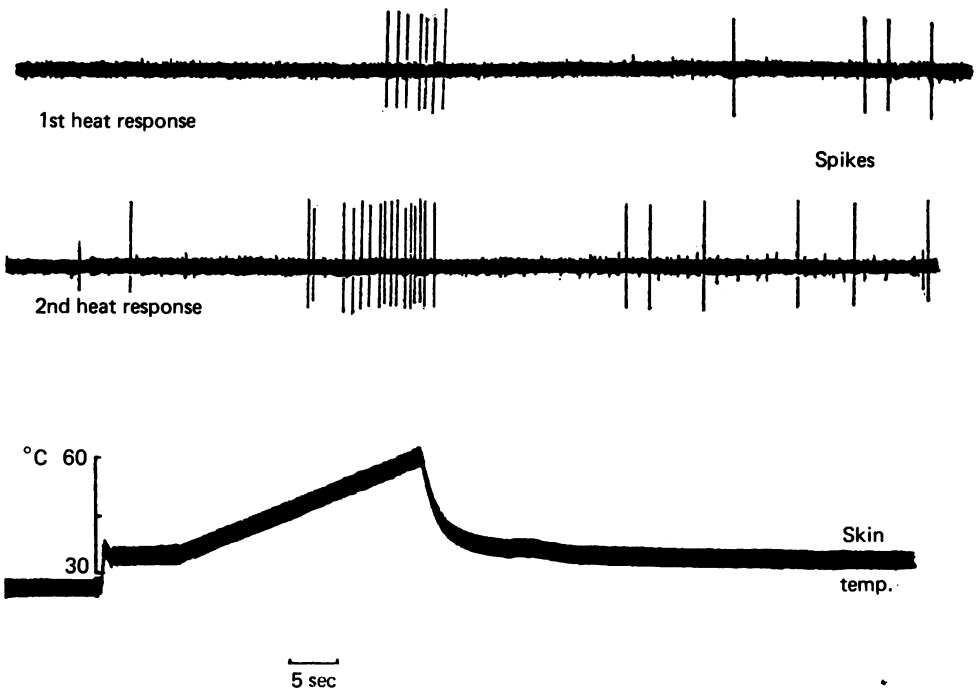

Fig. 1. The heat sensitization of a polymodal nociceptor. The receptive field was heated at 1 °C/sec to 58 °C twice with a 4 min interval between the stimuli. The bottom trace shows the skin temperature. The upper trace shows the response of the unit to the first heat run. It fired seven spikes and the threshold was 55 °C. Background firing developed after the heating. The middle trace shows the response to the second heat run. The unit fired sixteen spikes and the threshold was 48 °C. The background firing also increased.

exceeding 1 spike/sec. A typical example is shown in Fig. 2. This phenomenon occurred whether the nerve was intact or cut central to the recording point.

Of the twelve units with a nick 10 mm outside the receptive field, six (50%) developed spontaneous firing, the maximum frequency being 0·5 spike/sec.

(ii) *Heat responsiveness.* After the pause the receptive fields of the units were heated in the same way as described for the control units. Those with a nick 5mm away had a mean heat threshold of 45·6 ± 3·3 °C (± 5% confidence limits; C.L.). This is significantly lower than the mean heat threshold under normal conditions, which was 55·5 ± 2·6 °C (± 5% C.L.) ($P < 0·001$). Those units with an injury 10 mm away had a mean threshold of 49·2 ± 3·6 °C (± 5% C.L.) and this too is significantly below control values ($P < 0·01$).

The lowered heat thresholds were seen whether or not the sural nerve was cut centrally. The mean heat threshold of 4 units with an injury 5 mm outside the receptive field and with a cut sural nerve was 44·3 °C.

The effect of injury in the presence of local anaesthetic and of saline outside the receptive field

Since an injury 5 mm outside the receptive field was shown to be more effective than the one at 10 mm, the following experiments were all done with injuries at this distance from the polymodal nociceptor field.

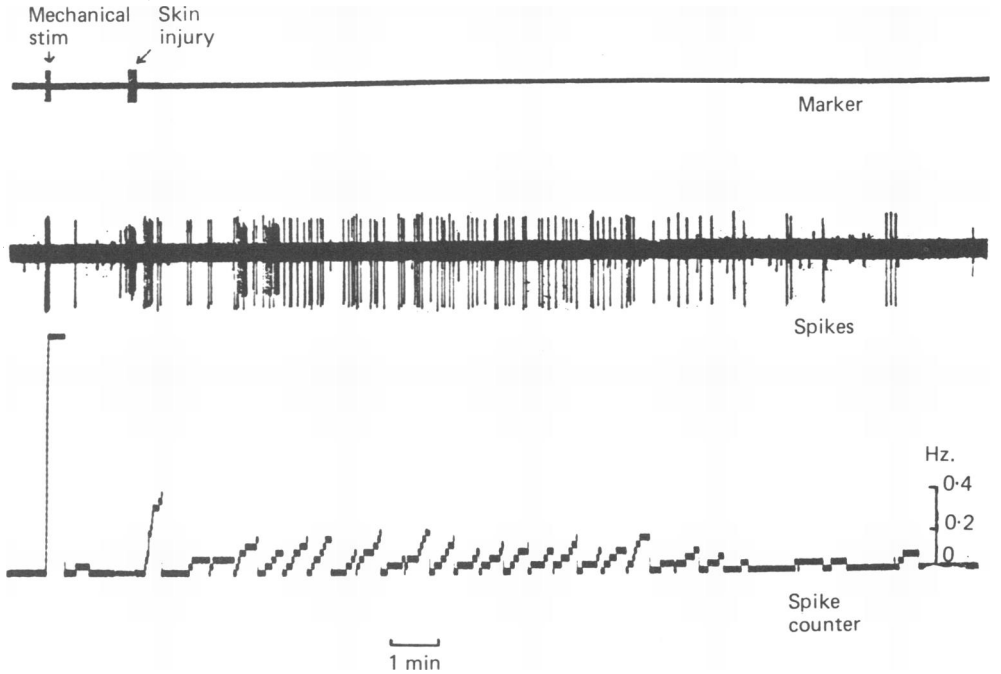

Fig. 2. The development of background firing by a polymodal nociceptor after an injury is made 5 mm from its receptive field. The unit is initially silent and gives a clear response to mechanical stimulation of its receptive field. Two min later a skin injury is made 5 mm away. Note that a smaller unit fires during this but the unit under investigation does not. Within a few seconds background firing begins and remains at a low frequency for 15 min although dying down towards the end of this period.

Exactly the same procedure was adopted as before except that first, the area about to be injured was injected subcutaneously with a bleb (0·05 ml.) of 0·5 % lignocaine hydrochloride or 0·9 % saline and then a nick was made in the resultant swollen area.

(i) *Saline injection and injury.* Eight out of ten of these units (80 %) developed spontaneous firing in the 10–15 min period between the nick and the first heat test. The maximum frequency was 0·16–3·0 spikes/sec. and the firing pattern was similar to that of units with an injury only outside the receptive field.

The mean heat threshold of these units was 48·5 ± 4·0 °C (± 5 % C.L.). This is not significantly different from the mean heat threshold of those units with an injury 5·0 mm away but no saline injection. It is significantly less than the mean heat threshold of the control units ($P < 0·01$).

It therefore seems that the presence of saline at the site of injury does not affect the sensitizing properties of a nearby injury on polymodal nociceptors.

(ii) *Local anaesthetic injection and injury.* Five out of ten (50 %) of these units developed spontaneous firing with peak frequencies of 0·16–0·3 spikes/sec. Thus these units developed less background firing than the units with just a plain injury or an injury in saline 5·0 mm from the receptive field.

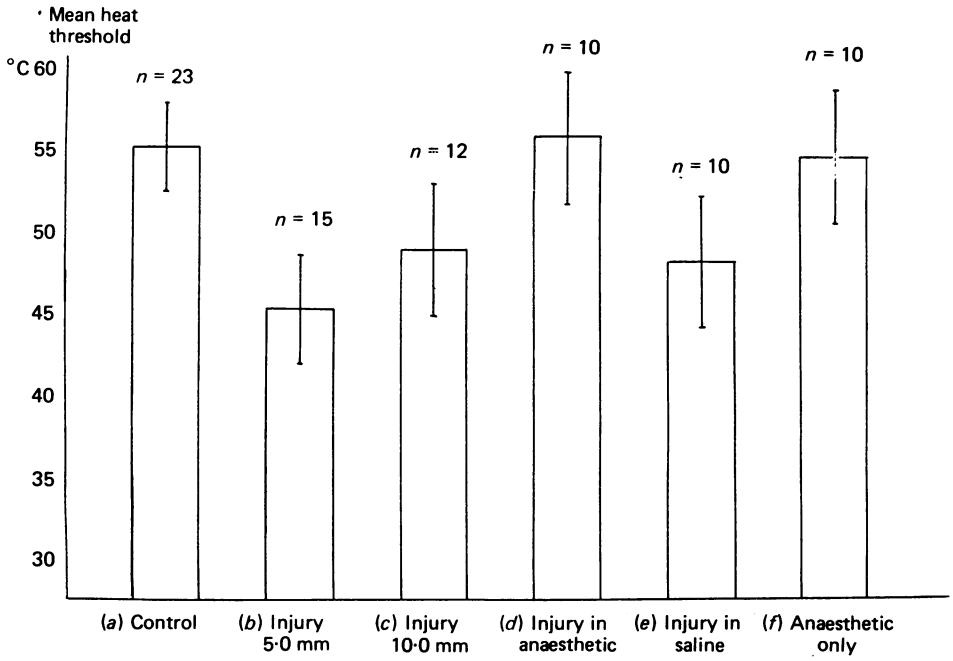

Fig. 3. Mean heat thresholds of six groups of polymodal nociceptors with 5 % confidence limits calculated from the pooled variance. (*a*) Control units, (*b*) units with an injury 5 mm from the receptive field, (*c*) units with an injury 10 mm away, (*d*) units with an injury 5 mm away in an area injected with anaesthetic, (*e*) units with an injury 5 mm away in an area of saline and (*f*) units with an area 5 mm away injected with anaesthetic but with no injury.

The presence of local anaesthetic in the site of injury, however, completely prevented the drop in heat threshold seen when an injury alone or in the presence of saline was made. The mean heat threshold was 56·1 ± 4·0 °C (± 5 % C.L.) and this is not significantly different from control values. It is however, significantly higher than the mean thresholds of those units with a plain injury ($P < 0{\cdot}001$) or an injury in saline ($P < 0{\cdot}01$) outside the receptive field. Fig. 3 summarizes the data presented. The mean heat thresholds of groups of polymodal nociceptors under the different experimental conditions are shown with 5 % confidence limits.

It was important to establish that the anaesthetic injected 5·0 mm outside the receptive field was not spreading into the fields of the polymodal nociceptors and directly anaesthetizing the nerve endings. Had this occurred, it would have appeared as an increased threshold to stimulation. Fig. 3, shows the mean heat threshold of a group of 10 units that had an injection of local anaesthetic 5·0 mm from the receptive field only. No injury was made. Under these conditions, the mean threshold 10–15 min later was 54·8 ± 4·0 °C (± 5 % C.L.) and this is not significantly different from control values. If the lignocaine were spreading into the receptive field, then

one would have expected the heat thresholds of the units to be elevated. Furthermore, testing the receptive fields of the polymodal nociceptors with von Frey hairs 10–15 min after the injection of local anaesthetic revealed that the mechanical thresholds were unchanged.

An analysis of variance was done on the heat thresholds of the six groups of polymodal nociceptors shown in Fig. 3. The six groups divide neatly into two parts. Using the N–K procedure (Armitage, 1971) it was found that groups (*a*), (*d*) and (*f*) are insignificantly different from each other, but are significantly different from groups (*b*), (*c*) and (*e*) which are insignificantly different from each other.

The effect of antidromic stimulation

Here, the effect of antidromic stimulation, at C fibre strength, of the sural nerve was examined on single polymodal nociceptor activity and responsiveness.

When a polymodal nociceptor had been isolated and its receptive field and von Frey threshold found, the whole nerve trunk was stimulated with 5–10 mA, 0·5 msec pulses (C fibre strength) at 1/sec for 6 min. The effect of stimulating at A fibre strength only was not tested. The stimulating electrodes were proximal to the recording point so that the actual polymodal nociceptor unit under examination was not stimulated. At the end of stimulating period, there was a pause of 10–15 sec and then the heat tests were started. As before, the heat was applied to the receptive field by a radiant heat lamp at 1 °C/sec. In five of the thirteen units studied, the nerve was intact centrally and in eight it was cut proximal to the stimulating electrodes.

Of the thirteen units studied, none showed any spontaneous firing either before, during or after the stimulation period. After heating the receptive field, however, background firing began as normal.

The mean heat threshold of polymodal nociceptors under these conditions was $48{\cdot}4 \pm 3{\cdot}7$ °C ($\pm 5\%$ C.L.) and significantly lower ($P < 0{\cdot}01$) than the mean control threshold. There was no difference in the results obtained according to whether the nerve was intact or cut centrally. The mean value for heat thresholds after antidromic stimulation of a cut nerve was $49{\cdot}1 \pm 5{\cdot}3$ °C (5% C.L.), whereas that for an intact nerve was $47{\cdot}1 \pm 7{\cdot}9$ °C ($\pm 5\%$ C.L.). These are not significantly different.

DISCUSSION

This study has shown that sensitization of polymodal nociceptors in the rabbit sural nerve can occur when no direct stimulus has been applied to the receptive field. A small injury in the skin 5 or 10 mm away from the receptive field results in their sensitization. After the injury is made, some background firing develops and heating the receptive field 10–15 min later revealed that the heat threshold had decreased significantly below control levels. This occurs whether or not the nerve is intact centrally. The degree of sensitization tends to decrease as the distance of the receptive field from the injury increases.

The parallel between this spread and the spread of hyperalgesia from a point of injury in man (Lewis, 1935–6) is very striking. Lewis described an area of soreness surrounding a localized skin injury which spread over several centimetres, reaching its full reaction in 15–30 min. The soreness decreased with distance from the point of injury. If the nerve trunk was blocked during the time of injury, the hyperalgesia

still developed immediately the block had worn off. The present results suggest that polymodal nociceptor sensitization could be the underlying mechanism for this spread of hyperalgesia.

In all the experiments reported here, injuries were made by nicking the skin. A few preliminary trials revealed that thermal injuries were not so effective. This may be due to the tough skin of the rabbit, since a hot copper probe of about 70 °C produces only a little reddening on rabbit skin. However, Croze, Duclaux & Kenshalo (1976) made burns of 60–500 °C in and around the receptive fields of monkey polymodal nociceptors and saw no spontaneous firing as a result of them.

In order to find out more about the underlying mechanism of the spread of sensitization, local anaesthetic was injected into the site where the injury was to be made. As a result, the heat sensitization normally caused by an injury was completely blocked. The mean heat threshold of this group was the same as the control group. Saline injections, however, did not prevent the spread of sensitization. It is interesting that although the presence of local anaesthetics blocked the heat sensitization caused by nearby injury, it did not completely block the development of background firing in these units. Spontaneous firing was less evident in those units with an injury in anaesthetized skin, and it never reached such high frequencies as when there was no anaesthetic in the region, but it was still present. It is possible that the two phenomena – the development of background firing and the heat sensitization – have different mechanisms, the former being perhaps due to release of chemicals from the damaged site. Perl (1976) also suggests a different mechanism for the two, since he notes that it is possible for a polymodal nociceptor to stop showing sensitization to heating and perhaps begin to fatigue, while the background firing is increasing.

The fact that the spread of sensitization is blocked by local anaesthetic in the site of injury suggests that the phenomenon is dependent on the generation of action potentials in the injured site. It is most likely that the activity arises in the injured nerve terminals. As discussed above, background firing of the polymodal nociceptor ending, 5 mm away, is not completely blocked by the presence of local anaesthetic at the injured site and this suggests that activity in the surrounding uninjured skin is not sufficient to produce sensitization there, the main requirement being activity from the injured area. Again, there is a parallel here with Lewis's experiments (1935–6) on human cutaneous hyperalgesia. Lewis found that the spread of hyperalgesia around skin damage did not occur if local anaesthetic was injected into the site of injury. It must also be borne in mind, however, that local anaesthetics act on other membranes besides neuronal ones, e.g. those of red blood cells (see Goldstein, Aronow & Kalman, 1974) and it has also been reported that they block axonal transport in sensory nerves (Fink & Kish, 1976). Therefore, it is possible that sensitization was blocked by some non-specific toxic effect.

The present results also show that sensitization of polymodal nociceptors occurs after antidromic stimulation of the sural nerve at C fibre strength. This occurs even when the nerve is cut centrally. It is possible that this is due to antidromic activity in the C fibres, but since A fibre stimulation alone was not tested, this is not certain. Chahl & Ladd (1976) have also investigated the effects of antidromic stimulation on the rat saphenous nerve. They found that it resulted in oedema and dye leakage and also in an increased excitability of sensory nerves to cutaneous stimulation as judged from multi-unit recordings. This increased firing only occurred if the antidromic stimula-

tion was at C fibre strength; at A fibre strengths there was no effect. In the present experiments, however, single polymodal nociceptors were being examined and furthermore the antidromic stimulation was not directly invading the nociceptor terminal, since dissection of single fibres necessitates cutting filaments out of the whole nerve. Thus, the sensitization observed here must have been a result of antidromic stimulation of other nerve terminals besides that of the nociceptor under investigation.

Antidromic stimulation of cutaneous nerve has been tested in man and results in hyperalgesia over the distribution of the nerve (Lewis, 1935–6; Chapman, Ramos, Goodell & Wolff, 1961). This too only occurs at C fibre strengths and furthermore is as effective in sympathectomized subjects.

Thus, these results show that electrical activity in nerve endings some distance away from a polymodal nociceptor ending, either due to skin injury or to antidromic excitation, results in and could be the cause of a spread of sensitization to that polymodal nociceptor. In the light of this, it would be interesting to see if a brief period of intense cutaneous electrical stimulation had the same effect.

What is not clear is quite how the activity in the region influences the nociceptor under investigation. Lewis (1935–6) suggested that there was a network of connecting nerves throughout the skin and that axon reflexes from one area resulted in the release of pain-producing substances and hyperalgesia in another area. It is unlikely that there is a straightforward axon reflex through the branches of polymodal nociceptor terminals in our preparation since the receptive fields of these receptors are too small to cover the area of spread. It is possible, however, that the terminals do have branches whose action potentials do not invade the main nerve, perhaps because of low-pass filtering at the junction point. This has been described in the leech (Yau, 1976). A further possibility is that there are low-resistance junctions between separate nerve terminals in the skin, as have been demonstrated in teeth (Matthews & Holland, 1975) and that under some circumstances, action potentials are propagated from one nerve terminal to another.

The spread of sensitization need not, however, occur through connecting nerve terminals. Another possibility is that activity in nerves in the injured area results in the release of sensitizing chemicals which spread into the region of the polymodal nociceptor terminals under investigation. This chemical spread would be blocked by local anaesthetics since the release would be dependent on the development of action potentials in the injured site. There have been several reports of substances being released from nerve endings which lower the threshold to firing of afferent fibres. Habgood (1950) stimulated one nerve and recorded from the other nerve of two pieces of frog skin placed so that the under surfaces were in contact and found that stimulation of the first resulted in spontaneous activity and lowered threshold to evoked activity in the second. He concluded that a neuro-humoral agent was being released that sensitized the nerve endings. Holton (1959) demonstrated that ATP was released from sensory nerve endings in the rabbit ear, albeit in very small quantities In studying the cutaneous perfusates after antidromic nerve stimulation and noxious skin stimulation in man, Chapman *et al.* (1961) isolated a substance which they named 'neurokinin'. This substance induced a burning pain and flare when injected into the skin.

Over-all, the results of the present experiments suggest that the spread of sensiti-

zation of polymodal nociceptors from a distant site depends on the development of nerve action potentials in that site. This might occur through direct nervous connexions, such as axon reflexes, resulting in the release of 'sensitizing' agents or by the local, activity-dependent release of such agents which spread into the surrounding inactive area.

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