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Long-term changes in discharge behaviour of cat dorsal horn neurones following noxious stimulation of deep tissues

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Summary Certain pathological types of afferent input are supposed to lead to long-term changes in the responsiveness of dorsal horn neurones. This mechanism might be of importance for the development of neurological disturbances such as chronic pain. The present study was undertaken in order to find out whether dorsal horn neurones — particularly those processing input from deep tissues — exhibit long-lasting changes in response behaviour after a short-lasting noxious stimulation of deep tissue.

In anaesthetized cats, the impulse activity of single dorsal horn cells was recorded extracellularly with glass microelectrodes. In a small number of cells that had multiple receptive fields (RFs), the algesic agent bradykinin was injected into a muscle RF and the properties of all RFs retested at regular time intervals. Following noxious chemical stimulation of one RF, the injected and the other RFs of the same neurone often showed changes which consisted of an increase in size, a lowering of mechanical threshold and appearance of new RFs.

In an attempt to assess the influence of a single noxious stimulus on the entire population of dorsal horn cells, the properties of a greater sample of neurones were compared before and after injection of bradykinin into the deep tissues of the hind limb. Every cell encountered was classified as being driven by (1) cutaneous receptors only, (2) deep receptors only, (3) both input sources, or (4) electrical stimulation only (cell without receptive field). Following injection of bradykinin, the proportion of cells with both deep and cutaneous input and of those having background activity rose, and the percentage of cells without a receptive field decreased. The data indicate that any noxious manipulation of the hind limb may elicit long-lasting changes in the response behaviour of dorsal horn neurones. This assumption was supported by the finding that in animals in which the hind limb had been operated on, the proportion of cells with deep and cutaneous input was significantly higher and that of cells with exclusively deep input lower than in animals with an intact hind limb.

Transferring these findings to the clinical situation, the data suggest that the increase in size of the RFs and the appearance of new RFs after a noxious stimulus might reflect the spread or irradiation of deep pain. Likewise, the increase in convergence of deep and cutaneous afferents might be of relevance for the referral of deep pain to the skin, while the decrease in mechanical threshold of deep RFs remote to the location of the noxious stimulus might be the neurophysiological basis of referred tenderness.

Key words: Dorsal horn neurones; Modulation; Convergence; Nociception; Deep pain; Referred pain

Introduction

It is well known that the excitability of dorsal horn neurones is not constant but shows spontaneous fluctuations and can be modulated by descending influences and primary afferent input [1,6,19,21]. Afferent input in nociceptive fibres has been reported to lead to a long-lasting increase in the neurones' responsiveness [8,14]. Similar alterations have been observed in alpha-motoneurones [24]. The underlying mechanism probably has a central component [3,23] which might be of importance for the development of neurological dis-

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turbances including chronic pain [18]. There are some reports in the literature showing that electrical stimulation of peripheral nerves or induction of an inflammation may change the size of the receptive field (RF) and/or the response behaviour of central nerve cells in the cat and rat [2,5,7,15], and the authors agree that an input via small-diameter afferent fibres (mainly group IV or C fibres) is a prerequisite for the changes. Group IV afferent units from skeletal muscle have been found to be particularly effective in this respect [22].

Most of the cited investigations dealt with neurones processing input from cutaneous receptors; studies aiming specifically at neurones with receptive fields in deep tissues (e.g., muscle, tendon, fascia, joint capsule) have not been performed up to now. Since deep pain is more likely to show phenomena such as irradiation and referral than is cutaneous pain, cells having deep input are probably of greater clinical importance. The present study was undertaken in order to find out whether a short-lasting noxious input to the deep tissues is capable of changing the response behaviour of cat dorsal horn neurones for prolonged periods of time. The observed alterations of the neurones offer a neurophysiological explanation for referred tenderness and might play a role in the chronification of deep pain.

Methods

The experiments were performed on 24 adult cats of either sex. Some of the animals were identical with those used in another study on the physiology and morphology of dorsal horn neurones having deep input (Hoheisel and Mense, to be published). Anaesthesia was induced by injecting alpha-chloralose 80 mg/kg i.p. followed by Ketanest 2.5 mg/kg i.m. Additional doses of chloralose were given i.v. as required in order to maintain a deep level of anaesthesia. The anaesthesia was considered to be deep if the pupils were maximally constricted and no changes in blood pressure occurred upon noxious stimulation of the extremities. Particular care was taken to keep the level of anaesthesia as constant as possible by checking these parameters frequently and by adding only small doses of the anaesthetic (10 mg/kg). The animals were paralyzed by i.v. injection of pancuronium (200 μg/kg) and artificially ventilated.

The following operations were performed: introduction of a catheter into the left cephalic vein for administration of drugs and into the left common carotid artery for measuring the blood pressure; introduction of a tracheal cannula for artificial respiration; bilateral pneumothorax; laminectomy from the second to the seventh lumbar vertebrae. To cover the laminectomy wound, a pool was formed out of skin flaps and filled with mineral oil. All experiments were carried out under cold block of the spinal cord. For this purpose a cooling thermode, through which water at 0 °C was circulated, was placed on the surface of the cord at the segmental level L2. Pilot experiments had shown that without cold block the input from deep tissues to dorsal horn neurones was largely reduced.

The muscles of the dorsal aspect of the left hind limb were surgically exposed following a skin incision along the dorsal midline. An oil pool was formed over the popliteal fossa which contained a stimulating electrode around the sciatic nerve. In some animals, the hind limb was not opened in order to avoid a possible sensitizing influence of this operation on peripheral receptors and central nervous neurones. In these cases, a stimulating electrode was attached to the proximal sciatic nerve through a small skin incision.

Mean arterial blood pressure, body core temperature and end-expiratory pCO_2 were continuously monitored and kept at physiological levels (above 80 mm Hg; 38 °C; 3.5–4.0%). The last value was of particular importance, since a raised pCO_2 widens the pupils and thus interferes with the judgement of the depth of the anaesthesia.

For extracellular recording of the impulse activity of single dorsal horn neurones at the lumbosacral level, glass micropipettes filled with a 10% solution of horseradish peroxidase and 0.5 M KCl in Tris buffer, pH 7.4 were used. The pipettes were connected to a ionophoresis system which allowed a marking point to be made at the record-

ing site. The tissue was later processed using diaminobenzidine as a chromogen. The tips of the micropipettes were so fine and the DC resistance so high (80–180 MΩ) that simultaneous recordings from two adjacent cells were never obtained. The study concentrated on dorsal horn neurones having input from deep tissues, either exclusively or in combination with input from the skin. The cells were characterized according to their responses to mechanical stimulation of their receptive field(s) in deep tissues and/or skin. HTM (high-threshold mechanosensitive) neurones required noxious stimulation (pinching) for activation; LTM (low-threshold mechanosensitive) elements responded to innocuous deformation (moderate pressure or touch) in a graded fashion. The stimuli were applied by hand using an artist's brush or broad forceps. A further classification was not attempted. Some LTM cells with deep receptive fields were also tested with noxious stimuli; they exhibited a multireceptive behaviour in that they gave maximal responses upon noxious intensities of stimulation. However, the labels 'multireceptive' or 'WDR' were not used for the

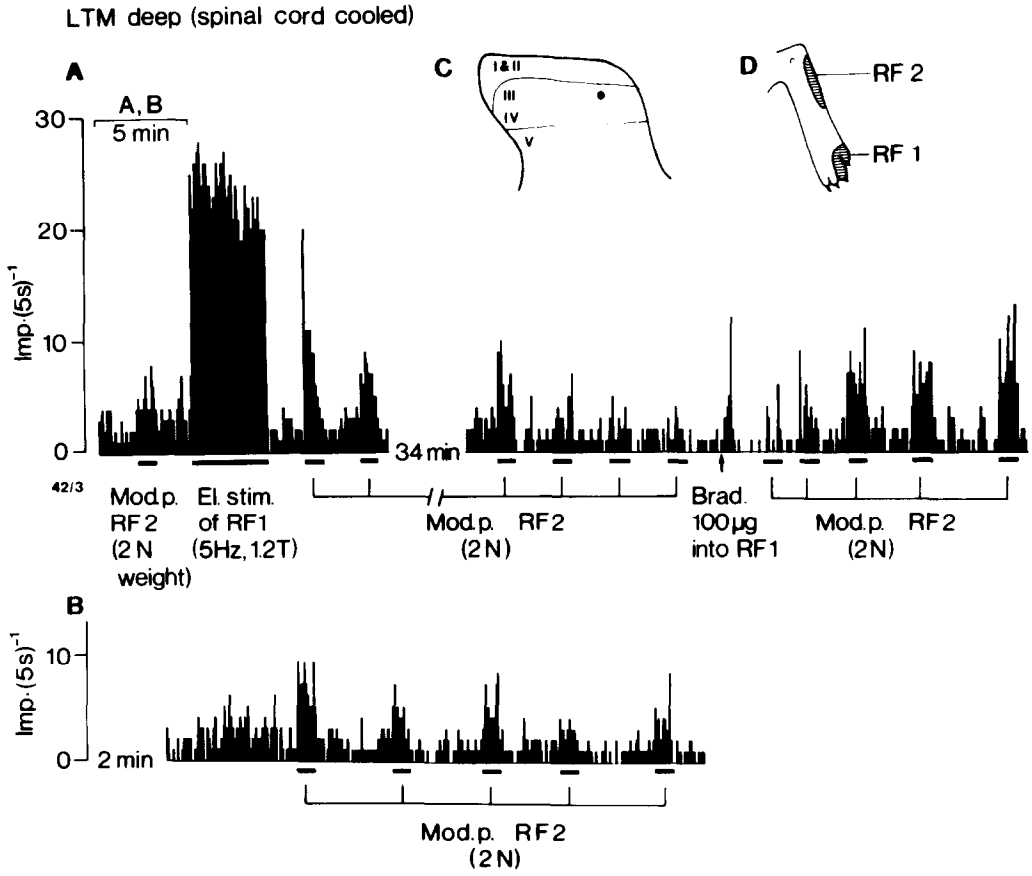

Fig. 1. Modulation of the properties of a receptive field (RF) by stimulating a second RF of the same neurone. A and B: peristimulus time histogram (PSTH) of neuronal activity, B is the continuation of A with an interruption of 2 min. The RFs 1 and 2 were situated in the deep tissues of the left hind paw (D), RF 2 had appeared after a previous electrical stimulation of RF 1 (not shown). Both RFs had low thresholds upon mechanical stimulation (LTM) and responded to moderate (innocuous) pressure (Mod. p.) which was applied with a weight of 2 N via a lever system. After the first mechanical stimulation of RF 2 in A, RF 1 was stimulated electrically at 1.2 times neuronal threshold using needle electrodes introduced into the RF. The injection of bradykinin (Brad.) was performed by infiltrating the deep tissues of RF 1 with 1 ml of tyrode containing the algesic agent. C: the marking point at the recording site in lamina III of the lumbar dorsal horn.

following reasons: (1) in neurones with deep input a maximal response to noxious stimuli does not necessarily reflect input from nociceptors, since muscle LT-mechanoreceptors behave in the same way [cf., 17], and (2) most of the cells did not have a separate response to electrically induced group IV fibre input.

The postsynaptic nature of the discharges was ascertained by using high-frequency electrical stimulation. A neurone was considered to be postsynaptic if it did not follow frequencies of 300 Hz and/or showed a clear jitter of the first action potential. Neurones whose input was apparently dominated by muscle spindles or tendon organs (short latency and low electrical threshold, slowly or non-adapting discharge upon muscle stretch) were discarded.

For recording and processing of the neurophysiological data, conventional electronic equipment was used: electrometer with ionophoresis circuit, amplifier and electronic filter, window discriminator and a laboratory computer for the construction of peristimulus time histograms (PSTHs).

Results

Changes in receptive field properties

In 4 cats, it was possible to record from 6 neurones for a sufficiently long period of time (more than 1 h) in order to study longer lasting changes of the RFs. (The requirement of long observation periods proved to be a problem, since the fine micropipettes used did not record the neurones' activity over a greater distance. Therefore, many neurones were lost after repeated manipulations of the RFs. On the other hand, coarser electrodes would have introduced a higher risk of recording from more than one neurone at a time.) Four of the 6 neurones had more than one RF, and in all cases a deep RF was injected with bradykinin (100 μg in 1 ml tyrode). Bradykinin in such a dose has been reported to excite muscle nociceptors and to elicit pseudoaffective responses in animals and pain in man [cf., 16,17]. Therefore, the chemical stimulus was considered to be painful. After injection of bradykinin, the properties of the RFs were again tested. It is known from previous experiments that the bradykinin stimulus will produce input to the spinal cord for several minutes at the most [17].

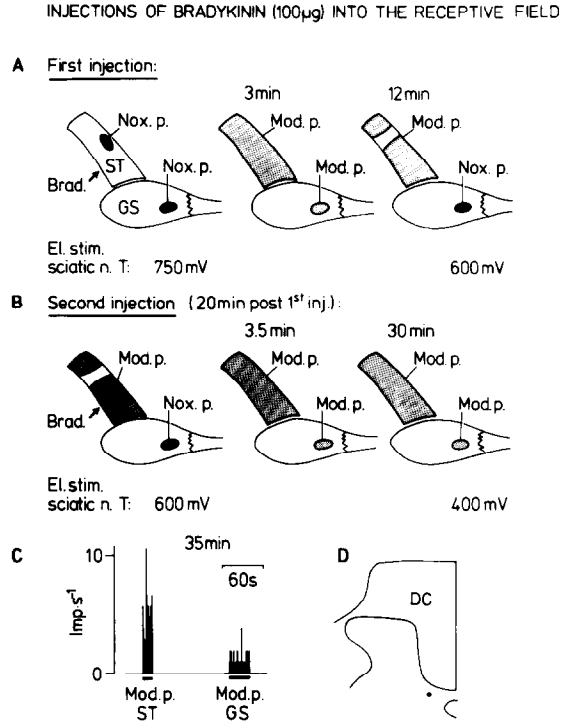

Fig. 2. Enlargement of the bradykinin-injected receptive field and lowering in mechanical threshold of both the injected and non-injected receptive field. A, left panel: situation before injection of bradykinin. The neurone had two RFs, one in the semitendinosus (ST), the other one in the gastrocnemius-soleus (GS) muscle. Both had high mechanical thresholds and required noxious pressure (Nox. p.) for activation. Middle panel: 3 min after infiltration of the ST muscle with bradykinin. The injected RF is greatly enlarged and has now a low mechanical threshold. The RF in the GS muscle likewise shows a decrease in mechanical threshold. Right panel: 12 min after injection of bradykinin. The RF in the GS muscle has regained its high mechanical threshold; in the ST muscle an insensitive strip has appeared. B, left panel: 20 min after injection of bradykinin; time of second injection into the RF in the ST muscle. After the second chemical stimulus, the mechanical threshold of the RF in the GS muscle was lowered for more than 30 min. The electrical threshold of the neurone dropped from 750 mV at the beginning of A to 400 mV at the end of B. C: PSTH of responses to stimulation of the RFs with Mod.p. 35 min after the second injection of bradykinin to show that the lowering in mechanical threshold was not only marginal. The Mod.p. stimulus was totally ineffective before injection of bradykinin. D: location of recording site. RFs marked in black have a high, shaded RFs a low mechanical threshold.

Three of the tested single cells exhibited changes as described below; the responsiveness of the others did not appear to be altered by the bradykinin injection. When first encountered, the neurone shown in Fig. 1 had a single LTM RF in the deep tissues of the 4th and 5th toes (RF 1). After the first electrical stimulation of RF 1 with needle electrodes for 5 min (not shown), another one (RF 2) appeared in the deep tissues just distal to the heel; it also had LTM properties. In Fig. 1, RF 2 was stimulated mechanically with an innocuous standard stimulus of 2 N applied with a mechanical stimulating apparatus. After the first response RF 1 was stimulated electrically for 5 min at 5 Hz with needle electrodes at an intensity of 1.2 times stimulation threshold of the neurone. This led to an increase in response amplitude to the mechanical stimulation of RF 2 for more than 0.5 h. The injection of bradykinin into RF 1 had a similar effect, except that the increase in response magnitude built up more slowly.

In Fig. 2, the results obtained from an HTM (presumably nociceptive) neurone are shown. The cell had two deep RFs, one in the semitendinosus (ST) muscle, the other one in the gastrocnemius-soleus (GS) muscle. After infiltrating the ST muscle with bradykinin, the injected RF lowered its threshold into the innocuous range; the neurone could now be driven by moderate (innocuous) pressure. Simultaneously, the RF expanded in size and now encompassed the entire ST muscle. Three minutes after bradykinin application, the non-injected RF in the GS muscle likewise showed a decrease in mechanical threshold which lasted for about 10 min (Fig. 2A). A second injection of bradykinin 20 min after the first one again de-

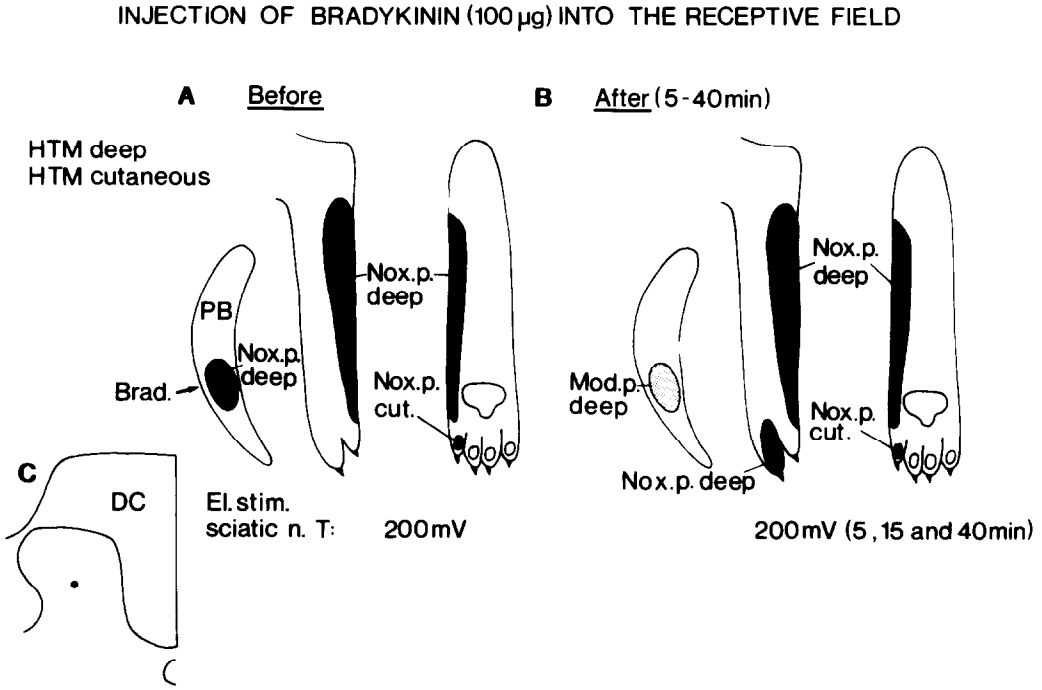

Fig. 3. Appearance of a new receptive field. The neurone had two receptive fields in deep tissues and a third one in the skin in locations as indicated in A. All RFs required noxious intensities of local pressure (cut. = cutaneous) for activation (A). Five minutes after injection of bradykinin into the RF in the posterior biceps (PB) muscle the mechanical threshold of the injected RF had dropped to innocuous levels and a new RF with a high threshold had appeared in the deep tissues of the 4th toe (B). The effect lasted for at least 40 min, at this time the recording of the cell was discontinued. The electrical stimulation threshold of the neurone (200 mV, i.e., in the group I/II range) was unaffected by the injection of bradykinin. C: location of the recording site. HTM, high-threshold mechanosensitive.

creased the threshold of the RF in the GS muscle, but this time the effect lasted for more than 30 min (Fig. 2B). Of course, the decrease in threshold of the injected RF can be attributed to a sensitization of nociceptors in the ST muscle, but the enlargement of the RF and the lowered threshold of the RF in the GS muscle cannot be explained by such a mechanism. In addition, the electrical threshold of the cell upon stimulation of the sciatic nerve likewise decreased after the bradykinin stimulus which cannot be due to events at the receptor site.

Another cell which had HTM RFs in both skin and deep tissues of the hind limb exhibited a new RF in the deep tissues of the toes following injection of bradykinin into an RF in the posterior biceps muscle. The new RF had HTM properties and was present for more than 40 min after the painful chemical stimulus (Fig. 3).

A direct excitatory effect of bradykinin did not appear to be a prerequisite for the long-term modulation of the neurones, since the cell shown in Fig. 2 did not respond to the chemical stimulus, and two other cells which were activated by bradykinin did not show changes in response behaviour.

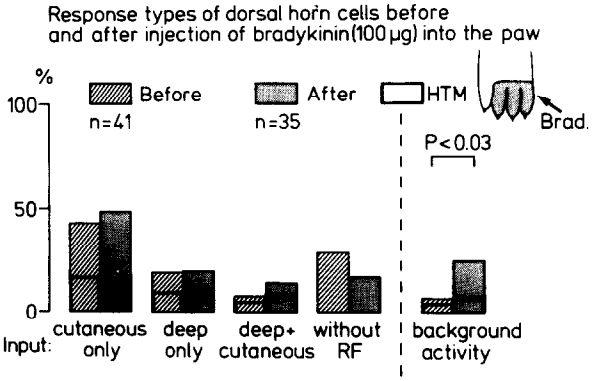

Fig. 4. Classification of unselected lumbar dorsal horn neurones before (hatched) and after (shaded) injection of bradykinin into the deep tissues of the 3th–5th toes of the left hind limb. Boxes of black bars mark the proportion of high-threshold mechanosensitive (HTM) cells. The classification is based on the source of input (cutaneous and/or deep). Cells without RF responded to electrical stimulation only. The two columns at the right-hand end of the figure show the significant increase in the proportion of neurones having background activity (χ^2 test, two-tailed). n indicates the number of cells recorded.

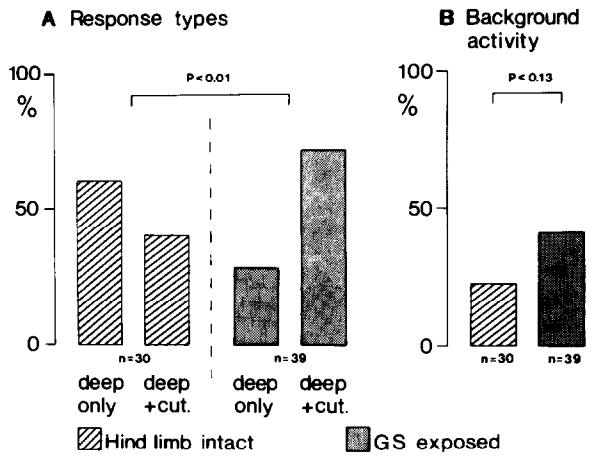

Fig. 5. Comparison of the properties of lumbar dorsal horn neurones with deep input in two series of experiments. In one series the hind limb was left intact (hatched) and in the other one the GS muscle was surgically exposed (shaded). A: proportion of neurones having exclusively deep input (deep only) or input from both skin and deep tissues (deep + cut.). B: proportion of cells having background activity. The χ^2 test (two-tailed) yielded a significant result for A only. The parameter n indicates the number of cells evaluated for the respective series.

As to the location of the neurones it is apparent from Figs. 1–3 that the recording sites were quite deep in the dorsal horn (laminae III–VII). The recording sites of the other 3 cells were not marked; judging from the micrometer reading they were located in and around lamina III.

These data show that a short-lasting noxious stimulus to the deep tissues is capable of changing the response behaviour of individual dorsal horn neurones with deep input for long periods of time. In order to see to what extent such a stimulus would affect the entire population of dorsal horn neurones the following sample studies were performed. Recordings were made from about 10 cells in 6–9 tracks before application of bradykinin and from a similar number of elements during 6 h after the noxious stimulus in tracks about 500 µm rostral to the previous ones. Each cell encountered was classified in terms of input source (cutaneous only, deep only, cutaneous plus deep) and mechanical stimulation threshold (LTM or HTM). The injection of 100 µg bradykinin into the GS

muscle proved not to be followed by clear changes in the response behaviour of the neurones, but the same injection into the deep tissues of the toes of the left hind limb led to detectable changes.

As can be seen in Fig. 4, there was a small increase in the proportion of units having input from both skin and deep tissues, a larger decrease in the proportion of cells having no detectable RF, and a significant increase in the number of neurones displaying background activity (defined as discharges in the absence of intentional stimulation).

Of course, operations at the beginning of an experiment constitute noxious stimuli and are likely to have the same effect. In order to test this assumption, the results of two series of experiments were compared which differed in one aspect only: in one series the hind limb was left intact, and in the other one the GS muscle together with its nervous and vascular supplies was exposed surgically. In these experiments only cells having deep input were studied. The data of Fig. 5 show that the animals in which the hind limb had been opened possessed a smaller proportion of cells having deep input only and a larger proportion of neurones with RFs in both skin and deep tissues. The difference was statistically significant. In support of the data shown in Fig. 4, the proportion of neurones having background activity was increased (non-significantly) in the experiments in which the hind limb had been operated on.

Discussion

The results demonstrate that a short-lasting noxious stimulation of deep tissues leads to long-lasting alterations in the response behaviour of dorsal horn neurones processing deep input. This poses a problem (in addition to differences in anaesthesia) [4] if one wishes to compare results from studies using more or less extensively operated animals. As bradykinin was effective in inducing the changes, the afferent fibres involved probably belong to groups III and IV, since these are known to be the only ones which are activated by injection of the algesic substance into deep tissues [16].

Probably both peripheral and central mechanisms contribute to the observed alterations. The decrease in mechanical stimulation threshold of the bradykinin-injected RF (cf., Fig. 2) is likely to be due to a sensitization of nociceptors by the algesic agent [17]. The enlargement of the injected RF cannot be explained by such a mechanism unless it is assumed that initially insensitive receptive endings have become responsive after contact with bradykinin (in the experiment shown in Fig. 2 the entire ST muscle had been infiltrated with the substance).

The decrease in mechanical threshold of the non-injected RF and the appearance of a new RF in Fig. 3 probably reflects an increase in excitability of the dorsal horn neurones. However, axon reflexes cannot be totally excluded as a possible cause, although the number of afferent fibres with branched axons is probably small (for a recent discussion of this question see [10]). Moreover, the appearance of contralateral RFs in spinal neurones has also been described following noxious input, and this effect cannot be explained by branched primary afferent fibres [24]. In the present study the decrease in electrical stimulation threshold following application of bradykinin (Fig. 2) likewise speaks in favour of a central mechanism. Whether or not the lowered electrical threshold is associated with a greater response to electrical stimulation is not yet known. The finding that not all the neurones that showed an increase in responsiveness had a decreased electrical threshold (cf., Fig. 3) can be explained by assuming that the excitability by nociceptive (group III and IV fibre) input was increased, while the electrical threshold is determined by the (additional) group I/II fibre input. Upon electrical stimulation, none of the single cells tested showed a response to group IV fibre input, and no obvious differences in electrical threshold existed between the cells that were changed after bradykinin injection and those that were not.

The finding that a painful injection into skeletal muscle was less effective for changing the neurones' responsiveness than was an injection into the deep tissues of the toes is surprising since muscle input has been described to be particularly powerful in inducing central nervous changes [22].

It should be kept in mind, however, that the evaluation of the data was such that the alterations shown in Figs. 1–3 would not have led to a change in the frequency distribution of Fig. 4, with the exception of a higher proportion of LTM units which is just recognizable in the 'cutaneous only' and 'deep + cutaneous' category. Of course, the higher innervation density of the distal limb might contribute to the stronger effect of a bradykinin injection into the toes.

As to the effects of the hind limb operation (Fig. 5), the statistical evaluation showed that the change in the bivariate distribution is not due to chance. A probable interpretation is that the skin incisions and/or the surgical exposure of the muscles and nerves produced an input to the spinal cord which elicited changes in the neurones' responsiveness. The operation may also sensitize nociceptors that lie close to the incisions, but this is not the reason for the existence of RFs with LTM properties, since many neurones with deep LTM RFs have also been encountered in animals with intact hind limbs.

The mechanism(s) underlying the long-term changes of the neurones' responsiveness is (are) still obscure. Apparently, supraspinal pathways are not involved, since all data were obtained in cats with a cold block of the spinal cord. The delayed time course of the effect argues against phenomena such as wind-up and post-tetanic potentiation; a speculative explanation would be that the small-diameter deep afferent units release neuropeptides at their spinal terminations which induce slow postsynaptic potentials in dorsal horn neurones [20,25] and thus modulate the excitability of the cells. Such a mechanism has been recently discussed as a possible function for non-myelinated afferent fibres, in addition to the transmission of information on the stimulus that excites them [11].

Since similar alterations of central nervous cells occur in both rat and cat, it seems reasonable to assume that neurones in human beings will show comparable changes following noxious stimulation. The observed decrease in the mechanical threshold of remote, non-injured RFs might be the neurophysiological basis of the remote 'deep tenderness' which is often associated with painful lesions of deep tissues [9,12]. Likewise, the increase in size of the RFs and the appearance of new RFs might be the correlate of the spread or irradiation of deep pain, and the increase in the number of cells with convergent input from skin and deep tissues (cf., Figs. 4 and 5) might reflect the referral of deep pain to the skin [9,13].

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