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BRADYKININ-INDUCED MODULATION OF THE RESPONSE BEHAVIOUR OF DIFFERENT TYPES OF FELINE GROUP III AND IV MUSCLE RECEPTORS

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SUMMARY

1. In order to test the hypothesis that bradykinin has a sensitizing action on muscle receptors (e.g. during a myositis), the response properties of single group III and IV afferent units from the cat gastrocnemius–soleus muscle were compared before and after infiltration of their receptive fields with a bradykinin solution. According to their responses to graded natural stimuli (local pressure, stretch, contractions and temperature changes) the units were classified as (a) nociceptors, (b) low-threshold pressure-sensitive (LTP) receptors, (c) contraction-sensitive (CS) receptors and (d) thermosensitive receptors.

2. Bradykinin activated the majority of both the nociceptive and low-threshold (LTP, CS and thermosensitive) receptors but a sensitization was prominent only among the nociceptors. Most of the sensitized nociceptors showed increased responses to mechanical, but not to thermal, stimuli. The sensitization appeared to be quite specific in that the nociceptors were sensitized either towards local pressure stimulation or to active contractions, but never towards both forms of stimulation.

3. Both group III and group IV nociceptors were sensitized by bradykinin, the proportion of sensitized receptors being greater for group III units.

4. Some of the low-threshold receptors (particularly the CS units) showed a desensitization under the influence of bradykinin.

5. Although bradykinin (by lowering the mechanical thresholds of nociceptors into the innocuous range) could produce the symptom of allodynia, it was not capable of eliciting all the changes in receptor behaviour which are known to occur in inflamed tissues. For instance, no ongoing activity of longer duration and no substantial sensitization of low-threshold receptors have been observed in the present study.

INTRODUCTION

In the course of pathological alterations of skeletal muscle tissue (e.g. inflammation and soreness) the sensations arising from the muscle often change in that spontaneous

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pain and allodynia (pain upon innocuous stimulation) occur. These changes are usually ascribed to an altered responsiveness of nociceptors caused by the release of sensitizing substances from the affected tissue. At the level of single nociceptors, sensitizing phenomena have been observed in the skin (Bessou & Perl, 1969; Perl, Kumazawa, Lynn & Kenins, 1976; Fitzgerald & Lynn, 1977; LaMotte, Thalhammer, Torebjörk & Robinson, 1982), knee joint (Guilbaud, Iggo & Tegnér, 1985; Schaible & Schmidt, 1985) and skeletal muscle (Berberich, Hoheisel & Mense, 1985) following thermal noxious stimulation or induction of an inflammation, respectively. It is well known that under these circumstances various substances are released from the tissue which might affect the resting activity and responsiveness of nociceptors, e.g. bradykinin, histamine, 5-hydroxytryptamine (5-HT) and prostaglandins (Brocklehurst, 1971; Di Rosa, Giroud & Willoughby, 1971; Perl *et al.* 1976). The altered state of the receptors, which is characterized by an increase in resting activity and responsiveness and a lowering in mechanical threshold, has been called sensitization by Bessou & Perl (1969). Up to now, only a few studies have been published that deal with the modulation of the responsiveness of receptive endings by single substances which are released from inflamed tissues. Bradykinin has been reported to increase the heat responses of cutaneous nociceptors in the cat (Beck & Handwerker, 1974) and to sensitize group III and IV receptors in the canine heart towards mechanical stimulation (Uchida & Murao, 1974). Histamine and 5-HT likewise increase the mechanical excitability of myelinated afferent units from the skin (Fjällbrant & Iggo, 1961), and prostaglandin E_2 (PGE_2) has been found to enhance the stimulating effects of bradykinin on cat muscle receptors with non-myelinated afferent fibres (Mense, 1981).

In a recent publication from this laboratory (Mense & Meyer, 1985) four different types of receptors were reported to exist among the thin myelinated (group III, conduction velocity 2·5–30 m/s) and non-myelinated (group IV, conduction velocity less than 2·5 m/s) afferent units in the gastrocnemius–soleus (GS) muscle and tendon of the cat: (1) Nociceptive units which probably mediate deep pain, (2) low-threshold pressure-sensitive (LTP) units which might be involved in the mediation of pressure sensations from deep tissues, (3) contraction-sensitive (CS) units which might be responsible for the adjustment of respiration and circulation during muscular work and (4) thermosensitive units which might play a role in thermoregulatory processes.

The aim of the present investigation was to find out whether bradykinin, besides its well-known excitatory action on group III and IV receptors (Fjällbrant & Iggo, 1961; Beck & Handwerker, 1974; Mense & Schmidt, 1974; Kumazawa & Mizumura, 1977), also has a sensitizing influence on these endings, and whether the different types of group III and IV muscle receptors are differentially affected by this substance. The results of the present investigation show that bradykinin is capable of lowering the mechanical thresholds of group III and IV muscle and tendon receptors. The effect was prominent among nociceptive endings, while the majority of low-threshold receptors were not sensitized. A preliminary account of part of the data has been published (Mense & Meyer, 1981).

METHODS

Some of the cats from which the results were obtained were identical with those used in a previous investigation (Mense & Meyer, 1985), and details of the experimental procedure are described in that report. In short, the animals were anaesthetized with α-chloralose, 60–70 mg/kg I.P. or 40–60 mg/kg I.V., after induction with Ketanest, 10–15 mg/kg I.M. Additional doses of the anaesthetic were given in order to maintain a deep level of anaesthesia characterized by maximal constriction of the pupils and the absence of flexion reflexes. The animals breathed spontaneously. The left gastrocnemius–soleus (GS) muscle with its nerves and vessels was surgically exposed, and over the muscle a pool was formed out of skin flaps which was filled with liquid paraffin. A second pool covered a laminectomy wound from vertebrae L1 to L7. Recordings of single-fibre activity were made from thin filaments of the dorsal roots L7 and S1. Only afferent fibres that could be activated by electrical stimulation of the GS nerves and conducting at less than 30 m/s were studied. The borderline between group III (thin myelinated) and group IV (non-myelinated) afferent units was drawn at a conduction velocity of 2·5 m/s.

Each unit was tested with the following stimuli: (1) local pressure; this was applied by hand and graded as touch (slightly touching the tissue repeatedly (about once every second) with an artist's brush), moderate pressure (steady innocuous deformation of the tissue with broad forceps) and noxious pressure (squeezing the tissue with the same forceps); (2) muscle stretch graded in increments of 3 mm; length increases of more than 8 mm were considered to be unphysiological, since this was the maximal stretch that could be attained by bending the paw; (3) isometric rhythmic contractions of the GS muscle induced by electrical stimulation of the muscle nerve (a train of 50 Hz and 500 ms duration was applied every second for 30–60 s); the voltage required for maximal contractions never exceeded the electrical thresholds of the units under study; the force of contraction was measured by a strain gauge attached to the calcaneal tendon; (4) thermal stimulation with thermodes in contact with the GS muscle; warm (42–43 °C) or cold (26–28 °C) water was circulated through the thermodes; (5) injection of 0·2–0·3 ml bradykinin solution (86 μg bradykinin base/ml Tyrode solution) into the mechanosensitive receptive field; the substance was applied in order to see whether the responses of a given unit to the stimuli (1)–(4) were changed after the receptive ending had come into contact with this substance.

The decisive criterion for the classification of a unit was its strongest response to innocuous stimulation (cf. Mense & Meyer, 1985). Although the great majority of the receptors showed maximal reactions to noxious local pressure they were not considered to be nociceptors, since in skeletal muscle all receptors (even muscle spindles) behaved in this way. A unit was considered to be nociceptive only if it showed no clear-cut response upon innocuous stimulation. Conversely, a receptor responding with a considerable percentage of its maximal discharge frequency to innocuous stimuli was classified as non-nociceptive, even though the maximal response occurred upon noxious stimulation.

Sensitization was thought to have occurred if a unit showed either a qualitative change in responsiveness, i.e. presence of a reaction to a stimulus that was ineffective before application of bradykinin, or a large quantitative increase in the magnitude of response to a given stimulus, i.e. change of a liminal reaction (in a unit without resting discharge, a few spikes per response) into a clear response (a prolonged train of spikes with a frequency of more than about 1 Hz). The same criteria were used in an inverse manner to define desensitization of a unit.

In order to minimize the chance of recording from receptors which might have been sensitized by the non-sterile exposure of the muscle or by repeated testing with strong mechanical and chemical stimuli, the following precautions were taken: (1) all animals received an intramuscular injection (into the contralateral forelimb) of Totocillin (0·1 g/kg) in order to prevent bacterial infections, and (2) for each cat a maximum of three units which had non-overlapping receptive fields were studied.

RESULTS

The present report is based on results obtained from fifty-three receptors in twenty cats. Of these, thirty-three units (seventeen nociceptive, eight low-threshold

pressure-sensitive, six contraction-sensitive, and two thermosensitive ones) were tested for sensitization.

Nociceptive units

These receptors showed the clearest signs of bradykinin-induced sensitization and the highest proportion of units being sensitized. The sensitization was characterized mainly by a lowered threshold to local pressure stimulation. Since the stimuli were applied by hand, no quantitative statements concerning a change in responsiveness to suprathreshold stimulation can be made. A persistent increase in resting discharge was not produced by the bradykinin injections.

In most of the sensitized nociceptive endings touching of or slightly pressing upon the muscle elicited clear responses. These stimuli were ineffective prior to application of bradykinin (Fig. 1). In some of these units, a weak additional sensitization towards active contractions or temperature was also present but these responses were usually liminal. A nociceptor that was clearly sensitized towards the contraction stimulus (but not towards local pressure stimulation) is shown in Fig. 2. In contrast to most of the other sensitized nociceptors which were excited by the bradykinin injection, this receptor did not respond to the injection of the algesic agent. Two of the nine sensitized nociceptors behaved in this way. The lack of a bradykinin response in spite of the occurrence of a sensitization suggests that the dose of bradykinin required for sensitization is lower than that for activation. The responses of the nociceptor to stretch and contractions (Fig. 2*C* and *D*) were quite typical for sensitized receptors in that they were erratic (long-latency response to 3 mm stretch) and not well graded (decrease in magnitude of response in spite of increased contraction force).

No systematic attempts were made to determine the duration of the bradykinin-induced sensitization. However, from the data obtained from two nociceptive endings it can be inferred that the sensitizing effect of bradykinin did not last for a long period of time. Both units had regained their high mechanical threshold about 30 min after injection of bradykinin.

Low-threshold pressure-sensitive (LTP) units

The LTP receptors were usually not sensitized by the injection of bradykinin. A typical example of the behaviour of such a unit is given in Figs 3 and 4. The responses to contractions in Fig. 3*A* were not due to the increase in intramuscular tension (as in most CS receptors) but were a side-effect produced by the movements of the contracting muscle in the pool. The mechanical sensitivity of the ending was so high that shaking the muscle with forceps not touching the receptive field elicited a response of a similar magnitude. The significance of the after-discharge in Fig. 3*B* following the noxious pressure stimulus is not clear; similar discharges were also observed in other LTP units prior to application of bradykinin. An attempt was made to sensitize this unit with substances other than bradykinin, namely prostaglandin E_2 (PGE_2, 20 μg) and KCl (4·7 mg) injected into the receptive field (Fig. 4). Following application of PGE_2 the responses to touch were reduced, and after KCl the touch stimulus was ineffective. Thus, bradykinin did not notably change the responsiveness of the receptor, and PGE_2 and KCl apparently induced a desensitization.

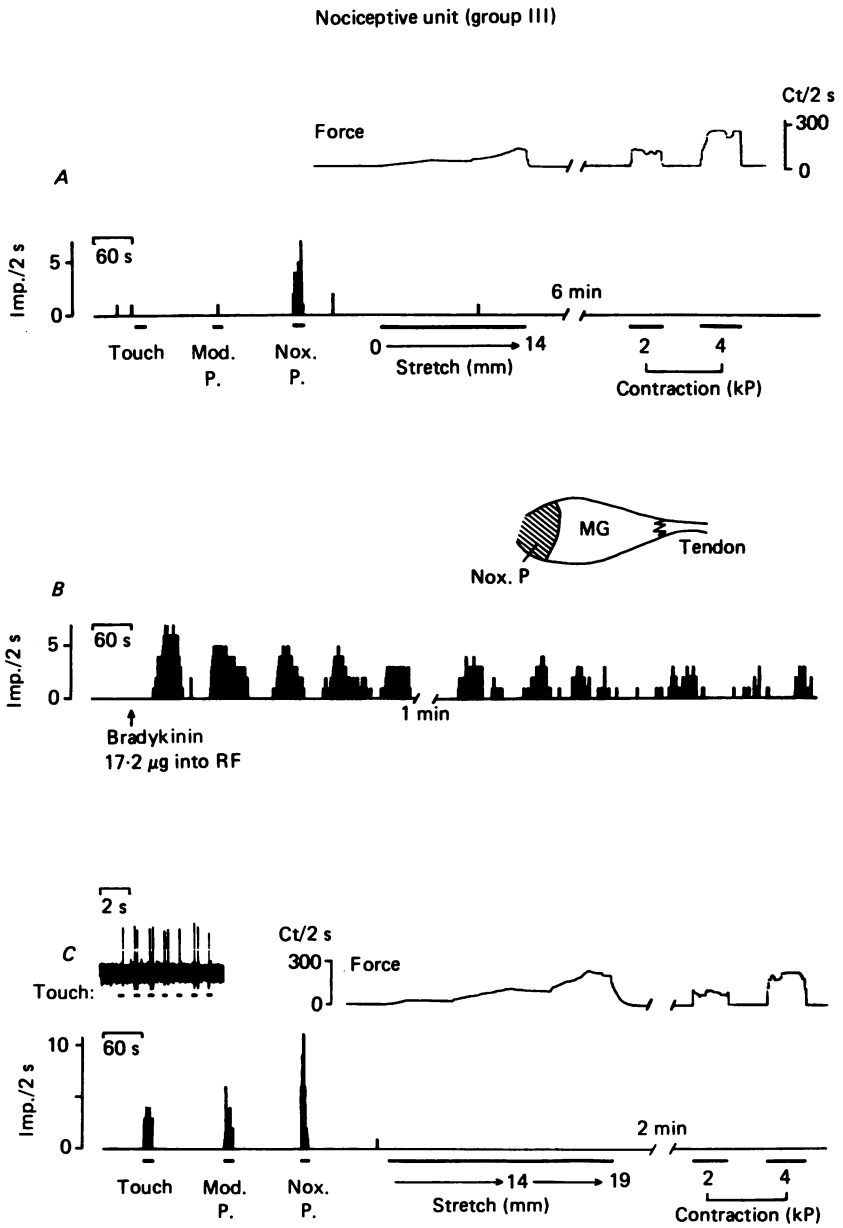

Fig. 1. Responses in impulses (imp.)/2 s of a nociceptive unit sensitized towards local pressure stimulation. Group III afferent fibre, conduction velocity 6·2 m/s. The receptive field is marked by the hatched area on the medial gastrocnemius (MG) muscle, lateral view. Bin width of peristimulus time histogram of the fibre activity: 2 s. The duration of the stimuli used is indicated by the length of the bars underneath the histogram. *A*, Mod. P., moderate pressure; Nox. P., noxious pressure. The scale of the force registration above the histogram is given in arbitrary units (counts (Ct)/2s). *B*, arrow: injection of 0·2 ml Tyrode solution containing 17·2 μg bradykinin into the receptive field (RF). *C*, repetition of *A*. The inset shows original registrations of action potentials elicited by touching the receptive field. The muscle was stretched up to 19 mm in order to see if a sensitivity to stronger stretch was present.

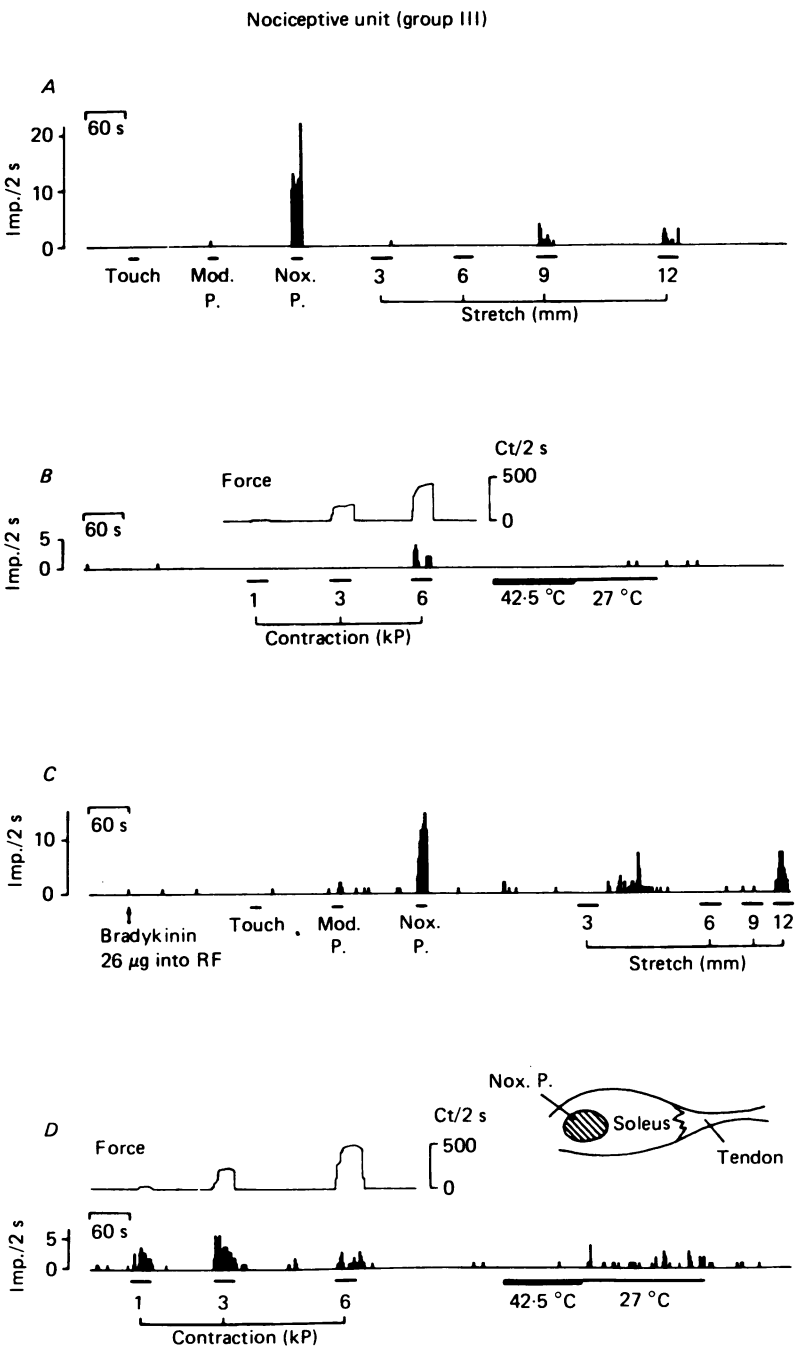

Fig. 2. Nociceptive unit sensitized towards active contractions. Group III afferent fibre, conduction velocity 6·3 m/s. Labelling of receptive field and stimulation procedures as in Fig. 1. *B*, values of cold and warm stimulation indicate temperature of water circulating through thermodes in contact with the receptive field. Please note that prior to application of bradykinin the receptor responded only weakly to noxious stretch (exceeding 8 mm) and maximal contractions (6 kP).

Of the eight units tested with bradykinin all were activated by this substance but only one showed signs of a sensitization. The response to moderate pressure of this unit was increased after bradykinin and the threshold to mechanical stimulation with von Frey hairs lowered from 1·8 to 1·4 P (the receptive field was located deep within the muscle; there was no response to touching the surface of the muscle). One unit appeared to be desensitized by bradykinin; it failed to respond to the touch

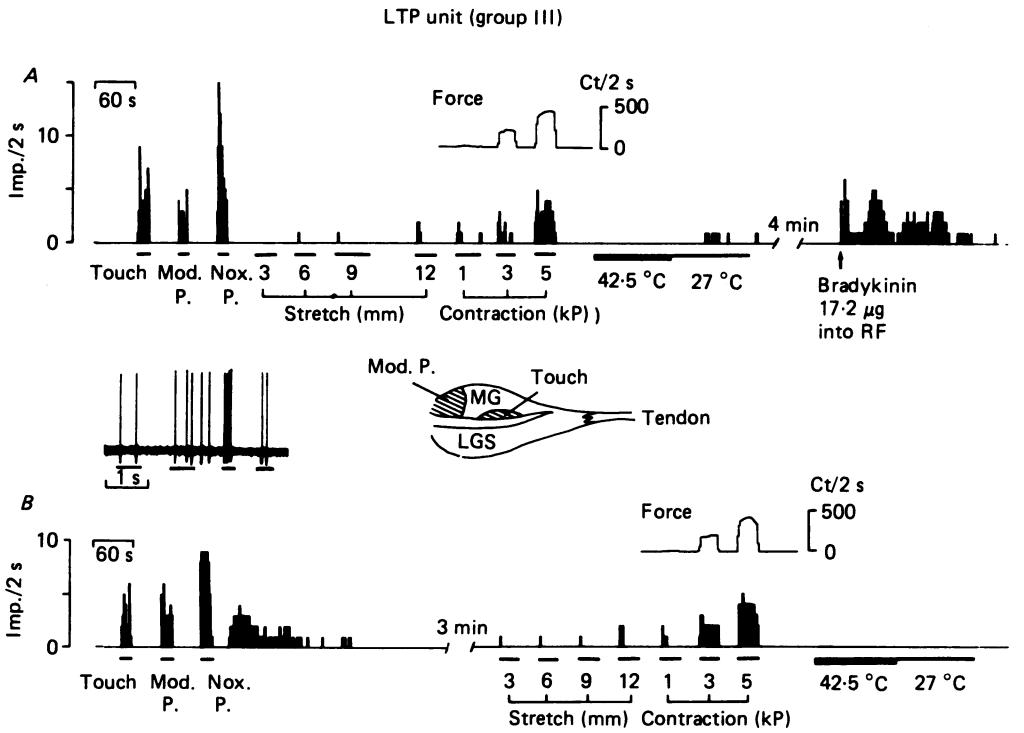

Fig. 3. Low-threshold pressure-sensitive unit not sensitized by bradykinin. Group III afferent fibre, conduction velocity 11·5 m/s. Labelling of receptive field (dorsal view) and stimulation procedures as in Fig. 1. *B* starts directly after the end of *A*. The discharges during contractions were due to relative movements between the receptive field(s) and surrounding structures, therefore, the unit was not considered to be contraction sensitive in the strict sense. The inset shows discharges elicited by the touch stimulus in *A*. Local pressure stimulation and bradykinin were applied to the touch-sensitive receptive field in the middle portion of the MG muscle.

stimulus after application of the algesic agent. The other LTP receptors showed no marked change in response behaviour after injection of bradykinin into their receptive field.

Contraction-sensitive (CS) units

Receptors of this type behaved in a similar way to LTP units in that most of them were not sensitized by bradykinin. However, a large proportion of the CS receptors exhibited a decrease in their contraction-induced responses after injection of bradykinin, i.e. they were desensitized.

Of six CS units tested, none showed signs of a sensitization. Four receptors were desensitized to contraction following application of bradykinin and the remaining two receptors were unchanged.

Thermosensitive units

In the present study, only two thermosensitive receptors (one cold- and one warm-sensitive unit) were tested for possible sensitization, and only the responses to

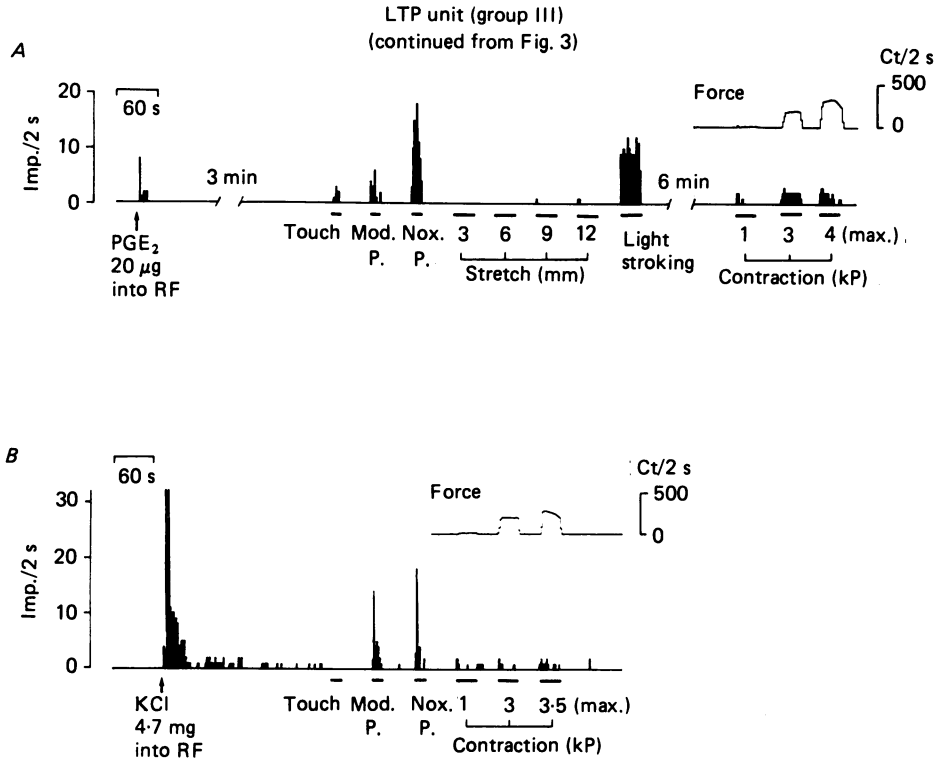

Fig. 4. Same unit as in Fig. 3 showing a desensitization rather than a sensitization following injection of prostaglandin E_2 (PGE_2) and KCl into the receptive field. Note that after KCl application the response to touch was absent. The maximal contraction force decreased from 4 kP in *A* to 3·5 kP in *B* during the testing procedure.

temperature stimuli were compared. In these units no changes in the thermally induced activations could be observed after injection of bradykinin into their receptive fields; also the units were not activated by the algesic agent.

Group III versus group IV fibres

Among the thirty-three units that were tested for bradykinin-induced sensitization, nineteen were group III receptors (six LTP, four CS and nine nociceptors); seven of these (37 %) were sensitized (one LTP and six nociceptors). Of the fourteen group IV units tested (two LTP, two CS, eight nociceptors and two thermosensitive), three (21 %) were sensitized (all nociceptors). The difference between group III and IV receptors becomes clearer if only the nociceptive units are evaluated: of nine

group III nociceptors six (67%) were sensitized, whereas among eight group IV nociceptors only three (38%) showed signs of a sensitization. Thus, group III afferent units appear to be more readily sensitized by bradykinin than group IV units.

Activation versus sensitization by bradykinin

When the receptors responding to innocous stimulation (low-threshold receptors, LTP, CS and thermosensitive units) are compared with those having a high mechanical threshold (nociceptive units), it is apparent that a high proportion of both populations can be activated by bradykinin (Fig. 5*A*). In fact, the percentage

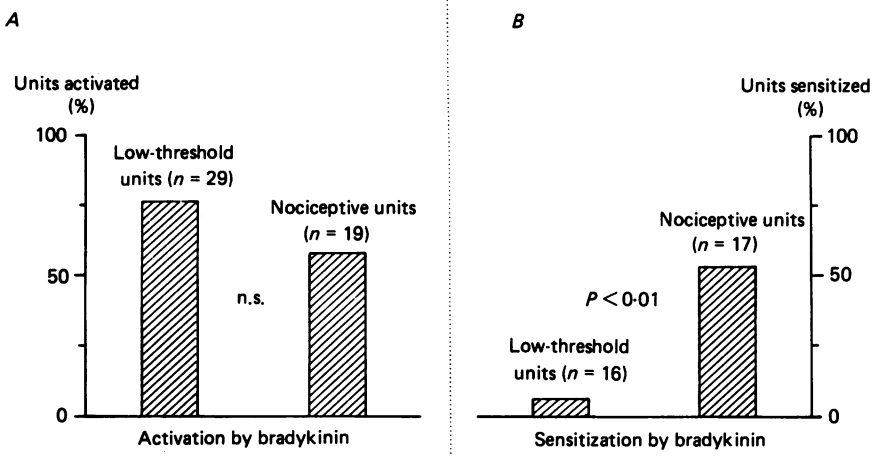

Fig. 5. Response types and reactions to bradykinin. *A* shows the proportion of units being activated by bradykinin. Only part of these units (those shown in *B*) were tested for a bradykinin-induced sensitization. Low-threshold units include LTP, CS and thermosensitive receptors. *n* indicates the number of units tested. In *A*, the difference in the proportion of responding receptors was not statistically significant (n.s.; $P > 0{\cdot}1$, χ^2 test, two-tailed); for the sensitized receptors in *B* it was significant ($P < 0{\cdot}01$).

of units responding to bradykinin was slightly higher among low-threshold receptors, and many of these units were more vigorously excited by the algesic agent than were nociceptive endings. However, a significant difference existed in the proportion of sensitized units between low-threshold receptors and nociceptors (Fig. 5*B*). Of the sixteen low-threshold units tested only one was sensitized, while nine out of seventeen high-threshold receptors showed signs of a sensitization. Thus, a sensitization by bradykinin appears to be a more reliable indication of the nociceptive nature of a receptive ending than an activation by this substance.

Three nociceptive endings were clearly excited by the injection of bradykinin without being sensitized. The reason for the lack of sensitization in these cases is not clear; possibly skeletal muscle (and tendon) contain different types of nociceptors which may behave differently with respect of sensitization. An alternative explanation would be that the changes in responsiveness were so small that they could not be detected by the rather coarse testing methods used.

The question of unwanted sensitization

Since sensitized nociceptors behaved in a similar way to the LTP receptors of the present study (compare Figs 1*C* and 3*A*), the possibility had to be considered that (in spite of the precautionary measures described in Methods) the latter types were originally nociceptors that had been sensitized by the exposure of the muscle and/or testing of the receptive field with noxious local pressure. The following evaluations were performed in order to obtain data pertaining to this question.

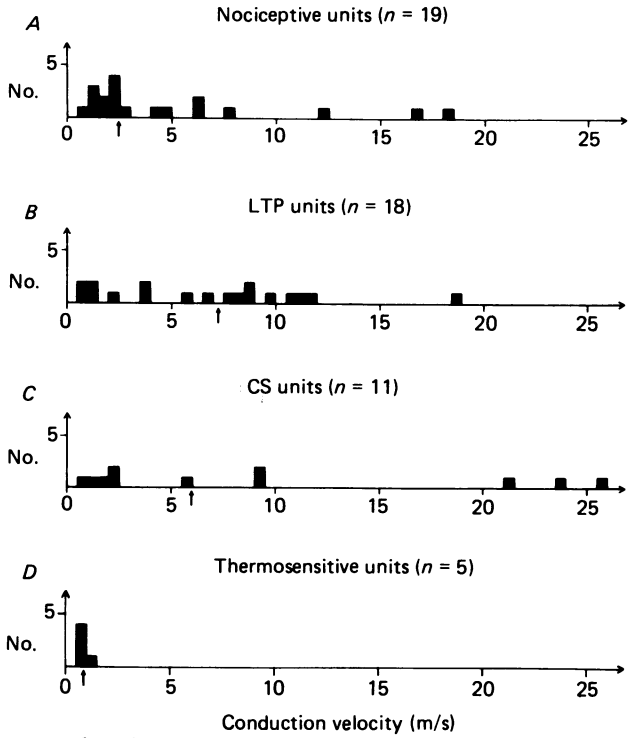

Fig. 6. Frequency distribution of conduction velocities of the four response types. In addition to the data shown in Fig. 5 this Figure contains afferent units which were functionally identified but not tested with bradykinin. Bin width of abscissa: 0·5 m/s. The arrows mark the median values.

Comparison of conduction velocities. If the low-threshold receptors were sensitized nociceptors the distribution of conduction velocities of the four types should be identical. As can be seen from Fig. 6 this is not the case. Although the data are not sufficient for a statistical evaluation, it is apparent that the shape of the distributions and the median values are quite different: 2·44 m/s for nociceptive, 7·23 m/s for LTP, 5·93 m/s for CS, and 0·86 m/s for thermosensitive units.

Comparison of background activity. Sensitization is often combined with the development of background activity in formerly silent units (Perl *et al.* 1976). Thus, an increased background activity in LTP, CS and thermosensitive units (in comparison with nociceptors) would be consistent with the assumption that those receptors are in reality sensitized nociceptors. However, Fig. 7 shows that (besides

the thermosensitive receptors) the nociceptive endings were the ones that had a high level of background activity, while LTP and CS receptors were much less active in the absence of intentional stimulation.

These data do not support the assumption that the low-threshold receptors of this report (and of a recent one (Mense & Meyer, 1985)) are sensitized nociceptors. The observed differences in the bradykinin-induced sensitization between low-threshold (LTP, CS and thermosensitive) and high-threshold (nociceptive) units most probably reflect functional differences between nociceptive and non-nociceptive endings.

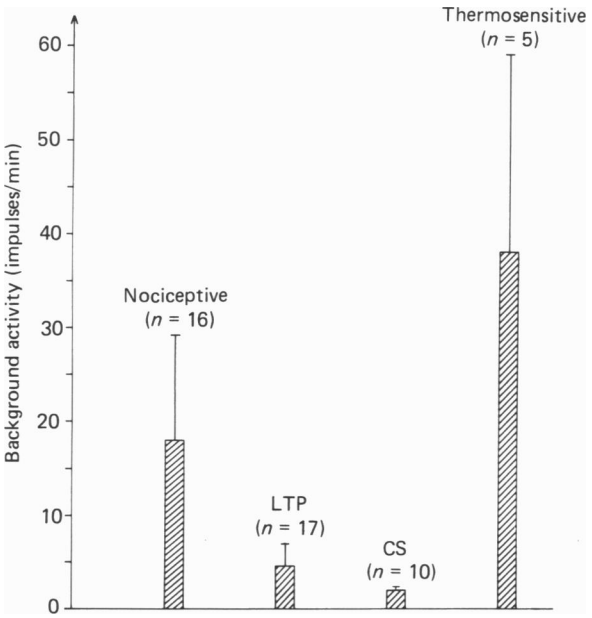

Fig. 7. Background activity in the four response types (mean ± S.E.M.). The activity was determined during the first minute of sampling of quantitative data, i.e. at a time corresponding to the first 60 s of panel *A* in Figs 1, 2 and 3. *n* indicates the number of units evaluated.

DISCUSSION

The results show that bradykinin lowers the mechanical threshold of nociceptors and thus is capable of inducing that change in the response properties of these endings which is supposed to underlie the allodynia in cases of inflammatory or other lesions of deep tissues. Such lesions are known to release bradykinin from its precursor molecule kallidin, a decapeptide contained in the plasma proteins (Brocklehurst, 1971).

Since in the present study bradykinin was found to sensitize some units without exciting them, it is assumed that for activating a nociceptor a higher concentration of bradykinin is required than for sensitizing it. This does not mean, though, that upon increasing the bradykinin concentration a lowering in mechanical threshold always precedes an increase in discharge frequency. In the present sample, there were three units that were activated by bradykinin but showed no signs of a lowered

mechanical threshold. Apparently, the increase in discharge frequency and the lowering of the stimulation threshold are quite independent phenomena. This notion is supported by data from group III and IV muscle afferent units in cats with an artificial myositis showing that a long-term increase in background activity can occur without any detectable lowering in the mechanical stimulation threshold (Berberich *et al.* 1985). A similar dissociation between ongoing discharge and lowering in threshold has been observed in polymodal nociceptors of the rabbit skin (Fitzgerald, 1979).

With one exception, the non-nociceptive endings (LTP, CS and thermosensitive units) showed either no sensitization or were desensitized following application of bradykinin. Therefore, tissue lesions in the course of which bradykinin is released should be associated with a reduced input via low-threshold group III and IV afferent fibres to the spinal cord. In the present study, two large-calibre afferent units (one group II secondary ending of muscle spindle and one tendon organ) were also tested with bradykinin. Neither responded to the algesic agent but showed a reduced sensitivity to muscle stretch after bradykinin. If a desensitization of low-threshold afferent units is a consistent consequence of tissue lesions releasing bradykinin, this might add to the painful sensations arising from that tissue by reducing non-nociceptive input to the dorsal horn.

In a study on cutaneous afferent units in the cat, Fjällbrant & Iggo (1961) likewise described activation of non-nociceptive (low-threshold) receptors by bradykinin, with the exception of group IV afferent units which were not excited by the bradykinin preparation used by the authors. Following the application of histamine and serotonin they observed effects similar to those of the present report, namely weak activation of mechanoreceptors (and thermoreceptors) which was followed by a reduced sensitivity to natural stimuli.

Concerning the observed differences in sensitization between group III and IV afferent units, the available data in the literature are heterogeneous, partly due to the different models used. It has been reported that both myelinated and non-myelinated nociceptive units in the skin can be sensitized by heating (Fitzgerald & Lynn, 1977; Campbell, Meyer & LaMotte, 1979; Fitzgerald, 1979) but among the mechanoheat-sensitive nociceptors only those having non-myelinated afferent fibres have been assumed to mediate the hyperalgesia following injury by heat (LaMotte *et al.* 1982). This finding is supported by data obtained from afferent units from an inflamed muscle in the cat (Berberich *et al.* 1985) showing that only group IV receptors exhibited a significant increase in mechanical excitability. This change appears not to be due to a release of prostaglandins since the mechanosensitivity of group IV units from the cat knee joint (in contrast to group III units) has been reported not to be influenced by PGE_2 and PGE_1 (Heppelmann, Schaible & Schmidt, 1984). Slowly conducting afferent units from arthritic joints have been found to be sensitized towards local pressure stimulation in the rat (Guilbaud *et al.* 1985) but not in the cat (Schaible & Schmidt, 1985). The reason for this difference is unknown.

As to the mechanism underlying the bradykinin-induced sensitization, no generally accepted theory is available. It is not even known whether the observed changes in responsiveness are due to a direct action of bradykinin on the endings or to an indirect action mediated by a substance released by bradykinin from tissue cells. In

fact, bradykinin has been reported to be one of the most potent endogenous agents releasing prostaglandins (PGE_2 and PGI_2) (Juan, Sametz, Petronijevič & Lembeck, 1984) via activation of phospholipase A_2 (Juan, 1977). Therefore, the observed sensitization could also be caused by prostaglandins (e.g. PGE_2; Heppelmann *et al.* 1984; cf. also Ferreira & Nakamura, 1979) or other substances which are probably released by the bradykinin injections, such as substance P and leukotrienes (Lembeck & Holzer, 1979; Samuelsson, 1983).

The intramuscular injection as such is a tissue lesion and may release sensitizing substances, irrespective of the composition of the injected solution. In fact, preliminary results in this laboratory (U. Hoheisel & S. Mense, unpublished) have shown that the infiltration of a rat muscle with Tyrode solution causes a transient accumulation of leukocytes outside blood vessels. Apparently, the normal control procedure of injecting the solvent without bradykinin elicits inflammatory reactions and therefore cannot be considered to be a real control. For this reason receptors in non-injected muscles were used as a control population. In comparison with the effects of the large amounts of bradykinin injected in the present study, the influence of the injection procedure itself is probably small.

Although bradykinin produces all the signs of an inflammation if introduced into living tissue (Elliott, Horton & Lewis, 1960), the behaviour of group III and IV muscle receptors under the influence of this substance differs from that in an inflamed muscle. Preliminary results have shown (P. Berberich, U. Hoheisel & S. Mense, unpublished) that in an inflamed muscle many receptors exhibit an increase in background activity. The development of an ongoing activity outlasting the direct bradykinin response has never been observed in the present study. Moreover, in an inflamed muscle low-threshold mechanosensitive receptors also show signs of a sensitization in that they develop an increased background activity and/or a lowered mechanical threshold. These changes in the discharge behaviour of non-nociceptive endings are probably not due to bradykinin but to other substances released from inflamed tissues, or to a combined action of bradykinin with other substances. Such combinations of inflammatory mediators have been found to be much more effective in oedema formation than single substances (Amelang, Prasad, Raymond & Grega, 1981). In our experiments, bradykinin in isolation produced a lowering in mechanical threshold almost exclusively in nociceptors and thus may be responsible for the allodynia of an inflamed muscle. Since the nociceptors were either sensitized towards local pressure or to contractions, it is possible that the tenderness to pressure stimulation and the pain during movements arising from an inflamed muscle are mediated by different populations of nociceptors. Bradykinin activated many nociceptors for some minutes but did not produce an ongoing discharge in these receptors, which is supposed to be the neurophysiological correlate of spontaneous pain. The occurrence of persistent spontaneous pain in cases of myositis may require a continuous release of bradykinin, the release of inflammatory substances other than bradykinin, or a combined action of bradykinin with these substances.

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