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The effects of locally applied capsaicin on conduction in cutaneous nerves in four mammalian species

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1 By examination of compound action potentials in the saphenous nerve of the anaesthetized rat it has been shown that capsaicin causes a rapid, dose-dependent, failure of conduction in many C-fibres when applied directly to the nerve. A large reduction in C-fibre conduction occurs with concentrations as low as 110 μM. After a 15–30 min exposure to capsaicin, only partial recovery occurs in 1 h.

2 Similar block of C-fibre conduction occurs in the ferret. However, only smaller, reversible, reductions in C-fibre conduction were seen in the guinea-pig and rabbit, even at the highest concentration of capsaicin used (33 mM).

3 A small reduction in the Aδ component of the compound action potential occurred in all four species. In the rat and ferret the effects were much less than those on C-fibres.

4 At high doses, small reversible effects were also seen on the fastest conducting A$\alpha\beta$ component of the compound action potential in the rat, rabbit and guinea-pig; no effects were seen on the A$\alpha\beta$ fibres in the ferret.

5 Decreases in amplitude of the compound action potential were accompanied by some slowing of conduction in most cases. The slowing was less than 5% except for the rat A$\alpha\beta$ and C-fibres and the ferret C-fibres where 9–15% changes occurred at the highest doses of capsaicin.

6 Opening the connective tissue sheath of the nerve did not significantly increase the effectiveness of capsaicin.

Introduction

Capsaicin treatment, either by local application to nerve trunks or by subcutaneous injection, leads to (a) the depletion of substance P and other neuropeptides from somatic and visceral afferent neurones and (b) a reduction in behavioural responses to noxious stimuli and in neurogenic inflammatory reactions (e.g. see Fitzgerald, 1983). This and other evidence has led to the suggestion that substance P plays an important role in nociception and neurogenic inflammation (Lembeck & Gamse, 1982). However, there are a number of situations where the extent or time course of peptide depletion does not match the functional changes. For example, when capsaicin is applied locally to a cutaneous nerve in the rat the effect of antidromic stimulation on vascular permeability is abolished within a few hours, well before any major change is seen in peptide levels (Gamse *et al.*, 1982). Because of these mismatches, the functional role of substance P and other neuropeptides in nociception and neurogenic inflammation has been questioned (Wall & Fitzgerald, 1982).

In the case of local application it has been proposed that the early functional changes might arise if, in addition to its long-term action on peptide levels, capsaicin produced an immediate block of nerve conduction in afferent C-fibres (Gamse *et al.*, 1982). Direct electrophysiological examination of conduction in rat nerves exposed to capsaicin has, however, yielded conflicting results. Wall & Fitzgerald (1981) reported no effects on conduction whilst Petsche *et al.* (1983) found substantial, but rather variable, conduction block in C-fibres. Our preliminary results in the rat indicated that marked effects on both C-fibre and A-fibre conduction did occur (Pini, 1983; Lynn *et al.*, 1984).

As well as being relevant to the question of how capsaicin produces its effects on nociception and neurogenic inflammation, these results are of interest in their own right. Capsaicin appears to produce a particularly powerful and long-lasting block of conduction in afferent C-fibres and is therefore potentially

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of interest as a selective local anaesthetic agent. For this reason we have looked in detail at the dose-dependence of capsaicin's action on conduction in A and C-fibres in nerves in the rat. Preliminary experiments in the rabbit failed to show any nerve blocking action (Lynn & Pini, 1985b). In order to establish that capsaicin did act in a range of mammalian species, we have looked at the rabbit in more detail and at two other species, the ferret and the guinea-pig.

Methods

Experiments have been performed on hindlimb nerves of deeply anaesthetized animals. Rats, ferrets and rabbits were anaesthetized with urethane ($1.5-1.8\,g\,kg^{-1}$) given intraperitoneally (rats and ferrets) or intravenously via the marginal ear vein (rabbits). Guinea-pigs were anaesthetized by the neuroleptanaesthesia procedure described by Evans & Harrison (1980); initial i.p. doses of droperidol ($5\,mg\,kg^{-1}$), phenoperidene ($1\,mg\,kg^{-1}$) and sodium pentobarbitone ($30\,mg\,kg^{-1}$) were followed by approximately hourly injections of phenoperidene ($1\,mg\,kg^{-1}$) and pentobarbitone ($3\,mg\,kg^{-1}$). Blood pressure was monitored via the carotid artery; systolic pressure was usually above 100 mmHg and recordings were stopped if it fell below 60 mmHg. Rectal temperature was measured with a thermistor probe and was maintained at 37.5 ± 1°C.

Recordings were made from the saphenous nerve in the upper leg in all four species and, in addition, from the sural nerve in the popliteal fossa in some rabbits. The arrangement of the electrodes and the treatment site were similar in all preparations and are shown in Figure 1a. The nerve was cleared proximally from the surrounding tissues over a length of about 7 mm and cut at the central end. Recordings were made using two platinum wire electrodes, one at the cut end of the nerve and one 2–4 mm distal. In some rat experiments the nerve was desheathed at the recording site to improve the signal-to-noise ratio. In some ferret experiments the recordings were made from the nerve distally to the stimulation points and with it left in continuity. Neither of these changes altered the general pattern of the results obtained. A pair of platinum wires were used for stimulation and were placed 9–54 mm from the recording point. A 3–5 mm length of nerve between the distal stimulation point and the recording site was cleared for application of capsaicin. In some experiments a second pair of stimulating electrodes was positioned nearer to the recording site and proximal to the treatment point, enabling conduction in untreated nerve to be monitored. A barrier (Figure 1a) was positioned immediately proximal to the treatment site to stop spread of capsaicin to the proximal stimulating electrodes or to the recording point. As far as possible the blood supply to the nerve was preserved. The temperature close to the nerve was checked in a series of similar experiments and was always within 1°C of the rectal temperature.

Capsaicin was dissolved in olive oil, a solvent that was found in control experiments to be without effect on conduction. The solution was applied with small pieces of cotton wool which were packed around the nerve. The nerve sheath was normally left intact at the treatment site. However, in a small number of rabbit and guinea-pig experiments the sheath was slit longitudinally in the treatment area with a small piece of razor blade. Capsaicin was applied for 15 or 30 min. Very little extra effect occurred after 15 min except in the rabbit and the time course of recovery was similar for both treatment times. Data from both treatment times has been pooled where appropriate. After removal of the capsaicin-soaked cotton wool the treated area was washed twice with olive oil and twice with saline. Only one treatment was applied to each nerve except where the first treatment was a low dose that had no effect, in which case a second treatment was applied after an interval of at least 30 min.

Conduction was assessed by recording compound action potentials using an amplifier with a low frequency time constant of 1 s and high frequency time constants of 30 μs for A-fibre and 1 ms for C-fibre potentials. The C and Aδ components of the compound action potential (c.a.p.) were usually diphasic in form, despite recording from a cut end (e.g. see Figure 1b). The most reliable measure of the size of the C potential was its peak-to-peak amplitude. Attempts to use area measurements were not pursued because of the problems arising from the complex shape of many of the potentials. Amplitudes were measured with just maximal stimulus strengths for each major component of the c.a.p. and latencies were measured to the beginning and/or the peak of each component, usually at twice the threshold stimulus strength. Changes in peak-to-peak amplitude will only accurately reflect changes in numbers of fibres conducting if there are no marked shifts in the spread of unit conduction delays. As a check, a small sample of single fibres has been examined during application of a maximal dose of capsaicin in the rat and rabbit. In the rat many C-fibres were blocked by capsaicin, mostly those of the polymodal nociceptor type, as reported by Petsche *et al.* (1983). In the rabbit both c.a.ps and single units were examined in two preparations. In one preparation there was no fall in the c.a.p. amplitude and 3 single C-units examined were also not blocked. In the second preparation a large, reversible reduction in the c.a.p. occurred and 5 single units were also blocked with subsequent recovery. So in this small sample there was an excellent correlation between c.a.p. measurements and the behaviour of single C-units.

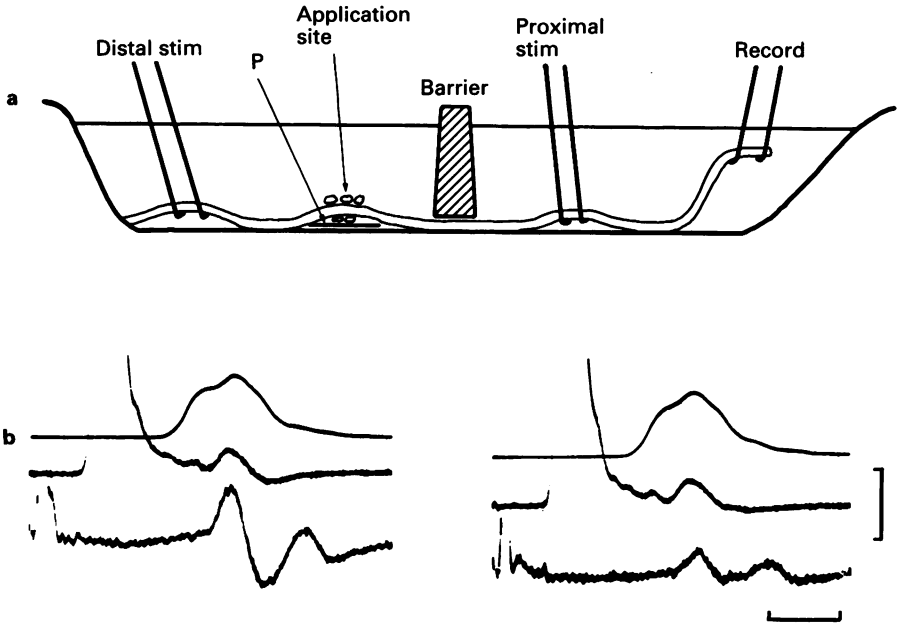

Figure 1 (a) Diagrammatic representation of the preparation. The barrier consisted of packed pieces of cotton wool soaked in saline in most experiments. In some rat experiments with 33 mM capsaicin, a piece of thin acetate sheet embedded in alginate dental impression material was used. P = polythene sheet to reduce spread to adjacent tissues. In some experiments only the distal stimulating electrodes were used. Distance from distal electrodes to recording electrodes ranged from 9–54 mm. (b) The different components of the compound action potential in the rat saphenous nerve before and during the application of 0.33 mM capsaicin in olive oil. Left panel, control traces immediately before application; right panel, 12 min after applying capsaicin. In each panel, upper traces show the Aαβ component, time calibration 0.4 ms, amplitude calibration 2 mV; middle traces show the Aδ component, calibrations 1.0 ms, 0.4 mV; lower traces show C component, calibrations 10 ms, 100 μV.

Further aspects of this problem of relating conduction block to c.a.p. amplitude will be considered in the Discussion.

The significance of differences between means was determined by use of *t* tests unless otherwise stated. Drugs used were: capsaicin (8-methyl-*N*-vanillyl-6-nonenamide), Merck; droperidol (Droleptan), Janssen; phenoperidene hydrochloride (Operidine), Janssen; sodium pentobarbitone (Sagatal), May & Baker.

Results

The effect of capsaicin on conduction in cutaneous nerves in four mammalian species has been examined by recording compound action potentials (c.a.ps). The general shape of the c.a.p. was similar in all the species. The A-fibres gave a major fast-conducting peak that will be referred to as the αβ component. The slower A-fibres gave a series of peaks, with usually one clear-cut component at 8–13 m s^{-1} conduction velocity. This was the slowest component and will be called here the δ c.a.p. However, it should be noted that in all nerves there were other smaller peaks that also conducted with velocities in the δ range. The C-fibre component of the c.a.p. was always clearly separated from the A-fibre components. Its fastest fibres conducted at 1–1.5 m s^{-1} and the shape was di- or multi-phasic.

Compound action potential amplitudes were smaller for distal than for proximal stimulation, presumably because the action potentials in individual fibres become desynchronized and so summate less well. Peak-to-peak amplitudes of both A-fibre and C-fibre components were approximately inversely proportional to the conduction distance over the range of conduction distances used in this study. For example, in 8 rat experiments with two sets of electrodes the average control c.a.p. amplitudes were 6.07 mV (A) and 264 μV (C) for proximal stimulation with an average conduction distance of 10.8 mm and 2.25 mV (A) and 101 μV (C) for distal stimulation at 26.3 mm. Thus for an approximate 2.5 fold increase in

conduction distance, and so in average conduction time, the c.a.p. amplitudes fell to 37–38%.

In the four species examined the pattern of c.a.p. changes following capsaicin application differed, so the results from each will be considered in turn.

Rat

As shown in Figure 1b, capsaicin applied directly to the saphenous nerve produced a profound reduction in the size of the C-fibre component of the c.a.p. with only a small shift in latency, indicating a substantial degree of conduction block in the treated segment of the nerve. Conduction in the untreated, proximal, part of the nerve was unaffected. The onset of the conduction block was rapid, within 1 min at high concentrations. As shown in Figure 2c, the maximum effect was reached in 5–15 min. On removal of the capsaicin the c.a.p. slowly increased in size but 1 h later was still substantially below control levels. This failure of recovery was not due to any general deterioration since the fast Aαβ component recovered fully and also in 13 experiments where the A and C components were recorded with stimulation proximal to the treatment site, these remained stable throughout the period studied.

The effect of different concentrations of capsaicin is shown in Figure 2c. In the rat, 11–33 μM produced no significant effect whilst 110 μM produced a large reduction in C-fibre c.a.p. Interestingly, even at the highest concentrations used (1%; 33 mM) the C-c.a.p. was not usually completely abolished. Recovery, even from low doses, was slow and a substantial effect was still present 45 min after removing capsaicin (see Figure 2c). As in Figure 1b, the C-c.a.p. often comprised two components in which case the larger early component was usually reduced more than the late component. Changes in C-c.a.p. amplitude were accompanied by increases in conduction delay and these are plotted in Figure 2f. With 33 mM capsaicin there was an average increase of 19% (± 4%, s.e.mean, $n = 4$) whilst with 110 μM the increase was only 7% (± 3%, $n = 5$).

The Aαβ component of the c.a.p. was not significantly affected by low doses of capsaicin (e.g. see Figure 1b) but was reduced by 33 mM, the largest concentration used. As can be seen from Figure 2a, this component fell by 30% during a 30 min application and then largely recovered to control levels in 40–60 min. As with the C-c.a.p., these amplitude changes were accompanied by latency increases averaging 12% (± 3%, $n = 7$) (see Figure 2d).

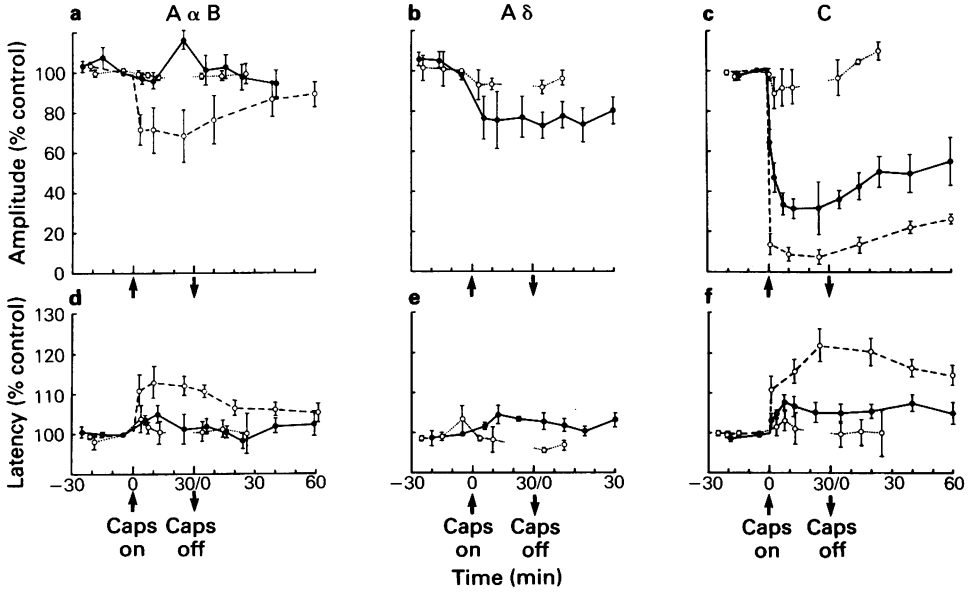

Figure 2 Amplitudes (a–c) and latencies (d–f) of Aαβ (a,d), Aδ (b,e) and C (c,f) components of the compound action potential (c.a.p.) in the rat saphenous nerve at various times before, during and after the application of capsaicin (Caps) at 3 different concentrations: (––○––) 33 mM, $n = 7$; (—●—) 0.11–1.1 mM, $n = 8–9$; (···○···) 33 μM, $n = 2–3$. Error bars show s.e. When only 15 min applications were used, this is shown by a break in the graph and post-application points have been plotted from the same reference time as with 30 min applications.

The slowest component of the A-fibre c.a.p., the δ component, was studied in most rats, but not in any of those treated with 33 mM capsaicin. This component was too small to measure in some nerves and was often the first component to suffer general deterioration during long recordings. Data on the δ fibres is thus rather less complete than that on the $\alpha\beta$ or C-fibres. However, significant reductions were seen at concentrations of 110 μM–1.1 mM in several nerves (although not the one in Figure 1b) and on average there was a fall of 25% ($\pm$ 11%, $n = 6$). These reductions in c.a.p. amplitude are significantly smaller than the fall in C-fibre c.a.p., but are in turn significantly greater than the effect on $\alpha\beta$ fibres at these concentrations. The relatively small changes in δ-c.a.p. amplitude were not accompanied by any significant increases in latency, although there was a slight trend in this direction (see Figure 2e).

*Ferret (*Mustela putorius furo *L)*

The main results from the ferret are summarized in Figure 3 together with traces showing typical c.a.ps from the ferret saphenous nerve. In general, ferret c.a.ps were much like those in the rat, but the A-fibres conducted about 20% faster. The C-c.a.p. was reduced markedly by capsaicin just as was found in the rat, although an approximately 3 times greater concentration was required to produce a large effect (see Figure 3b). The duration of the reduction again lasted for at

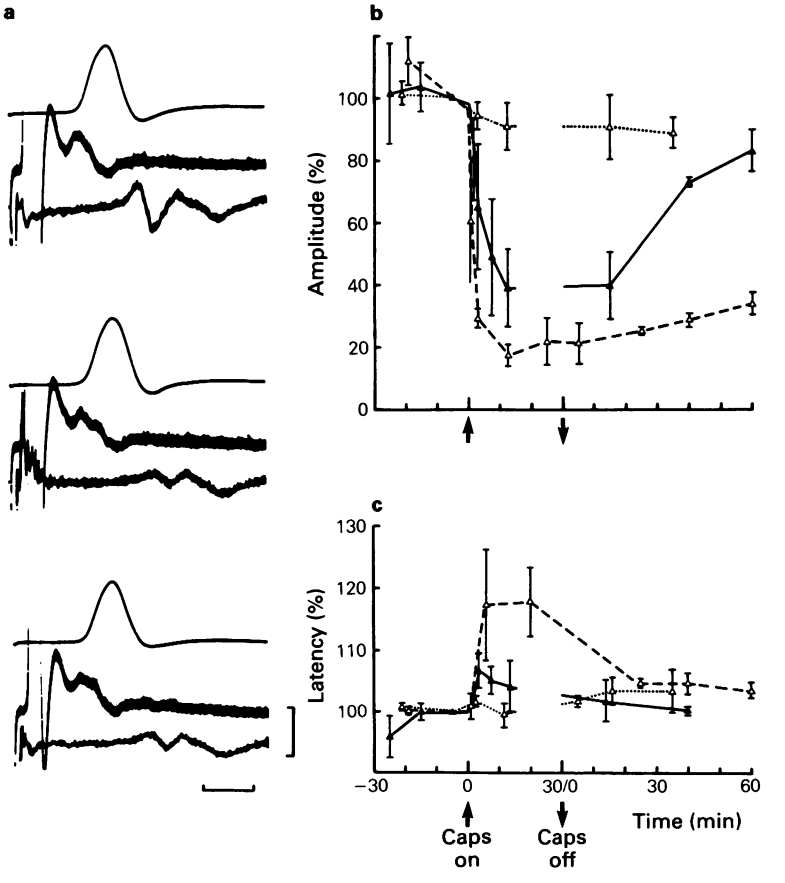

Figure 3 Effect of capsaicin (Caps) on c.a.ps recorded from the saphenous nerve of the ferret. (a) Typical traces recorded 7 min before (upper panel), 13 min after starting (middle panel) and 58 min after ending (lower panel) an application of 33 mM capsaicin in olive oil. In each panel traces are as follows: upper = A$\alpha\beta$ component, time calibration 0.4 ms, amplitude calibration 2 mV; middle = Aδ component, calibrations 2 ms, 100 μV; lower = C component, calibrations 10 ms 100 μV. (b,c) Time course of amplitude (b) and latency (c) shifts of C-c.a.p. at 3 concentrations: (– – Δ – –) 33 mM, $n = 4$; (—▲—) 0.33 mM, $n = 3$; ($\cdots\Delta\cdots$) 33–110 μM, $n = 3$. Error bars show s.e.

least 1 h after removal of the capsaicin, although after the lowest effective dose (33 μM) a complete recovery was made by some nerves in 40 min. Some slowing of conduction occurred at the highest concentration, although the changes in latency were rather variable (see Figure 3c) and only reach statistical significance if the data from 330 μM and 33 mM are pooled. There were no significant effects on either the Aαβ or Aδ components of the c.a.p. at any of the concentrations tried.

Guinea-pig

Typical c.a.ps from the guinea-pig saphenous nerve are shown in Figure 4a. The potentials are notable for the relatively large amplitude of the C-fibre component which was typically 2–3 times larger than in the rat or ferret. Capsaicin had little effect on this potential, as can be seen from Figure 4d. The average reduction with the highest concentration (33 mM) was only 31% (± 7%, $n = 7$), which although highly statistically significant ($P < 0.01$) is much smaller than the reduction seen in the rat and ferret. There were also no significant shifts in latency, the average increase with 33 mM being only 1.7% (± 1.7%, $n = 7$). Finally, the effects on C-c.a.p. amplitude recovered fully in 30 min, again unlike the long-lasting changes seen in the rat and ferret.

The Aδ c.a.p. (Figure 4c) showed exactly the same pattern of changes as the C-c.a.p., although the data vary rather more because of the greater difficulty in measuring the smaller Aδ potential. The Aαβ c.a.p. amplitude was also significantly reduced by 33 mM capsaicin (Figure 4b). However, a paired comparison within nerves showed that on average the effect on the Aαβ c.a.p. was significantly less than that on the Aδ and C components.

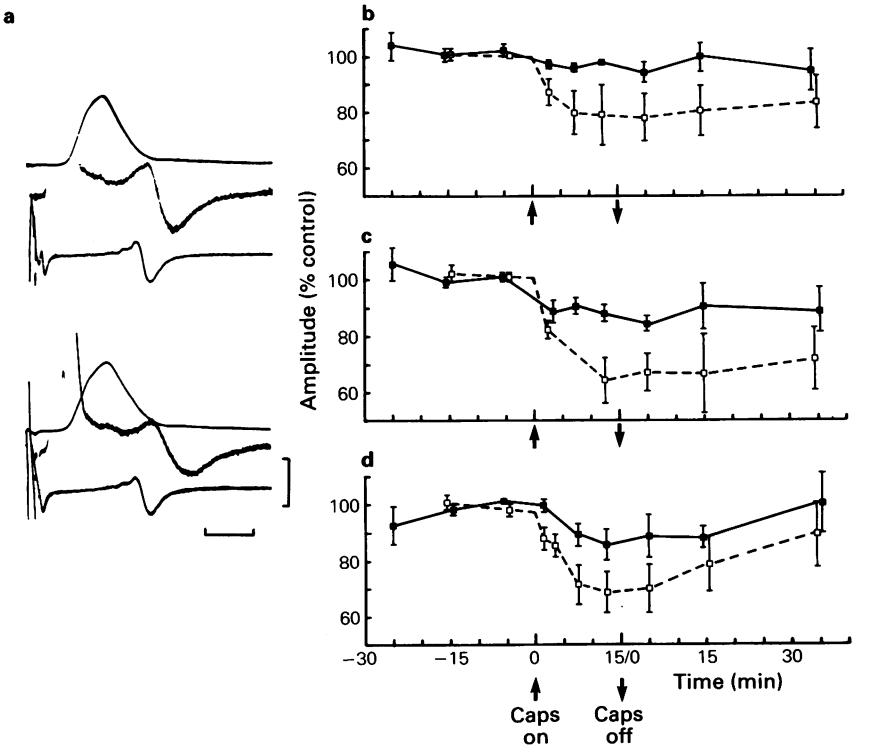

Figure 4 Effect of capsaicin on c.a.ps from the saphenous nerve of the guinea-pig. (a) Typical traces recorded before (upper panel) and during (lower panel) the application of 33 mM capsaicin. Top traces Aαβ component, time calibration 0.4 ms, amplitude calibration 1 mV; middle traces, Aδ component, calibrations 1 ms, 0.2 mV; lower traces, C component, calibrations 10 ms, 0.4 mV. Conduction distance 15 mm. Note relatively large C-c.a.p. and lack of effect of capsaicin. (b–d) Average (± s.e.) c.a.p. amplitudes before, during and after a 15 min exposure to 33 mM (□, $n = 7$) or 3.3 mM (■, $n = 5$) capsaicin; (b) Aαβ-fibres; (c) Aδ-fibres; (d) C-fibres.

Rabbit

The c.a.p. was examined in both the saphenous and sural nerves in the rabbit. In both nerves its shape was very like that recorded in the guinea-pig saphenous nerve and it behaved similarly in response to 33 mM capsaicin. Significant effects were only seen at 10 and 33 mM, these concentrations reducing all components of the c.a.p. (see Figure 5). After 10–15 min exposure to 33 mM capsaicin, the C-fibre component of the c.a.p. was reduced by 34% (±9%, $n = 6$), the Aδ component by 48% (± 12%) and the Aαβ component by 17% (± 7%). With longer applications a further reduction occurred and by 20–30 min all components were on average significantly reduced. The slow onset of the effect and its continuing increase over 30 min were in contrast to the situation in the other three species. The amplitude reductions varied markedly between preparations, whilst the effects on different components in a given preparation were fairly similar. Analysis of variance revealed that within nerves there was a significantly smaller effect on the Aαβ component than on the Aδ and C components. The amplitude decreases were accompanied by small but significant increases in latency of about 5% at 20–30 min.

The time course of recovery was very variable. The 5 nerves whose data are pooled in Figure 5 showed no significant remaining effect at 1 h post-treatment. Two other nerves studied in preliminary experiments also showed no fall in c.a.p. amplitudes with 33 mM capsaicin. However, in 2 other preparations there were large irreversible falls in all c.a.p. components. It is possible that these reductions result from a general deterioration in the preparation, but it may also be that a minority of rabbit nerves are considerably more sensitive to capsaicin than is indicated by the averages plotted in Figure 5.

To test if the relative ineffectiveness of capsaicin in the rabbit and guinea-pig was due to the connective tissue sheath around the nerve, this was slit open at the application site in 1 rabbit and 3 guinea-pig nerves. Capsaicin (33 mM) applied to these nerves produced an average fall in c.a.p. amplitude (all components) to 80.2% compared with 70.3% for nerves with sheath intact. Thus it appears that the nerve sheath does not act as a significant barrier to the diffusion of capsaicin.

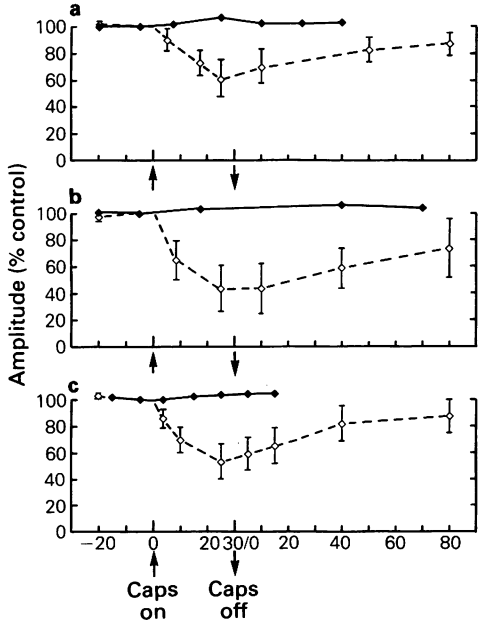

Figure 5 Amplitudes of different components of the c.a.p. before, during and after 30 min application of 33 mM (◇) or 3.3 mM (◆) capsaicin to cutaneous nerves in the rabbit. (a) Aαβ component; (b) Aδ component; (c) C component. Averages for 4 nerves (3.3 mM) or 5 nerves (33 mM); nerves used were sural (2) and saphenous (2 or 3). Error bars for 33 mM, show 1 s.e.; errors for 3.3 mM were smaller than the symbol size.

Comparison between the four species

The C-c.a.p. amplitudes and latencies during the application of different concentrations of capsaicin in all the species examined are plotted in Figure 6. The ferret and rat are clearly much more sensitive to direct axorial application of capsaicin than are the rabbit or guinea-pig. Also, the effects seen in these latter 2 species reversed within 1 h of removal of capsaicin, whilst the effects on the rat and ferret lasted well in excess of this time.

Significant effects on the A-fibre components of the c.a.p. only occurred with the highest concentration used (33 mM). The amplitude changes for the Aαβ and Aδ components are summarized in Figure 7 along with those of the C-c.a.p. at this concentration. Ferret Aαβ components were unaffected whilst guinea-pig, rabbit and rat Aαβ c.a.ps, were reduced by 17–29%. On average, the Aδ c.a.ps were affected more than the Aαβ ones, but were not reduced by as much as C-c.a.ps in the rat and ferret. Latency shifts were never as marked as the amplitude changes, but in most cases significant amplitude decreases were accompanied by significant increases in conduction delay.

Discussion

Assessment of conduction block from compound action potentials

It is important to consider first the extent to which the c.a.p. amplitude gives a reliable measure of conduction

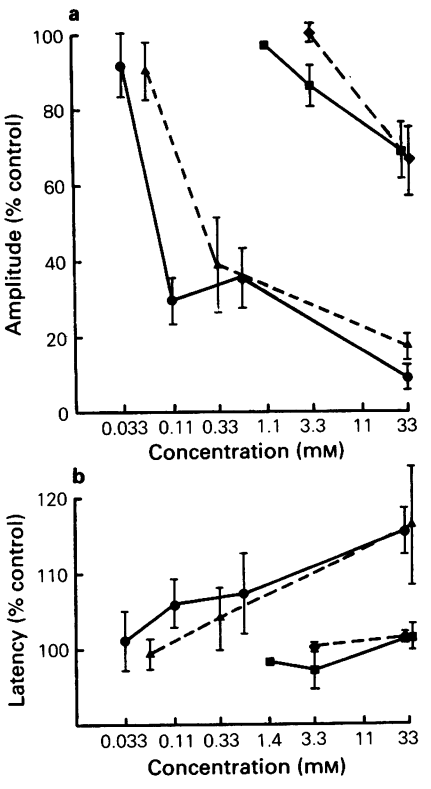

Figure 6 C-fibre c.a.p. amplitudes (a) and latencies (b) during capsaicin application to cutaneous nerves in 4 species. Average values from 3–7 nerves measured 10–15 min after beginning application and expressed as % of the immediate pretreatment value: (●) rat; (▲), ferret; (■), guinea-pig; (◆), rabbit.

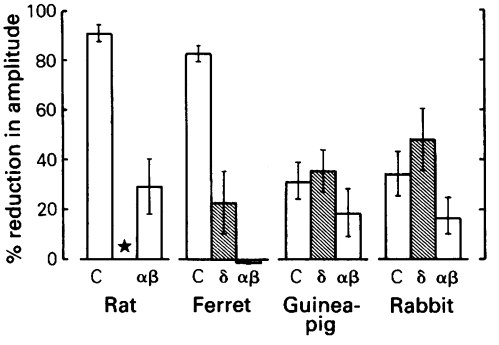

Figure 7 Reduction in size of different components of the compound action potential in four species measured 10–15 min after applying 33 mM capsaicin. Average results, with s.e., from 7 nerves in rat and guinea-pig, 2–4 in ferret and 5 in rabbit. *No data are available for δ fibres in the rat at 33 mM, but at 0.11–1.1 mM an average reduction of 24.9% (± 11.4, $n = 6$) was found (see Figure 2b).

block. If conduction in single axons is not slowed then, for a given conduction distance, the c.a.p. amplitude will vary directly with the number of axons conducting. However, if there is differential slowing of conduction in single axons then the c.a.p. amplitude will fall without any conduction block. For a population of axons conducting at different but constant velocities, differential slowing will occur simply with increasing conduction distance. We have found that the amplitude of both A and C components of the c.a.p. are approximately inversely proportional to the conduction distance, and so to the conduction latency. Capsaicin treatment caused latency increases of less than 20%, so if these were uniform shifts for all fibres, then the associated changes in amplitude would be small. If shifts in latency only occurred in a subpopulation of fibres, then the latencies of c.a.p. components might not show any change. However, if a large group of fibres were differentially slowed this ought to produce a marked change in the shape of the c.a.p., but such effects were not seen. It appears, therefore, that a small degree of the observed amplitude reduction might be due to a slowing of conduction. However, the major effects, such as those of C-fibres in the rat and ferret, must be due largely to conduction block. This is also in agreement with the results of single unit recordings (Petsche *et al.*, 1983; Lynn & Pini, unpublished data) which show that many afferent C-fibres are blocked by capsaicin.

The sensitivity of cutaneous nerve fibres to capsaicin in different mammalian species

Our results clearly show that capsaicin exerts a powerful blocking action on C-fibres in cutaneous nerves in the rat, thus confirming the findings of Petsche *et al.* (1983). The negative results of Wall & Fitzgerald (1981) may have been due to their use of Tween 80/alcohol vehicle which itself caused some conduction block. Capsaicin does not block all C-fibres in the rat; even at high concentrations some remain conducting with velocities in the normal range. Sympathetic postganglionic C-fibres are unaffected by capsaicin (Handwerker *et al.*, 1984) and it may be largely these fibres that form the capsaicin-resistant component of the C-c.a.p. Capsaicin also blocks C-fibres in the ferret and has been reported to block C-fibres in the monkey (Chung *et al.*, 1985) and the cat (Such & Jancso, 1985). In contrast, in the guinea-pig and rabbit the effects of capsaicin are smaller, only occur at high concentrations and are not selective for

C-fibres. One possible explanation for the difference between the rat and ferret and the rabbit and guinea-pig might be that the latter two species have a higher proportion of sympathetic C-fibres in their cutaneous nerves. This would be consistent with the relatively large C-c.a.ps in rabbit and guinea-pig nerves. However, there is no reason to expect such a difference and a previous single unit study found that, as in the rat, the great majority of C-fibres in the saphenous nerve of the rabbit had cutaneous receptive fields and so presumably are afferent, not efferent, fibres (Lynn, 1979).

In the rat the blocking action of capsaicin occurs at concentrations of 110 μM, some 300 times less than the 33 mM (1%) used in many studies and this demonstrates the importance of restricting the spread of capsaicin during experiments designed to show local effects. It also raises the possibility that when rats are given large subcutaneous or intramuscular injections of 50 mg kg^{-1} or more, tissue concentrations might reach levels that cause C-fibre conduction block. This is consistent with the rapid onset of the hypo-algesia reported in adult rats after a single injection of capsaicin (Hayes *et al.*, 1980).

Conduction was affected in most myelinated as well as unmyelinated fibres when they were exposed to high concentrations (33 mM) of capsaicin. Reductions in Aδ fibre c.a.p. amplitudes have also been found in cat and monkey (Such & Jancso, 1985; Chung *et al.*, 1985), and in A$\alpha\beta$ c.a.p. amplitudes in the cat (Such & Jancso, 1985). At lower concentrations ($<$1.1 mM) the only effects were on Aδ fibres in the rat. The duration of the action on Aδ fibres was hard to assess in our experiments because this potential tended to deteriorate during long recording periods. Whether the action is selective for different functional types of Aδ fibres is not known.

Mechanism of conduction block

In vitro experiments have shown that capsaicin depolarizes mammalian C-fibres (Ault & Evans, 1980; Hayes *et al.*, 1984) and their cell bodies (Heyman & Rang, 1985) and that the extent of depolarization correlates well with the degree of conduction block (Marsh, 1985). In rat C-neurones this depolarization is due to a non-specific increase in ionic permeability (Heyman & Rang, 1985). The conduction block could arise from the axons accommodating to the maintained depolarization and the slowing of conduction may also be due to accommodation in the treated area. In fact the change in conduction velocity locally must be substantial since this part of the nerve formed less than 25% of the total conduction distance.

Capsaicin has little effect on axonal conduction in the rabbit or guinea-pig. However, rabbits and especially guinea-pigs are sensitive to the neurotoxic and irritant effects of capsaicin (Jancso, 1960; Buck & Burks, 1983). Possibly axons, cell bodies and peripheral terminals show different relative sensitivity to capsaicin in different species. On the basis of structure-activity relations it has been suggested that capsaicin interacts with a specific membrane receptor (Szolcsanyi & Jancso-Gabor, 1975). If so, receptors may be evenly distributed over all the membrane of neurones with C-axons in rat and ferret, but be restricted to the terminals in the rabbit and guinea-pig. In contrast, rat neurones with myelinated axons show no effects from capsaicin application to the cell bodies (Heyman & Rang, 1985) although we have shown clear effects on axons. If these axonal effects are also due to interaction with a specific receptor then it appears that the distribution of receptors can vary between types of neurone as well as between species.

The long duration of the blocking action of capsaicin in the rat and, at high concentration, in the ferret is of interest. Exposure to capsaicin is known to cause swelling of vagal nerve C-fibres (Marsh, 1985) and disintegration of processes in cultured dorsal root ganglion cells (P.G. Hogan, unpublished results). It may be, therefore, that the long lasting reduction in C-fibre potentials results from axonal damage caused by capsaicin. Consistent with this is our preliminary finding that C-fibre conduction in the treated segment remains reduced for 1–2 days after exposure to capsaicin (Lynn *et al.*, 1984).

Conduction block and nociceptive reactions

In many previous studies of the action of capsaicin, attention has focussed on its ability to deplete sensory neurones of substance P and other neuropeptides. However, peptide depletion is slow, becoming significant only 24–96 h after treatment, whilst reductions in nociceptive reactions and in neurogenic inflammatory reactions may occur within a few hours (Gamse *et al.*, 1982). It is now clear that as proposed by Gamse *et al.* (1982), these rapid actions are due to an immediate effect of capsaicin on conduction in afferent C-fibres. This blocking action can clearly resolve many of the discrepancies between the time course of nociceptive changes and of changes in peptide levels that were highlighted by Wall & Fitzgerald (1982). The long duration of capsaicin's action on C-fibres, which lasts for more than 4 months (Lynn & Pini, 1985a), also requires consideration when interpreting the long-term functional consequences of capsaicin treatment in adult rodents.

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