The vasodilator component of neurogenic inflammation is caused by a special subclass of heat-sensitive nociceptors in the skin of the pig

B. Lynn*, S. Schütterle and F.-K. Pierau

*Max-Planck-Institut für physiologische und klinische Forschung, W. G. Kerckhoff-Institut, Parkstrasse 1, D-61231 Bad Nauheim, Germany and *Department of Physiology, University College London, Gower Street, London WC1E 6BT, UK*

1. Skin blood flow has been imaged during stimulation of fine nerve filaments containing small numbers of identified C fibre units. Filaments were dissected from the saphenous nerve of anaesthetized pigs.

2. Stimulation of filaments containing C heat nociceptor units gave small areas of elevated blood flow (average increase 96%, $n = 11$) restricted to the afferent receptive field. The extent of the areas of raised blood flow was imaged completely for 8 units. The average extent of vasodilatation in the direction of greatest spread was 8 mm and the maximum spread in any unit was 13 mm.

3. Stimulation of C polymodal nociceptor units never caused increases in blood flow in or near their receptive fields.

4. Localized noxious stimuli (55 °C or intradermal injection of capsaicin) caused flare extending 7–15 mm in the same skin region.

5. In agreement with the axon reflex model, spread of flare was restricted to the zone innervated by the terminals of single C fibre units.

6. It is concluded that the C heat nociceptor units are the major class of afferent involved in the flare reaction in the skin of the pig. C polymodal nociceptor units do not appear to be involved in flare in this species. The probable situation in human skin, which is also innervated by heat nociceptors, is discussed.

Neurogenic inflammation forms part of the tissue response to injury and may contribute to arthritis (Levine, Moskowitz & Basbaum, 1985), migraine (Moskowitz, Brody & Liu-Chen, 1983) and asthma (Barnes, 1989). It is caused by the release of neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) (Levine, Fields & Basbaum, 1993) from the distal terminals of nominally afferent neurones with their cell bodies in the dorsal root ganglia and possessing fine, usually C fibre, axons. The best-known example of neurogenic inflammation is axon-reflex-mediated vasodilatation (flare) around cutaneous injuries (Lewis, 1927). It is unknown which dorsal root fibres cause flare. Most authors have assigned the role to C fibre nociceptors, giving them dual afferent–efferent functions (Holzer, 1988). Amongst the cutaneous nociceptors it has been proposed that the capsaicin-sensitive polymodal nociceptors (Bessou & Perl, 1969) play the major role (e.g. see Szolcsanyi, 1984). However, little attention has been paid to the fact that polymodal nociceptors respond to relatively low pressures that themselves do not produce flare (Lynn & Cotsell, 1992). We have addressed this question by stimulating nerve filaments containing identified afferent units while imaging skin blood flow (Wardell, Naver, Nilsson & Wallin, 1993). Our results show that, at least in the pig, a distinctive type of nociceptor, the heat nociceptor (Lynn, Faulstroh & Pierau, 1995*a*), is specialized to produce vasodilatation in the skin.

A preliminary report of these findings has been published (Pierau, Lynn, Schütterle & Basile, 1995).

METHODS

C fibre units were recorded from the saphenous nerve in pigs (strain Deutsches Landschwein; body weight, 12–52 kg) using the same methods as previously (Lynn *et al.* 1995*a*). Following premedication (azaperone (Stresnil, Janssen, Belgium), 2 mg kg^{-1} I.M.), pigs were anaesthetized with halothane (1·5–2%) in 60% N_2O and 40% O_2. The electrocardiogram, rectal temperature and expired CO_2 were monitored continuously. The room temperature was kept between 24 and 26 °C, the pig was covered with paper drapes and a heating pad was switched on if necessary to prevent any fall in temperature. Under these conditions rectal temperature was stable between 37 and 37·5 °C throughout the experiment. Rarely, pigs of this strain develop a rapid rise in rectal temperature and heart rate (malignant hyperthermia). If this occurs, the experiment must be

immediately stopped and the pigs given Dantrolene by I.M. injection. In fact, in this particular series we did not have any problems with malignant hyperthermia. With sterile precautions, the saphenous nerve was exposed in the thigh and one fascicle was cut and separated for dissection into fine filaments. Filaments were placed on platinum wire electrodes and further electrodes were placed on the whole nerve distally for stimulation. The conduction velocity of recorded unitary potentials was determined from the conduction delay following nerve stimulation. Fourteen filaments with small numbers of units (1–6) conducting at <5 m s^{-1} were studied. Filaments with large numbers of inexcitable units were not studied whilst filaments with nociceptor units were always investigated. The sample is therefore biased towards nociceptors. The skin was searched using light touch, strong pressure, and with a Peltier thermode at 10–15 °C and at 52–55 °C. From their responses, units were classified into afferent types (Lynn, 1994). For units with cutaneous receptive fields, the identity of unit spikes was checked by observing latency increases to electrical stimulation following natural stimulation of the skin (Lynn *et al.* 1995). Sensitivity to pressure was assessed using a set of calibrated, von Frey-type, bristles (range, 0·1–245 mN (0·01–25 g); diameters, 0·045–0·5 mm). Receptive fields were mapped with von Frey bristles exerting 2–5 times threshold force. For heat units, receptive fields were mapped with a blunt needle approximately 1 mm in diameter that was heated to approximately 55 °C. Sensitivity to irritant chemicals was tested by intradermal injection of 20 μl of capsaicin or bradykinin. Capsaicin stock solution (1%, 33 mM) was dissolved in Tween 80 and alcohol and diluted to 0·3–3 μM with saline. Bradykinin (0·1–1 μM) was dissolved in saline.

At the end of an experiment, the wound was cleaned and the skin sutured. After a recovery period of at least 1 week, some animals were used for a second experiment on the other leg.

Blood flow images were obtained using a Lisca perfusion imaging system (Lisca Developments, Linkoping, Sweden) (Wardell *et al.* 1993). Scanning rate was 1000 pixels min^{-1} with a resolution of 0·6–1·2 mm pixel^{-1}, and scans took 1–3 min to complete. Initial scans were made before and during stimulation of the whole fascicle from which filaments were dissected. The region of increased flow was marked and subsequent scans were limited to this area. Scans were made immediately before, during, and after filament stimulation via the recording electrodes. If previous heat stimulation had elevated local blood flow, baseline scans were repeated at intervals until the vasodilatation had subsided. Stimulation consisted of 0·5 ms pulses at 1–2 Hz for the duration of one or two scans, i.e. 1–5 min. Stimulus strength was set at 2·5–20 V for most trials. In two cases, filament threshold was determined by a modification of the collision method (Andrew, Matthews & Coates, 1996) and was 0·5–0·8 V, so all trials are likely to have been well above threshold. Spread of stimuli to the rest of the fascicle did not appear to occur since the background flux in areas outside identified receptive fields never increased during stimulation.

Afferent receptive fields for units present in filaments were marked with small pieces of black adhesive tape for some control scans. Images during stimulation or immediately afterwards were subtracted from control scans on a pixel-by-pixel basis to give difference images. Where two successive scans showed the same pattern of elevated blood flow, these were averaged. In some instances images from successive stimulation periods were averaged. Images were scaled as percentage above average background, determined by calculating the mean flux for all pixels on the pre-stimulation scan.

RESULTS

Blood flow responses to stimulation of identified C fibre units

Twenty-eight identified cutaneous afferent nerve fibres with conduction velocities either in the C fibre range (0·6–1·2 m s^{-1}, 23 units) or slightly faster (2·2–4·3 m s^{-1}, 5 units) were antidromically stimulated whilst imaging skin blood flow in order to establish which types of afferent can cause vasodilatation. The types of units and their properties are given in Table 1. Eleven units were specialized heat nociceptors (Lynn *et al.* 1995*a*) that fired to noxious skin heating with high frequency, often in bursts, and with average firing at >10 Hz. Firing was delayed by 3–8 s from the start of near threshold stimuli. Seven heat nociceptor units had no response to strong mechanical stimulation and four units fired only to very high forces (von Frey force thresholds, 42–250 mN). Intradermal injection of bradykinin (0·1 μM) or capsaicin (0·3–3 μM) was tested after filament stimulation on four of the heat nociceptors and excited them all. With one exception, clear increases in skin blood flow were seen during and immediately after antidromic stimulation of filaments containing heat units. The increases were restricted to the afferent receptive fields of heat units in all but one instance (Figs 1 and 2). The exceptional unit is shown in the upper part of Fig. 1. An area of raised blood flow extends approximately 5 mm down (posterior) from the mapped afferent field. Afferent firing from the heat unit might have been missed in this area because heat stimuli there excited high frequency firing from the sensitive warm thermoreceptor unit whose field was immediately adjacent. Regions of increased blood flow were approximately elliptical in shape, with the largest extent (diameter) ranging from 5–13 mm ($n = 8$) and averaging 8·4 ± 2·4 mm (mean ± S.D.). The spread of vasodilatation in the narrowest direction ranged from 4–7 mm and averaged 5·7 ± 1·3 mm. The average increase in blood flow within the main response area was 96 ± 16% (mean ± S.E.M.). This compares with increases averaging 140% for stimulation of the whole saphenous nerve. The area of increased blood flow was usually still present on scans taken 1–2 min after the end of stimulation, but not for scans taken at >3 min.

Increases in blood flow could not be elicited by stimulation of any other type of fibre (see Table 1). Nine units of the polymodal nociceptor type that responded to pressure (force thresholds, 7–60 mN) and relatively weakly to noxious heat were present in filaments that were antidromically stimulated. No vasodilatation was detected in their receptive fields and the average blood flow changed by only −1 ± 3% (S.E.M.). In several cases heat units and polymodal nociceptors were present in the same filaments and clear vasodilatation was present only in the receptive fields of the heat units (see examples in Figs 1 and 2). A small number of other identified afferents were also stimulated as noted in Table 1. A mechanical nociceptor with no responses to heating, a warm-sensitive thermoreceptor and two sensitive

Table 1. Properties of identified C units tested for their ability to increase skin blood flow

Type of afferent	*n*	Conduction velocity ($m\ s^{-1}$) Av	Min	Max	Mechanical threshold (mN) Av	Min	Max	Receptive field extent (mm) Av	Min	Max	* Blood flow increase in receptive field (%) Av	Min	Max
Polymodal nociceptor	9	2·18	0·70	4·3	15·0	6·6	58·9	13	9	18	−0·9	−16·0	15·0
Heat nociceptor	11	0·86	0·64	1·02	—	41·6	>245	8	6	13	96·3	1·0	176·0
Mechanical nociceptor	1	0·74	—	—	>245	—	—	Small	—	—	3·0	—	—
Mechanoreceptor	2	1·51	0·81	2·2	0·55	—	—	8	—	—	−6·0	—	—
Warm thermoreceptor	1	0·76	—	—	>245	—	—	8	—	—	2·0	—	—
Inexcitable	4	0·86	0·60	1·23	—	—	—	—	—	—	No responses visible		

*Blood flow was the average in the central zone of receptive fields measured as described in the caption to Fig. 1. *n*, number of afferents; Av, average; Min, minimum; Max, maximum.

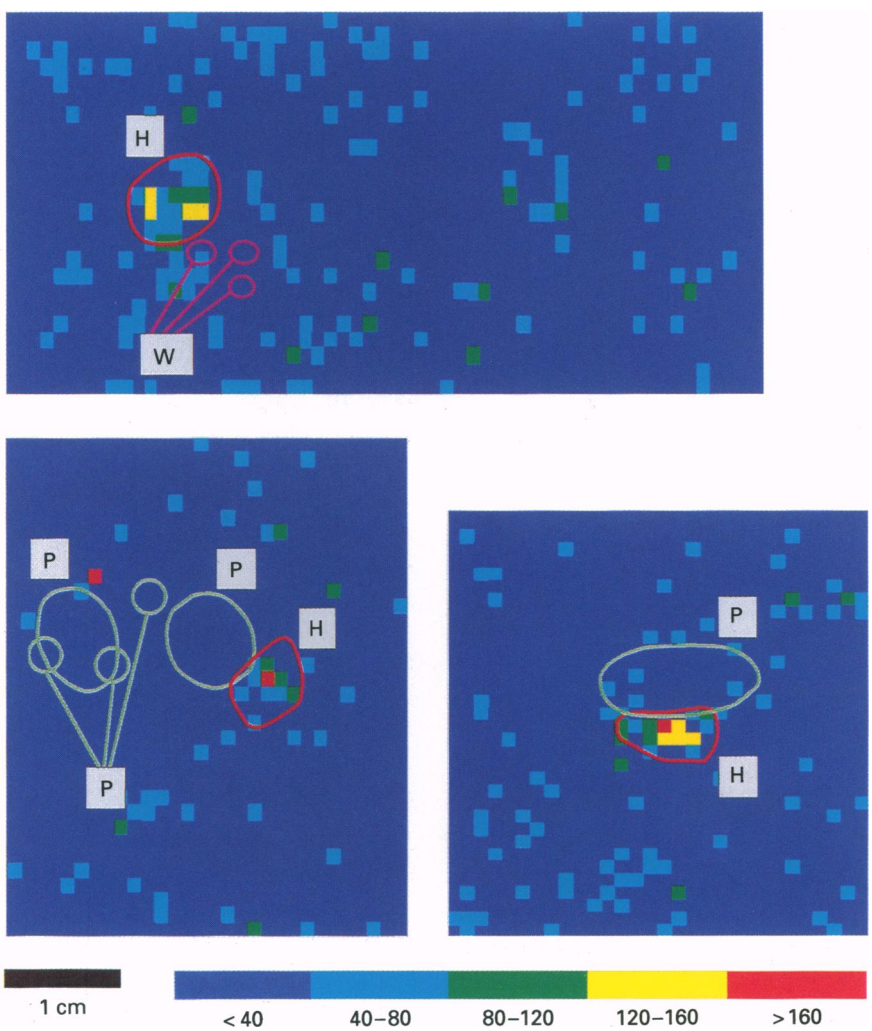

Figure 1. Low resolution blood flow images during electrical stimulation of 3 different filaments

Receptive fields of afferent units recorded from the same filaments are marked by lines. Note that in 2 instances, receptive fields consisted of 3 distinct small zones. Vasodilatation was seen within receptive fields of heat nociceptor units (H), but not polymodal nociceptors (P) or a warm thermoreceptor unit (W, upper image). Three difference images were averaged for each of the images displayed. The images have been scaled so that colour levels represent fixed percentages above the average baseline level and have been oriented so that proximal is to the right and anterior is at the top.

slowly adapting mechanoreceptors with axons conducting at less than 2·2 m s^{-1} all gave negative results. Four units with no response from the skin (inexcitable or 'silent' units) were also stimulated antidromically while scanning the entire skin area innervated by the nerve fascicle. No regions of elevated blood flow were seen, except in the receptive fields of heat units that were present sometimes in the same filaments and so were simultaneously stimulated. No attempt was made to further characterize these silent units as afferent or efferent.

Blood flow (flare) responses to localized noxious stimulation

In order to compare the extent of the flare generated by a noxious skin stimulus with the size of the blood flow areas generated by single unit stimulation, experiments were carried out to image the skin area around localized skin injuries. Typical flare reactions are shown in Fig. 3. Responses were roughly elliptical in shape with the major axis aligned along the long axis of the limb, although there were considerable variations in shape (e.g. see flare in right panel, Fig. 3). Maximum radius of flare, measured from the edge of the stimulator, ranged from 7 to 11 mm for noxious heat stimuli (55 °C, 10 s; 7 trials in 3 animals). Vasodilatation following intradermal injections of capsaicin spread up to 10–15 mm from the injection site (4 trials in 2 animals). Flare was always present at full size in the first scan taken 15–90 s after stimulation and was approximately the same extent in the next scan (1·5–2·5 min). From 3 min, flare gradually reduced in extent and intensity and by 4–8 min for heating or 5–20 min for capsaicin responses consisted only of small areas of dilatation at the stimulus or injection site.

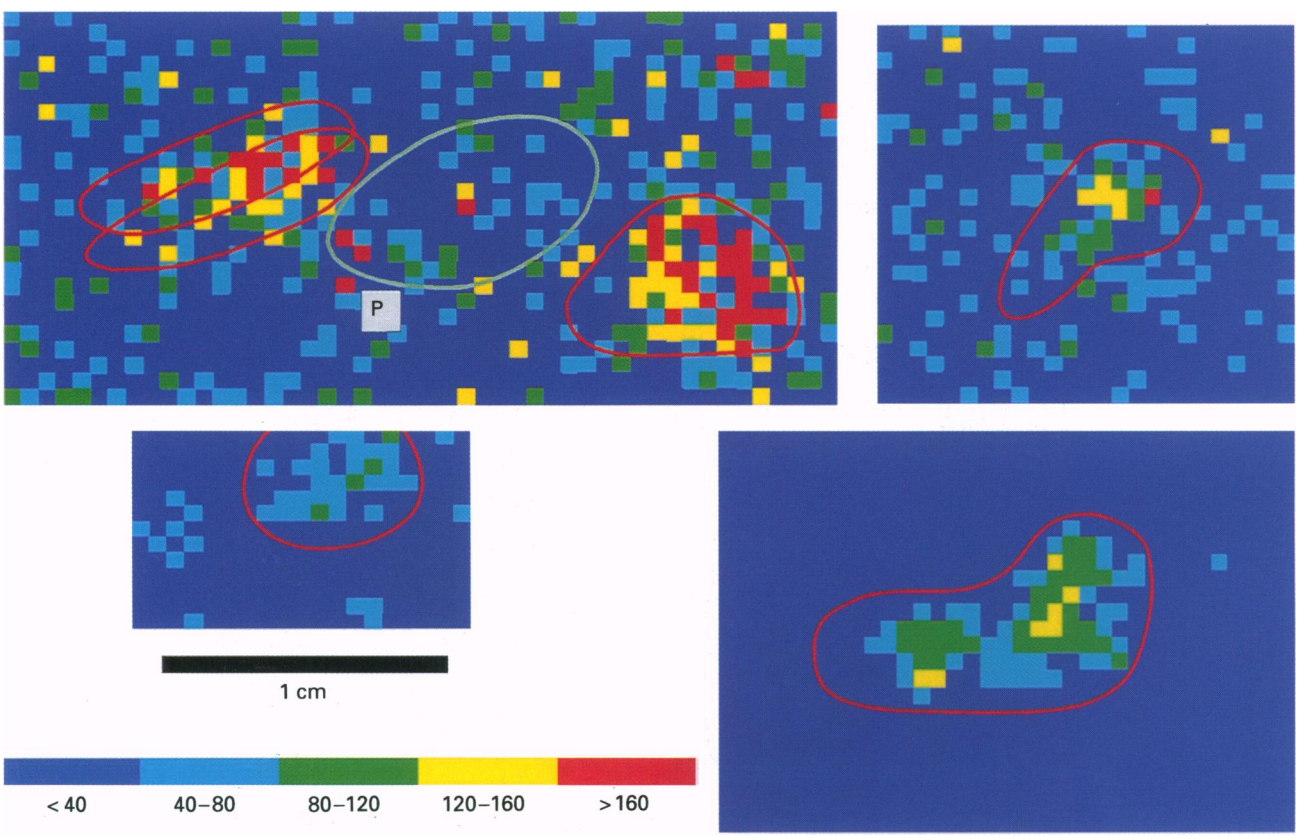

Figure 2. High resolution blood flow images during stimulation of 4 different filaments containing 1 (upper right and lower images) or 3 (upper left image) heat nociceptor units

The upper left filament also contained a polymodal nociceptor unit (P). The outlines of afferent receptive fields are marked with lines and scaling is as in Fig. 1. The upper left image is from a single scan during a stimulus lasting 1 min 45 s. The other images are averages of 2 or 3 scans during and 1–2 min after stimulation. The lower left unit had a receptive field that ran on to the lateral surface where it was not possible to scan. Note that flow increases are restricted to the independently mapped regions of afferent sensitivity to heating. As in Fig. 1, no blood flow increase is seen in the afferent receptive field of the polymodal nociceptor (upper left image) although there do appear to be small areas of significantly raised blood flow outside the afferent receptive fields. The upper left image comes from a single scan and for this reason is rather noisy. No repeat scans were possible so the reliability of these scattered regions of increased flow could not be determined.

DISCUSSION

By using the novel technique of laser Doppler imaging together with the stimulation of identified afferent C fibres in a species with highly responsive skin vasculature it has been possible to directly assess the contribution of different types of C fibre to flare. The key finding is that it is the relatively small number of heat nociceptors that are involved, not the more common polymodal nociceptors. Heat nociceptors form a distinctive group within the C fibre afferent population in the saphenous nerve of the pig (Lynn *et al.* 1995*a*). They show high frequency, often bursting, firing in response to skin heating and the onset of firing is often markedly delayed with near threshold stimuli. In contrast, polymodal nociceptors respond to skin heating with relatively low frequency firing, without delay near threshold, and never in bursts. Heat units may develop a degree of pressure sensitivity following skin heating (Lynn *et al.* 1995*a*). This was a problem in the present study where extensive heat testing was often carried out to delineate the receptive fields of heat units as accurately as possible. Some units that initially appeared unresponsive to pressure search stimuli had measurable von Frey thresholds of 250 mN or less. It is these latter values that are given in Table 1. Our identification has therefore depended on the pattern of heat responses as well as on the minimal pressure sensitivity. In addition to differences in responses to heat and pressure stimuli, several other measures differed between heat units and polymodals. As noted by Lynn *et al.* (1995*a*) receptive fields of heat units were smaller than those of polymodals and conduction velocities of heat units fell in a rather narrow band in the middle of the C fibre range whilst polymodal units often had faster conducting axons, occasionally into the very slow A-delta range. As can be seen from Table 1, the units in this sample also showed this pattern. Finally, as has been reported briefly (Lynn, Schütterle, Pierau, Faulstroh & Basile, 1995*b*), the axonal spike duration of heat units tended to be a little greater than those of polymodal units. In the five filaments in this study where both heat and polymodal units were present, the heat units always had the longer spike duration.

The use of laser Doppler imaging enabled us to assess directly the spatial extent of blood flow increases from stimulating single C afferents and so to examine directly the validity of the axon reflex model. The axon reflex model (Lewis, 1927) predicts that the extent of flare responses around localized skin injuries will be equal to the spatial extent of single unit fields. The values of maximum spread of flare (15 mm) are close to the values for maximum extent of the zones of increased blood flow seen on antidromic stimulation of single heat units (13 mm). It thus appears that the spread of flare is limited by the spread of the terminals of single C fibre afferents, as predicted by the

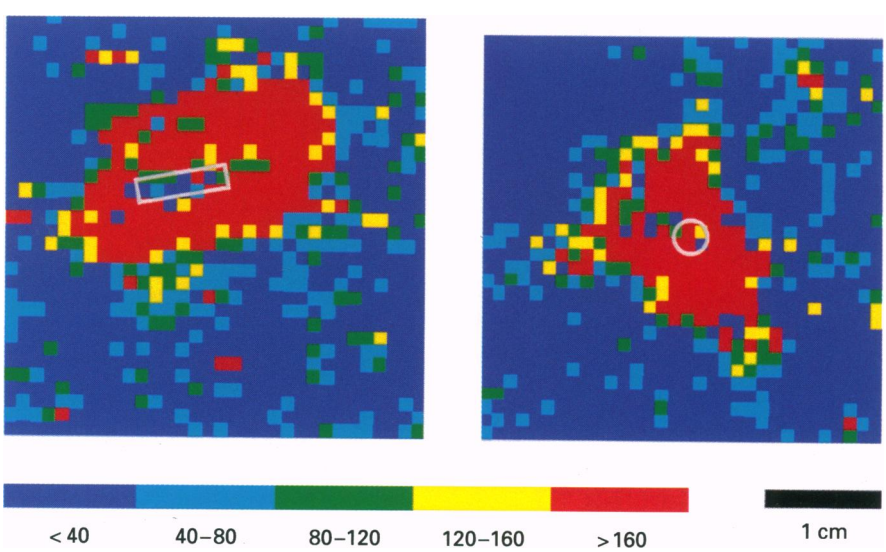

Figure 3. Blood flow images of flare responses in the saphenous area of the pig following heat stimulation (left image) or intradermal injection of capsaicin (right image)

Images are scaled as percentage above baseline flow as in Figs 1 and 2. The edge of the heat thermode (approximately 8 mm by 2 mm) at 55 °C was pressed on the skin for 10 s and the scan was taken from 20 to 80 s after removal of the thermode. The region contacted by the thermode (marked by the rectangle) is initially less dilated, although in later scans a large blood flow increase was seen. The surrounding area shows greatly elevated blood flow up to 11 mm from the edge of the stimulus in the antero–proximal direction. For the right image, capsaicin (20 μl, 300 μM) was injected intradermally and the scan taken from 25 to 95 s later. The injection site is marked by a circle. Again, blood flow is greatly increased around the injection site, spreading up to 15 mm in the postero–proximal direction. With these stimuli, visible flare responses were present that matched closely the region of vasodilatation detected in the scans.

axon reflex model (Lewis, 1927). In fact, these results provide the first direct confirmation of this model. An unresolved question is whether individual terminals are both afferent and efferent in function or whether there are separate afferent and efferent terminals (Szolcsanyi, 1988; Lisney & Bharali, 1989). The close similarity of most afferent and efferent fields would be consistent with terminals with a dual function, but would also occur if separate afferent and efferent terminals were intermingled. So the data presented here cannot definitely resolve this question. It does appear, however, that the cascade scheme proposed in the past to explain the spread of flare (Lembeck & Gamse, 1982; Lynn, 1988) can be discounted. In the pig, the branching of single C fibres can clearly account for the spread of flare. In man, flare spreads rather further and recent microneurography data indicate that the afferent fields of single C fibres can be equally extensive (Schmidt, Schmelz, Forster, Ringkamp, Torebjork & Handwerker, 1995).

The results of stimulating afferent fibres fit well with previous observations that flare can only be produced by very strong pressure stimuli, stimuli that will begin to excite a few heat units. Moderate pressure stimuli, on the other hand, that will excite most C polymodal nociceptors, do not cause flare (Lynn & Cotsell, 1992), and, as shown by the present results, neither do C polymodal nociceptors cause vasodilatation when stimulated directly.

Heat nociceptors are found in significant numbers in primates where they comprise 6% of C afferents in hairy skin in man and 7% in monkeys (Baumann, Simone, Shain & LaMotte, 1991; Schmidt *et al.* 1995). This class of afferent has received relatively little attention in the past, but clearly more detailed examination is required to determine whether they play a similarly dominant role in generating the excellent flare responses present in primate skin. Also, the possible role of heat nociceptors in other facets of the neurogenic inflammatory response, such as increased vascular permeability (Jancso, Jancso-Gabor & Szolcsanyi, 1967) and leucocyte adhesion (Smith, Barker, Morris, MacDonald & Lee, 1993) needs to be investigated. These are important issues since if the heat nociceptors do turn out to be the key neurones involved, then it opens up the possibility of controlling pathophysiological inflammatory processes, e.g. those proposed to be involved in arthritis, in a highly selective manner. For example, it might be possible to knock out pro-inflammatory actions of heat nociceptors whilst leaving the important afferent functions of polymodal nociceptors intact.

One reason for the limited information on heat nociceptors is that they are extremely uncommon in the rat (Lynn & Carpenter, 1982; Fleischer, Handwerker & Joukhader, 1983), a species used for many studies on nociceptors and on neurogenic inflammation. For studies involving cutaneous vasodilatation the pig may be a more appropriate species than the rat since pig skin has large vascular responses to injury, more like those in human skin. Rat skin, on the other hand, shows relatively small vascular reactions to injury and does not have flare around skin injuries (B. Lynn & B. Cotsell, unpublished observations). However, antidromic vasodilatation is seen in rat skin (Lembeck & Holzer, 1979) and single unit stimulation has shown that C polymodal nociceptors can increase microvascular permeability (Kenins, 1981; Bharali & Lisney, 1992). So, although in the pig a major role for C heat units is indicated, in the rat the C polymodal nociceptors, or at least a sub-group of them with low mechanical sensitivity, must be involved in the generation of antidromic vasodilatation.

Andrew, D., Matthews, B. & Coates, T. W. (1996). A method for determining the electrical thresholds of single fibres in dissected nerve filaments. *Journal of Physiology* **493.P**, 6*P*.

Barnes, P. J. (1989). Airway neuropeptides: roles in fine tuning and in disease? *News in the Physiological Sciences* **4**, 116–120.

Baumann, T. K., Simone, D. A., Shain, C. H. & LaMotte, R. H. (1991). Neurogenic hyperalgesia: the search for the primary cutaneous afferent fibers that contribute to capsaicin-induced pain and hyperalgesia. *Journal of Neurophysiology* **66**, 212–227.

Bessou, P. & Perl, E. R. (1969). Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *Journal of Neurophysiology* **32**, 1025–1043.

Bharali, L. A. & Lisney, S. J. W. (1992). The relationship between unmyelinated afferent type and neurogenic plasma extravasation in normal and reinnervated rat skin. *Neuroscience* **47**, 703–712.

Fleischer, E., Handwerker, H. O. & Joukhader, S. (1983). Unmyelinated nociceptive units in two skin areas of the rat. *Brain Research* **267**, 81–92.

Holzer, P. (1988). Local effector functions of capsaicin-sensitive sensory nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. *Neuroscience* **24**, 739–768.

Jancso, N., Jancso-Gabor, A. & Szolcsanyi, J. (1967). Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment with capsaicin. *British Journal of Pharmacology* **31**, 138–151.

Kenins, P. (1981). Identification of the unmyelinated sensory nerves which evoke plasma extravasation in response to antidromic stimulation. *Neuroscience Letters* **25**, 137–141.

Lembeck, F. & Gamse, R. (1982). Substance P in peripheral sensory processes. In *Substance P in the Nervous System*, ed. Porter, R. & O'Connor, M., *Ciba Foundation Symposium*, vol. 91, pp. 35–54. Pitman, London.

Lembeck, F. & Holzer, P. (1979). Substance P as neurogenic mediator of antidromic vasodilatation and neurogenic plasma extravasation. *Naunyn-Schmiedeberg's Archives of Pharmacology* **310**, 175–183.

Levine, J. D., Fields, H. L. & Basbaum, A. I. (1993). Peptides and the primary afferent nociceptor. *Journal of Neuroscience* **13**, 2273–2286.

Levine, J. D., Moskowitz, M. A. & Basbaum, A. I. (1985). The contribution of neurogenic inflammation in experimental arthritis. *Journal of Immunology* **135**, 843–847.

Lewis, T. (1927). *The Blood Vessels of the Human Skin and their Responses*. Shaw & Sons, London.

LISNEY, S. J. W. & BHARALI, L. A. M. (1989). The axon reflex: an outdated idea or a valid hypothesis. *News in Physiological Sciences* **4**, 45–48.

LYNN, B. (1988). Neurogenic inflammation. *Skin Pharmacology* **1**, 217–224.

LYNN, B. (1994). The fibre composition of cutaneous nerves and the classification and response properties of cutaneous afferents, with particular reference to nociception. *Pain Reviews* **1**, 172–183.

LYNN, B. & CARPENTER, S. E. (1982). Primary afferent units from the hairy skin of the rat hind limb. *Brain Research* **238**, 29–43.

LYNN, B. & COTSELL, B. (1992). Blood flow increases in the skin of the anaesthetized rat that follow antidromic sensory nerve stimulation and strong mechanical stimulation. *Neuroscience Letters* **137**, 249–252.

LYNN, B., FAULSTROH, K. & PIERAU, F.-K. (1995*a*). The classification and properties of nociceptive afferent units from the skin of the anaesthetized pig. *European Journal of Neuroscience* **7**, 431–437.

LYNN, B., SCHÜTTERLE, S., PIERAU, F.-K., FAULSTROH, K. & BASILE, S. (1995*b*). The duration of axonal action potentials varies with the afferent type for C-fibres innervating the skin of the anaesthetized pig. *Japanese Journal of Physiology* **45**, suppl. 2, S243.

MOSKOWITZ, M. A., BRODY, M. & LIU-CHEN, L.-Y. (1983). *In vitro* release of immunoreactive substance P from putative afferent nerve endings in bovine pia arachnoid. *Neuroscience* **9**, 809–814.

PIERAU, F.-K., LYNN, B., SCHÜTTERLE, S. & BASILE, S. (1995). Heat-sensitive nociceptors induce flare-like antidromic vasodilatation in the pig skin. *Society for Neuroscience Abstracts* **21**, 648, 262.3.

SCHMIDT, R., SCHMELZ, M., FORSTER, C., RINGKAMP, M., TOREBJORK, E. & HANDWERKER, H. (1995). Novel classes of responsive and unresponsive C nociceptors in human skin. *Journal of Neuroscience* **15**, 333–341.

SMITH, C. H., BARKER, J., MORRIS, R. W., MACDONALD, D. M. & LEE, T. H. (1993). Neuropeptides induce rapid expression of endothelial cell adhesion molecules and elicit infiltration in human skin. *Journal of Immunology* **151**, 3274–3282.

SZOLCSANYI, J. (1984). Capsaicin-sensitive chemoceptive neural system with dual sensory-efferent function. In *Antidromic Vasodilatation and Neurogenic Inflammation*, ed. CHAHL, L. A., SZOLCSANYI, J. & LEMBECK, F., pp. 27–52. Akademiai Kiado, Budapest.

SZOLCSANYI, J. (1988). Antidromic vasodilatation and neurogenic inflammation. *Agents and Actions* **23**, 4–11.

WARDELL, K., NAVER, H. K., NILSSON, G. E. & WALLIN, B. G. (1993). The cutaneous vascular axon reflex in humans characterized by laser Doppler perfusion imaging. *Journal of Physiology* **460**, 185–199.

Acknowledgements

We thank Veronika Körber for skilful technical assistance, Silvio Basile who participated in some of the experiments, Holger Sann for help with the data analysis and Bruce Cotsell for help with preparation of the figures. Funding for Bruce Lynn to visit Bad Nauheim was provided by the Max-Planck-Gesellschaft.

Author's email address

B. Lynn: b.lynn@ucl.ac.uk

Received 4 September 1995; accepted 18 March 1996.