Flare and Hyperalgesia After Intradermal Capsaicin Injection in Human Skin

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Serra, Jordi, Mario Campero, and José Ochoa. Flare and hyperalgesia after intradermal capsaicin injection in human skin. J. Neurophysiol. 80: 2801–2810, 1998. We investigated the neurovascular mechanisms that determine the flare response to intradermal capsaicin injection in humans and delineated the associated areas of mechanical and heat hyperalgesia. The flare response was monitored both visually and with infrared telemeterphotography. The areas of mechanical and heat hyperalgesia were determined psychophysically. Thermography detected very large areas of flare. As an early event underlying the flare and before onset of the area of rubor of the skin, thermography detected the appearance of multifocal spots of increased temperature caused by dilatation of cutaneous arterioles. Repetition of capsaicin injection days apart into the same forearm induced multifocal spots of temperature elevation identical to the ones obtained in the first session, indicating dilatation of the same arterioles. Reactive hyperemia also consisted in the appearance of multifocal spots of increased temperature, which were identical to the ones reacting during the flare response, suggesting participation of the same arterioles in both events. Strips of local anesthetic placed to block cutaneous nerves prevented the spread of both the thermographic flare and associated hyperalgesia. It is inferred that the cutaneous nerve fibers responsible for the thermographic flare branch, or have coupled axons, over a long distance. The large area of flare coincided with the area of mechanical and heat hyperalgesia. Equivalence of the areas of flare and mechanical and heat hyperalgesia induced by intradermal capsaicin injection suggests that all three phenomena are the consequence of neural factors that operate peripherally.

INTRODUCTION

After cutaneous injection of capsaicin, a flare may develop in a broad surrounding area. The flare is mediated neurogenically at the local cutaneous level (Lewis 1927), and it was proposed that it spreads through local axon reflexes involving C-polymodal nociceptors (Szolcsányi 1992). However, the hypothetical existence of a distinct subset of “nocifensor” nerve fibers responsive to noxious stimuli and specifically arranged for the flare reaction remains viable (Lewis 1937). Recent works on the development of the flare with thermography greatly improved our knowledge on its mechanisms and made interesting observations that are relevant to this question (Forster et al. 1995; Serra and Ochoa 1996; Serra et al. 1993, 1994a,b).

In addition to the flare, cutaneous hyperalgesia develops consistently surrounding the site of capsaicin injection (LaMotte et al. 1991; Simone et al. 1989; Torebjörk et al. 1992). A distinction was made between the hyperalgesia that appears at the site of a cutaneous injury, “erythralgia” or primary hyperalgesia, and the hyperalgesia beyond it, “nocifensor tenderness” or secondary hyperalgesia (Hardy et al. 1952; Lewis 1942). There is general agreement that primary hyperalgesia features both mechanical and heat hyperalgesia. However, there is some controversy regarding the existence of heat hyperalgesia in the area of secondary hyperalgesia. Although pioneer workers on this subject all found an increased pain response to heat in the area of secondary hyperalgesia (Hardy et al. 1952; Lewis 1942), more recent works deny its existence (Ali et al. 1996; LaMotte et al. 1991; Raja et al. 1984). It is accepted that primary hyperalgesia is due to sensitization of cutaneous nociceptor terminals (Campbell and Meyer 1983; LaMotte et al. 1982, 1983, 1992; Torebjörk et al. 1984). Failure to detect abnormal receptor properties in common polymodal C-nociceptors in the area of secondary hyperalgesia during capsaicin experiments in animals or humans (Baumann et al. 1991; LaMotte et al. 1992) led to the proposition that capsaicin-induced secondary hyperalgesia might be mediated by dorsal horn neurons sensitized by a primary C-nociceptor afferent barrage (LaMotte et al. 1991; Simone et al. 1991; Torebjörk et al. 1992).

In this study, by using thermography, we demonstrated that a flare response occurs on a large area and that it reflects underlying arteriolar dilatation. We also demonstrated that there is spatial coincidence between the areas of mechanical and heat hyperalgesia and the very large area of flare.

METHODS

Subjects

Twenty-seven healthy human volunteers, 12 males and 15 females, aged 19–46 (mean 33), participated in ±1 of 49 experiments after informed consent. The study was approved by the institutional Ethics Committee of the Good Samaritan Hospital, Portland, Oregon. Subjects reclined on a comfortable chair, with their limbs supported, in a room at 21°C. The subjects could not see the tested areas. Any procedure that might have caused irritation of the skin was avoided before the experiment. An initial training session familiarized the subjects with the methods for subjective estimation of painful mechanical and heat stimuli of different intensities.

Capsaicin injection

Flare and hyperalgesia were induced by cutaneous injection of capsaicin. A solution containing 1% capsaicin (8-methyl-N-vanillyl 6-nonamide) dissolved in 7.5% Tween 80 (poloxylethylensorbital monoooleate) (both Sigma) was prepared and then passed through a micropore filter (GS 0.2-µm pore size, Millipore) into a sterile glass vial for storage. In each experiment, a volume of 10 µl
containing 100 µg of capsaicin was drawn from the vial and injected intradermally in the skin of the anterior aspect of the forearm, midway between the elbow and the wrist, with a 28 gauge and ½-in.-long hypodermic needle.

**Reactive hyperemia**

To study the vascular events underlying reactive postischemic hyperemia, a standard sphygmomanometer cuff was placed around the upper arm of four subjects and inflated to 200 mmHg to arrest circulation for 15 min. After this the cuff was rapidly deflated and the ensuing reactive hyperemia was recorded thermographically and compared with the vascular change after capsaicin injection. In every subject the experiment was repeated on a separate day.

**Assessment of the visual cutaneous coloration (Visual Flare: VF)**

Five minutes after capsaicin injection the maximal area of reddening visible to the naked eye was outlined with a soft-tipped pen. The outlined profile was traced on acetate sheet, and its extent was measured with a planimeter (Aristo, Epic).

**Thermographic monitoring of the vascular reactions**

Changes in the cutaneous thermal emission profile were monitored under two circumstances: after capsaicin injection (Thermographic Flare: TF) and in the period of reactive hyperemia that followed deflation of the cuff. These events were monitored with a dynamic infrared telemeter thermography device (Mark V Flexitherm) and were videotaped for off-line analysis. A monochrome display system was used (50 grades from black to white, black representing high temperature) with a range of 2.5°C and a picture acquisition time of 1.9 s. Polaroid photographs were obtained on-line from the TV monitor screen or were subsequently retrieved from the videotape. Times to onset, peak, and disappearance of the flare and its maximal area were measured for both the visual and thermographic vascular responses. The outlines of the VF that was marked on the skin with a soft pen were outlined again with a round metal rod that was kept at room temperature (21°C). This produced a very short lived but distinct low temperature “profile” of the VF that was previously determined, thus allowing comparison with the TF. VF and TF were ultimately traced on acetate sheet, and their extents were measured with the planimeter.

**Determination of the areas of punctate mechanical and heat hyperalgesia**

The area of punctate mechanical hyperalgesia was determined 15 min after capsaicin injection with a nylon monofilament (1.02-mm diam) exerting a bending force of 2.02 N (24.75 bars). In normal skin this stimulus was clearly suprathreshold for mechanical pain in all subjects. The filament was applied at right angles for 5 s to each of a series of points 0.5 cm apart along each of 12 radial paths converging at the injection site. Stimulation started in normal skin proximal to the elbow, distal to the wrist, and on the dorsum of the forearm. These starting points were well beyond the area where hyperalgesia was typically detected. This method was used to ensure that no single skin spot was stimulated twice, thus avoiding possible sensitization of cutaneous nociceptors by repeated stimulation of the skin. The points at which the subject reported abnormal tenderness, that is, clearly enhanced pain compared with the immediately previous stimulation point, were marked on the skin with a soft pen. Heat hyperalgesia was determined in a comparable way with a 1-cm² Peltier thermode maintained at 47°C. In normal skin this stimulus was also suprathreshold for heat pain in all subjects. The thermode was applied by hand for 5 s to the same series of points along the 12 radial paths. The points at which the subject reported abnormal tenderness were marked on the skin with a soft pen. The mark was made midway between the center and the edge of the thermode. Eventually the dotted profiles of the areas of mechanical and heat hyperalgesia were traced on acetate sheet, and their area was measured. In five control experiments, this protocol was performed injecting saline instead of capsaicin to check for possible sensitization of the skin induced by the method itself.

**Magnitude estimation of pain induced by suprathreshold stimuli**

Subjective ratings of the magnitude of pain induced by suprathreshold heat and mechanical stimuli were determined by the method of magnitude estimation (Stevens 1975). In this method, each subject assigns numbers of their own choosing in proportion to their subjective magnitude of pain. These estimates were normalized in such a way as to eliminate the variability because of individual change of an internal standard, as described elsewhere (Simone et al. 1989). Estimates were obtained 60 min postinjection. Magnitude estimation of suprathreshold mechanical pain was determined with a monofilament (1.02-mm diam) exerting a force of 2.02 N (24.75 bars). Magnitude estimation of suprathreshold heat pain was determined with a 5-s pulse of heat at 47°C. Determinations were made within the area conventionally termed secondary hyperalgesia by delivering all stimuli within the previously recorded area of mechanical hyperalgesia but outside a circular area with a radius of 20 mm centered at the injection side. Baseline estimates were obtained in homologous areas of the contralateral forearm for comparison.

**Anesthetic blocks**

To determine whether the development of the flare depends on a system of intracutaneous nerve fibers that transmit neural activity from the site of injury to remote surrounding skin, a series of skin and nerve trunk anesthetic blocks was performed. In four experiments, a strip of skin 10 cm long was infiltrated intradermally with 2% lidocaine (a linear series of 5–8 injections of ~0.05 ml each) as described previously (LaMotte et al. 1991). A strip of transient cutaneous warming caused by the injection of lidocaine itself was consistently detected thermographically. After the temperature of the infiltrated skin normalized, capsaicin was injected on one side of the anesthetized strip. Development of the flare was monitored with thermography, and the areas of mechanical and heat hyperalgesia were mapped in the usual way. In four experiments development of the flare was monitored during block of the medial cutaneous nerve of the forearm at elbow level with 10 ml of 2% lidocaine. Capsaicin was injected at the center of the area that became anesthetic.

**RESULTS**

**Morphology and spatiotemporal course of the thermographic flare (TF)**

The time between capsaicin injection and initial thermographic detection of the flare response ranged between 1.9 and 10 s. The value of 1.9 s reflects the fastest scanning time of the thermography device. The first change in skin temperature recordable by thermography was a single round spot of increased temperature a few millimeters in diameter, usually located several centimeters from the injection site. The distance between the site of capsaicin injection and the center of the first thermographic spot varied among subjects.
The area of VF began to shrink 5–10 min after capsaicin injection. During this shrinkage the VF became speckled, and numerous islets of red skin remained enclosed by skin that returned to its baseline color. A small zone surrounding the injection site typically retained redness beyond 30–45 min, although the larger area of flare disappeared. The area of this “central” long-lasting VF, as measured at the end of the experiment (60–70 min postinjection), ranged from 10.7 to 36.1 cm² (mean 19.4 ± 2.26 cm², n = 13). The time it took for this central flare to eventually disappear was not measured. The VF could not be monitored in a black subject whose case will be discussed.

Localization of the spots of increased temperature: a constant feature

Capsaicin was injected into the skin of the forearm of each of six subjects on two different occasions, 16 ± 90 days apart. In the first session capsaicin induced the characteristic thermographic representation of the spots of increased temperature. In the extreme example, a single spot appeared as early as 1.9 s at a distance of 12 cm from the injection site. Immediately after appearance of the first spot, multiple similar spots appeared randomly in an area surrounding the injection site (Fig. 1). The time interval between detection of the first spot and of the last spot ranged from 20 to 50 s. Thereafter, preexisting spots grew in size.

Initially, the skin between hyperthermic spots was thermographically neutral, but, as the spots grew and became confluent, a diffuse hyperthermic area developed surrounding the injection site. Two examples of development of the TF are shown in Fig. 2. The number of hot spots was reckoned off-line from the video record 2 min after capsaicin injection, before eventual confluence precluded their individual identification. The total number of hyperthermic spots after injection of 100 μg of capsaicin ranged from 7 to 33 (mean 20, n = 21). Their density ranged from 1 spot per 3.2 cm² to 1 spot per 15.4 cm² (mean 1 spot per 5.4 ± 0.6 cm², mean ± SE, n = 21). The area of skin within which the spots occurred ranged from 48.7 to 134.2 cm² (mean 94.3 ± 4.9 cm², n = 21). Characteristically, a low temperature spot always developed at the capsaicin injection site.

Morphology and spatiotemporal course of the visible flare

Onset of the VF was between 4 and 20 s. Times of onset for the TF were always shorter than for the VF (P = 0.003, paired test). It was said that the VF grows slowly and eccentrically around an injury site for a period of several minutes (Lembeck and Gamse 1982), but we failed to observe this convincingly in the current experiments. On the contrary, the VF seemed to cover the whole area simultaneously. At first the flare was of a bright red color, suggesting arterial blood. The maximal area of this initial VF ranged from 50.3 to 144.1 cm² (mean 96.2 ± 4.9 cm², n = 21). There was no statistically significant difference between the overall areas of TF and VF (P = 0.785, Student’s t-test).

The area of VF began to shrink 5–10 min after capsaicin injection. During this shrinkage the VF became speckled, and numerous islets of red skin remained enclosed by skin that returned to its baseline color. A small zone surrounding the injection site typically retained redness beyond 30–45 min, although the larger area of flare disappeared. The area of this “central” long-lasting VF, as measured at the end of the experiment (60–70 min postinjection), ranged from 10.7 to 36.1 cm² (mean 19.4 ± 2.26 cm², n = 13). The time it took for this central flare to eventually disappear was not measured. The VF could not be monitored in a black subject whose case will be discussed.

Localization of the spots of increased temperature: a constant feature

Capsaicin was injected into the skin of the forearm of each of six subjects on two different occasions, 16–90 days apart. In the first session capsaicin induced the characteristic TF, i.e., the rapid appearance of several small spots of increased temperature surrounding the injection site. In the second session capsaicin was injected in the same forearm, but at a site 2–3 cm away from the first. This site was localized with idiosyncratic anatomic landmarks of each subject. As anticipated, capsaicin again induced the usual spot-like TF. When the two sets of thermographic records were compared, the spots of increased temperature on the two occasions were found to have developed in the same locations, replicating the morphology and distribution recorded in the initial session. Such striking uniformity of the neurovascular response was observed for all six subjects. The only observable differences were the intensity of peak warming, which was greatest closest to the sites of injection, and the recruitment of new spots of increased temperature in non-overlapping areas. Comparison of the responses induced in the two sessions was based on direct superimposition of acetate sheets where the individual areas of increased temperature were outlined, as shown in Fig. 3.

Thermographic assessment of reactive hyperemia

The reactive hyperemia that follows transient ischemia was characterized by the rapid appearance of multiple spots of increased temperature in a proximal–distal sequence covering the whole area that had become ischemic. Repetition of the experiment in the same four subjects days apart yielded exactly the same spots of increased temperature. The spatial distribution of spots of increased temperature during reactive hyperemia was compared, by direct superimposition of films, with that which followed capsaicin injection in the same individuals. The spots of increased temperature induced in these experiments coincided. Moreover, individual spots of reactive hyperemia were indistinguishable in shape from the spots that appeared after capsaicin injection given to the same subjects in the same area (Fig. 4).

Areas of punctate mechanical hyperalgesia and heat hyperalgesia

At the time of determination (15 min) of the areas of hyperalgesia to suprathreshold punctate mechanical and heat stimuli, all subjects reported disappearance of the spontane-
ous ongoing pain. No subject had doubts in signaling where the transition to hyperalgesia occurred along the centripetal series of mechanical and heat stimuli. The area of mechanical hyperalgesia ranged from 37.3 to 117.5 cm² (mean 87.1 ± 4.3 cm², n = 20), and that of heat hyperalgesia ranged from 41.9 to 115.4 cm² (mean 86.3 ± 4.1 cm², n = 20). None of the five control subjects who were injected with saline instead of capsaicin developed mechanical or heat hyperalgesia.

**Magnitude estimations of pain induced by suprathreshold stimuli**

In the area of hyperalgesia there was a significant increase in the magnitude estimates of suprathreshold pain induced by both mechanical (P < 0.001, paired test) and heat (P < 0.001; paired test) stimuli (see Table 1).

**Spatial matching between mechanical and heat hyperalgesia and flare**

There was no significant statistical difference among the areas of VF, of punctate mechanical hyperalgesia, and of heat hyperalgesia (P = 0.095; analysis of variance). It must be emphasized that the areas of VF reached their maximum shortly after injection of capsaicin. Therefore measurement of areas of VF >5 min of injection would have yielded smaller values. The area of long-lasting central flare was obviously smaller than the rapidly vanishing overall flare. It is important to note that the areas of mechanical and heat hyperalgesia clearly outlasted the initial, rapidly vanishing flare reaction.

The matching of the areas of the mechanical and heat hyperalgesias and the area of early visual flare could sometimes be shown to respect the finest details, particularly when the area of hyperalgesia was determined along more than the standard 12 radial paths converging at the injection site, as shown in Fig. 5. Although this was obvious to the naked eye in pale subjects, the matching between areas of flare and hyperalgesia was reassuringly evident in the experiment on the black subject. After capsaicin injection in this person, no change in skin color could be detected visually, and therefore it was impossible to map the area of VF or to be in any way cued by it. However, when comparing the resulting areas of hyperalgesia and TF, again there was equivalence.

**Intracutaneous local anesthetic block**

When capsaicin was injected on one side of a strip of anesthetized skin, development of the TF, the VF, and also of the resulting hyperalgesias was blocked beyond the line of anesthesia (Fig. 6).

**Nerve trunk local anesthetic block**

Anesthetic block of the medial cutaneous nerve of the forearm at the level of the elbow did not prevent development of the characteristic capsaicin-induced TF and VF within its cutaneous territory (Fig. 7). The results of the two types of block experiments demonstrate that the spread
FIG. 3. Constant localization of cutaneous spots of increased temperature on repetition of capsaicin injection in the same region. A: in the 1st session, capsaicin injection (cold spot at arrowhead) induced the typical multispotted TF. B: 5 wk later, capsaicin injected 3 cm away (arrowhead) again induced the expected pattern. C: strikingly, the spots appeared exactly in the same location in both experiments (broken line, A; continuous line, B).

of the extensive initial thermographic flare is neurally mediated at the local cutaneous level.

DISCUSSION

Areas of flare response

The areas of VF measured in these experiments are similar to the flare areas reported by Lewis (1942) but much larger than those reported by more recent workers (LaMotte et al. 1991; Simone et al. 1989) using similar stimuli in humans. This discrepancy is not due to our overestimating the area that becomes reddened after capsaicin injection, as the objectively measured thermographic change coincides with the maximal area of redness. We believe the assessed discrepancy relates to the time at which the VF is measured. The full extent of the VF develops rapidly after capsaicin injection and begins to shrink \( \approx 5\)–10 min. It is possible that what previous authors measured visually was mainly the long-lasting central flare close to the injection site, and we measured the extensive vascular flush that appears very early after capsaicin injection. In fact, the overall areas of flare reported previously by others using identical capsaicin injections are close to the areas of central flare measured in this study (19.6 cm\(^2\)). Simone et al. (1989) reported 31 cm\(^2\), and LaMotte et al. (1991) reported 21.6 cm\(^2\). Also, other workers that measured the area of flare did not report very large flares (Forster et al. 1995; Kilo et al. 1994). However, they used topical capsaicin and intradermal histamine, respectively, which may explain the difference.

Areas of hyperalgesia

This study addressed the area conventionally described as secondary hyperalgesia. The area of capsaicin-induced TABLE 1. Magnitude estimations for suprathreshold pain

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<th>Basal</th>
<th>Postcapsaicin</th>
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<tr>
<td>Suprathreshold MP</td>
<td>9.63 ± 0.62</td>
<td>15.55 ± 0.97</td>
<td>21</td>
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<tr>
<td>Suprathreshold HP</td>
<td>10.07 ± 0.72</td>
<td>15.81 ± 1.02</td>
<td>21</td>
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Values are means ± SE and reflect arbitrary units chosen by the subjects. Normalized magnitude estimations for suprathreshold mechanical pain (MP) and heat pain (HP).
punctate mechanical hyperalgesia was similar in overall size to what was reported by LaMotte et al. (1991) with the same dose of capsaicin. For heat hyperalgesia, however, the current results agree partially with those of LaMotte et al. in that clear heat hyperalgesia was identified for suprathreshold stimuli. Although LaMotte et al. did mapping experiments such as those reported here, they did not find heat hyperalgesia. However, they mapped the area of heat hyperalgesia with a 38°C heat stimulus, which would only be adequate to disclose heat hyperalgesia provided there was a reduction in the heat pain threshold but insufficient if the hyperalgesic response was mainly due to an increase in the suprathreshold pain magnitude. Actually, Hardy et al. (1952) emphasized that, in the area of secondary hyperalgesia, heat pain thresholds are basically unchanged, and the only manner to evoke heat hyperalgesia is by using suprathreshold stimuli. In these experiments the broad area of heat hyperalgesia could be reliably delineated by delivering stimuli well above pain threshold (i.e., 47°C), as recommended by Hardy et al. However, Simone et al. (1991) only found an increase in the suprathreshold magnitude of heat pain in the area of primary but not secondary hyperalgesia, with repeated stimuli delivered at the same skin area. Although repetitive stimulation at a same locus of skin is known to suppress the responses of nociceptive afferents (Adriansen et al. 1984), a factor that may have lessened the differences between normal and hyperalgesic skin, it is difficult to reconcile this discrepancy between that study and the current results. The difference may relate again to the fact that we applied strong, clearly suprathreshold stimuli to areas of skin that were not previously stimulated. Ali et al. (1996) also found no evidence of heat hyperalgesia. However, the dose of injected capsaicin was one-half the dose used in our study, and to elicit heat pain they used a laser-thermal stimulator, which unlike the Peltier thermode delivers stimuli to a smaller skin area. Apart from the early reports of Lewis (1942) and Hardy et al. (1952) unambiguously describing the presence of both mechanical and heat hyperalgesia in the area of secondary hyperalgesia, there are recent important reports showing that, under certain circumstances, flare and hyperalgesia may have similar extension (Schmelz and Kress 1996) and that heat pain thresholds are diminished in the area of secondary hyperalgesia after freeze injuries (Kilo et al. 1994).

**Nature of the components mediating the flare**

Lewis (1927) postulated that injuries to the skin trigger a triple vascular response that includes 1) local dilatation of the minute vessels (capillaries, postcapillaries, venules, and postvenules) confined to the site of injury; 2) increase in permeability of the walls of those vessels; and 3) widespread dilatation of the deeper “strong” arterioles, an event that Lewis (1927) singled as the key mechanism mediating the flare. Skin temperature is mainly controlled through dilatation and constriction of arterioles (Houdas and Ring 1982). It is known that the arteries supplying the skin form a deep
cutaneous arterial network that branches to make a vertical system of strongly contractile arterioles that connect with the subpapillary arterial network of smaller vessels (Taylor and Palmer 1987). Therefore it is reasonable to regard the capsaicin-induced multifocal spots of increased temperature as reflecting dilatation of these "strong" vertical arterioles.

The reactive hyperemia that follows a period of ischemia offers further insights on the vascular substrates of the flare. These results show that such reactive hyperemia is also underlaid by multifocal dilatation of vertical arterioles. This vasodilatation reflects hypotonia of the arterial muscle wall (Lewis 1927) and probably affects uniformly all the muscular vessels rendered ischemic. If so, the extent of arterial dilatation during reactive hyperemia detected by thermography is a likely measure of the overall population of cutaneous arterioles capable of dilatation. Our findings show that the particular arterioles engaged in the flare reaction in response to capsaicin injection are the same that react in the postischemic period. Thus probably every cutaneous arteriole capable of dilatation receives nerve endings from the neurovascular apparatus involved in the neurogenic flare induced by capsaicin. It follows that within the overall population of cutaneous arterioles there would be no specific subgroup arranged exclusively for the flare reaction.

On the other hand, the color of the flare is mainly determined by flooding of the "minute vessels" with arterial blood (Lewis 1927). The current results show that after capsaicin injection the spatial extent of the multifocal arteriolar dilatation detected by thermography coincides with the extent of the overlying redness. This spatial matching is unsurprising if dynamic opening of vertical arterioles floods the corresponding surface network of capillaries. Differences in morphology and temporal profile between the short-lived initial VF and the long-lasting central VF are not well understood; it is likely that those two profiles reflect different underlying mechanisms. Moreover, we believe it is important to emphasize the fact that our measurements of the flare were performed in this initial, extensive reaction and not in the long-lasting, much smaller redness surrounding the skin in the immediate vicinity of the injection site. This difference may be crucial in understanding the mechanisms of the flare response. Actually, Forster et al. (1995) confirmed our previous reports (Serra et al. 1993, 1994a, b) and suggested that the flare response consists of both a superficial and a deep component that may be organized differently in different layers of the skin. Lynn et al. (1996) have shown in the pig skin that antidromic release of vasoactive substances from heat-specific nociceptors gives rise to localized elevations of temperature that coincide with the afferent receptive field of the unit. This localized warming may extent for several millimeters, but it is still insufficient to explain the very large areas of focal arteriole dilatation seen in our thermographic recordings. Therefore, taking these findings together, it is conceivable that the flare response is not a single phenomenon but may be due to two underlying mechanisms responsible for the superficial warming and for the deep arteriolar dilatation.

Spread of flare

The most accepted hypothesis proposes that the flare spreads via cutaneous axon reflexes. The anatomic substrate for such mechanism would feature a distal branching of primary afferent neurons to supply both a cutaneous sensory ending and an effector ending near an adjacent blood vessel (Lewis 1927). An alternative hypothesis proposes that the flare would not spread via axon reflexes but through a "cascade phenomenon" (Lembeck and Gamse 1982). Yet another theory proposes that not only the endings of polymodal nociceptor units but also their preterminal varicosities would serve a receptor-effector function (Szolcsáiny et al. 1992). These axons would span some distance to reach the microvasculature of the skin and would be responsible for the spread of the flare over a few centimeters. Our thermographic results show that the primary event in the flare response is not a wave but a neurally mediated random multifocal dilatation of arterioles around the injury site. The consistent location of the foci of arteriolar dilatation recorded on different occasions in experiments in the same region proves the existence of a steady cutaneous neurovascular apparatus serving this function. This specific system connects points in the surface of the skin with underlying arterioles located up to many centimeters away, either through discrete long axons or through coupling between branches of different afferent neurons (Meyer et al. 1985). Moreover, the fact that the arterioles that respond are the same even when the noxious stimulus is not applied to the same site indicates that different cutaneous branches of this system converge to the same set of target arterioles.

What mediates the hyperalgiasia?

For Lewis (1937) the widespread arteriolar flare and resulting hyperalgasia after skin injury were due to activity in a "nocifensor" system of nerves, different from the nociceptor specific system mediating pain. Others also report dissociation of the nerve fibers involved in the vascular response and in pain (Cervero et al. 1993; Jänig and Lisney 1989; Treede 1992). Recently, LaMotte et al. (1991) hypothesized that the spread of mechanical hyperalgasia is due to activation of a previously not described class of chemonociceptor with widely arborizing branches (or small, functionally coupled branches), conceptually very similar to Lewis' nocifensor system. Schmelz et al. (1994) reported the existence of C- afferents in the human that have very large receptive fields and that may account for the spread of the hyperalgasia. These results confirm the existence of such a cutaneous nerve system. However, for LaMotte et al. (1991) these chemonociceptive afferents would not mediate sensitization of peripheral nociceptor units in the skin; instead they would terminate on dorsal horn interneurons that would become secondarily sensitized and then their projections to wide dynamic range and/or nociceptor-specific neurons would evoke pain. The area of polymodal hyperalgasia coincided with the area of early visual flare. Such matching was well described by Lewis (1935–1936). We submit that the matching between the areas of local cutaneous flare and hyperalgasia has meaningful implications. Even if nociceptive input to the dorsal horn might follow some somatotopic order (Bullit 1991), such input, if pathogenic, could not be so accurate as to result in sensitization of precisely those dorsal horn neurons whose receptive fields match a remote local vascular process of the skin. It appears more logical
to envisage this vascular-sensory matching as the consequence of related mechanisms processed at peripheral level. However, it still remains to be established how flare and hyperalgesia are linked, particularly when it is known that flare and hyperalgesia may occur independently, as it occurs after histamine injection. Also, Lamotte et al. (1991) found that, when they performed proximal nerve blocks before capsaicin injection into the anesthetic skin region, when the block wore off, either no hyperalgesia developed (although there was a visual flare) or it was much smaller than that after capsaicin into normal skin. It is important to remark that the mechanisms involved in “touch-evoked” low threshold mechanical hyperalgesia or allodynia, a phenomenon we did not deal with in these studies, might very well be different and perhaps caused by dorsal horn neuron hyperexcitability.

The common polymodal C-nociceptor does not change its properties in the area of secondary hyperalgesia (Baumann et al. 1991; Campbell et al. 1988; LaMotte et al. 1992). However, failure to detect peripheral receptor changes need not imply that secondary hyperalgesia cannot be due to sensitization of peripheral units. Recently discovered “silent” C or A-δ nociceptor units that become active during inflammation (Davis et al. 1993; Handwerker et al. 1993) appeal as likely subsets of peripheral nociceptors responsible for signaling secondary hyperalgesia. The behavior of these units was not studied in areas of secondary hyperalgesia. In a recent study (Serra et al. 1995) we found that there exist peripheral units fulfilling the criteria of “silent” nociceptors whose receptor properties change after remote skin injury. They may determine or substantially contribute to the pathophysiology of heat and punctate mechanical secondary hyperalgesia.

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