Cutaneous Limb Inflammation Produces Analgesia to Pressure Pain in the Ipsilateral Forehead of Healthy Volunteers

Lone Knudsen and Peter D. Drummond
School of Psychology, Murdoch University, Perth, Western Australia.

Abstract: To investigate the pain-modulatory effects of a local inflammatory stimulus on pain elsewhere in the body, capsaicin was applied topically to the forearm of 14 healthy female volunteers. Pressure-pain thresholds and sensitivity to sharpness were assessed on each side of the forehead twice per day during 48 hours of capsaicin treatment, and in the treated and contralateral forearm before and at the end of treatment. Heat was applied to the treated area to rekindle pain at times of forehead assessment. Hyperalgesia to sharpness, but not pressure pain, developed in the treated area whereas sensations remained stable in the contralateral forearm. Sharpness ratings decreased bilaterally in the forehead after 6 hours of treatment, and ipsilateral analgesia to pressure pain developed in the forehead when the capsaicin site was heated after 48 hours of treatment. These findings suggest that pain modulation involves unilateral regulatory mechanisms in addition to local and generalized pain control. The dissociated changes to sharpness and pressure pain indicate distinct cutaneous and deep central pain pathways.

Perspective: The findings lend support to an increasing body of research which demonstrates that pain modulation involves hemilateral mechanisms in addition to local and generalized controls. Elucidation of mechanisms that modulate ipsilateral pain processing may help to clarify the pathophysiology of complex regional pain syndrome, which is characterized by hemilateral hyperalgesia.

© 2011 by the American Pain Society

Key words: Diffuse noxious inhibitory controls, stress-induced analgesia, capsaicin, locus coeruleus, hyperalgesia.

The present understanding of the perception of pain is that it is the end result of a number of inhibitory and facilitatory influences on nociceptive neurotransmission in the central nervous system. Some well-known mechanisms that may be activated in response to a painful stimulus are the gate-control response, diffuse noxious inhibitory controls (DNIC), stress-induced analgesia, and stress-induced hyperalgesia. Also, the locus coeruleus (LC) nuclei have been implicated in descending inhibitory control. Apart from the gate-control effect, which is concerned with pain perception locally, the remaining mechanisms, when activated, appear to exert bodywide inhibitory or facilitatory influences on pain perception. The direction of such effects may depend on the type of conditioning and outcome stimuli.

However, findings are now beginning to emerge that challenge the concept of widespread inhibition and facilitation. For example, unilateral carageenan inflammation of the rat hindpaw was found to induce hyperalgesia not only in the injected hindpaw but also in the ipsilateral noninflamed forepaw 4 hours after the carageenan injection. Interestingly, the hyperalgesia in both the inflamed hindpaw and the ipsilateral forepaw was more severe in rats with LC lesions than in sham-operated rats, suggesting that an inhibitory influence, emanating from the LC, extended hemilaterally.

In humans, the effect of noxious stimulation on either ipsilateral or contralateral pain sensitivity has been studied over a range of stimulus modalities (eg, thermal, electrical, ischemic) including brief inflammatory pain. However, to the best of our knowledge, the remote effect of a noxious stimulus on bilateral sensitivity to pain has been assessed in only 3 human studies. Unilateral tourniquet-induced left arm pain resulted in analgesia to pressure and heat which was similar in the left and right thigh in a sample of...
In a small sample of 9 participants, intramuscular hypertonic saline injection into the contralateral and ipsilateral arm each reduced pain to electrical stimulation of the left leg, with a slightly greater reduction during ipsilateral arm injection. However, the difference between sides was not statistically significant. In a larger sample of participants, we reported bilateral analgesia to a sharp stimulus that was similar in the ipsilateral and contralateral forehead following cold-induced arm pain. Analgesia to pressure pain was also detected bilaterally in the forehead. However, analgesia was more marked on the ipsilateral side. These findings are at odds with studies in rats that demonstrated hyperalgesia in the ipsilateral forepaw after hindpaw injection of the inflammatory agent carrageenan, possibly because of differences in the conditioning stimulus modality (cold-induced pain versus acute inflammation), duration of pain (minutes versus hours) or location of assessment (forehead versus forepaw).

In the present study, sensory testing was performed on each side of the forehead in healthy humans during prolonged (48 hours) treatment of the forearm with topical capsaicin, an agent that induces neurogenic inflammation. As carrageenan inflammation was associated with hemilateral hyperalgesia in rats, we hypothesized that persistent inflammation of the human forearm would evoke hyperalgesia on the ipsilateral side of the forehead.

Methods

Participants

Fourteen healthy female university students with a median age of 26 years (range 18–41 years) participated in the study. Participants were excluded if they suffered from any medical problems including pain. Each participant provided written informed consent for the procedures, which were approved by the Murdoch University Human Research Ethics Committee.

Procedures

Inflammatory Hyperalgesia of the Forearm

After cleaning the skin with alcohol, a 27-cm² area of the volar forearm was treated with the topical application of capsaicin cream (10% capsaicin dissolved in ethoxycetate and incorporated into a base of acetyl alcohol, stearic acid, and fatty acid ester). The forearm on the nondominant side of the body was treated in 50% of cases and the dominant forearm in the remaining cases (determined randomly). The capsaicin cream was covered in bandages and left in place for 24 hours. The area of treatment was marked and a new amount of capsaicin was applied to the same cleaned skin for another 24 hours. A 45°C heat pack was placed on the treated area (on top of the bandages) to rekindle pain at times of sensory assessments. Heating capsaicin-treated skin reliably rekindles capsaicin-induced pain that otherwise diminishes 1 to 2 hours after topical application. Participants rated the pain intensity on a scale from 0 (no pain) to 10 (extremely severe pain) and also rated the distress associated with the pain in the forearm from 0 (no distress) to 10 (extremely severe distress).

Sensory Assessments

Pain thresholds to firm pressure (PPT) and the extent of sharpness produced by a firm nylon bristle were assessed twice in the area of capsaicin application and in the equivalent area of the contralateral forearm as well as on each side of the forehead. In the forearm, pressure was applied gradually at intervals of 200 g using a spring-loaded algometer with a rounded tip (1 cm in diameter). This was done to a maximum of 2.3 kg or until the participant felt pain. In participants who did not experience pain at 2.3 kg, a pressure-pain threshold of 2.3 kg was assumed. The mean value in each forearm was taken as the PPT for that arm. In the forehead, pressure was applied at 80 g increments. Sharpness was rated on a scale from 0 (not sharp) to 10 (stabbing) in response to a single application of the bristle (Filament 17; Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden). Sufficient force was applied to bend the bristle for 1 second. The order of assessments was randomized between participants to exclude order or time effects, but was kept constant within each participant to ensure that any change in sensitivity was not due to a change in the order of assessments.

Statistical Analysis

Student’s t-tests were used to assess side-to-side differences in forehead sensitivity to pressure pain and sharpness prior to testing, and to assess differences in pain and distress responses between the 2 capsaicin applications. The extent of pain and distress from the capsaicin and heat stimulation was investigated in Heating (before and during heating of the capsaicin-treated skin) × Time (the 4 assessments after the initial application of capsaicin) analyses of variance. The development of
hyperalgesia in the treated forearm was assessed in Side (treated forearm, untreated forearm) × Time (before capsaicin, after removal of capsaicin) analyses of variance for PPT and sharpness ratings. The influence of heating the capsaicin-treated skin on forehead sensations was investigated in Side (ipsilateral or contralateral to the capsaicin application) × Time (the 5 assessments) × Heating (before and during heating of the capsaicin-treated skin) analyses of variance for PPT and sharpness ratings. The Huynh-Feldt epsilon was used to correct for violations of sphericity. Changes across time points were investigated with simple contrasts, and student’s t-tests or analyses of variance were used as appropriate for post hoc analyses. In addition, Pearson’s correlations were performed between pain, distress ratings, sensations in the capsaicin-treated forearm (compared with the contralateral forearm) and changes in forehead sensitivity from before to after 48 hours of capsaicin treatment, to investigate whether the changes in forehead sensitivity were related to the pain intensity, distress or hyperalgesia produced by the capsaicin. Data are reported as the mean ± standard error of the mean and P < .05 was considered to be statistically significant.

Results

Symmetry of Forehead Sensations Prior to Capsaicin Treatment

The difference between the right and left sides of the forehead to pressure pain upon commencement of the experiment was 80 g or less in the majority of participants (86%) (range 0–160 g). There was no difference in 43% of participants. In the group as a whole, PPTs did not differ between the 2 sides [Mright = 625.71 ± 46.29 g, Mleft = 660.00 ± 47.99 g, t(13) = 1.71, P = .111]. The difference in sharp sensations between the right and left sides of the forehead was a rating of 1 or less in 93% of participants (range 0–4) with 64% reporting no difference in sensitivity to sharpness. The difference was not statistically significant [Mright = 1.82 ± .56, Mleft = 2.39 ± .54, t(13) = 1.96, P = .071]. Similar results were obtained after nonparametric analysis.

Pain and Distress from the Capsaicin

A burning pain marked by a red flare developed and persisted throughout the study in all participants. The most severe pain was reported by participants after the first application of capsaicin (M = 7.43 ± .52) with slightly less severe pain after the second application (M = 6.43 ± .70) [t(13) = 2.08, P = .058]. However, the 2 applications produced similar distress [Mfirst = 4.89 ± .74, Msecond = 4.11 ± .84, t(13) = 1.42, P = .180]. The pain peaked 5–7 hours after each application [Mfirst = 7.11 ± 1.97 hours, Msecond = 5.37 ± 1.46 hours, t(13) = .72, P = .483].

The pain immediately before each assessment was significantly lower (M = 2.12 ± .60) than the most severe pain reported after the 2 capsaicin applications (Mfirst and second application = 6.93 ± .57) [t(13) = 8.49, P < .001]. Nonetheless, the heat stimulation successfully rekindled the pain (M = 6.23 ± .46) [main effect for Heating F(1,13) = 110.19, P < .001] to a level similar to the most severe pain. Interestingly, a significant interaction between time and heating [F(3,39) = 4.37, P = .010] revealed that the heat was less successful at rekindling pain after 48 hours of capsaicin [simple contrasts P = .007] than during previous sessions [main effect for Time (pain rating after heating) F(1.88,24.48) = 5.99, P = .009] (Fig 1). No difference in the pain immediately before heat stimulation was observed across sessions [main effect for Time (no heat) F(3,39) = 1.30, P = .290] (Fig 1).

Distress ratings were also lower before each session (M = 1.34 ± .48) compared to when the pain was most severe after the 2 capsaicin applications (Mfirst and second application = 4.50 ± .74) [t(13) = 4.88, P < .001]. However, heat stimulation similarly rekindled distress (M = 3.89 ± .62) [main effect for Heating F(1,13) = 41.30, P < .001] to a level equivalent to when the pain was worst. Again a significant interaction between time and heating [F(3,39) = 5.78, P = .002] revealed that the heat was less successful at inducing distress after 48 hours of capsaicin [simple contrasts P < .001] compared to previous sessions [main effect for Time (pain rating after heating) F(3,39) = 12.04, P < .001] (Fig 1). The distress during assessments without heat stimulation was similar across all sessions (Fig 1) [main effect for Time (no heat) F(3,9) = .56, P = .66].

Primary Hyperalgesia Following Capsaicin

As shown in Fig 2, PPTs were similar in the 2 forearms [main effect for Side F(1,13) = .10, P = .755] and were unchanged in both forearms from before until after removal of the capsaicin 48 hours later [main effect for
Time $F(1,13) = 1.47, P = 2.47$, Time × Side interaction $F(1,13) = 1.41, P = .256$. Sharpness ratings were also similar in the 2 forearms before capsaicin treatment, but increased in the treated forearm $t(13) = 3.02, P = .010$, and not in the untreated forearm, after removal of the capsaicin (Fig 2) [Time × Side interaction $F(1,13) = 13.46, P = .003$]. This resulted in a greater sensitivity to sharpness in the treated than the untreated forearm at this time $t(13) = 4.04, P = .001$.

Figure 2. PPTs and sharpness ratings for the capsaicin-treated and untreated forearm before and after 48 hours of capsaicin. PPTs did not change in either forearm whereas sharpness ratings increased in the treated (*$P < .01$) but not the untreated forearm, resulting in greater sensitivity to sharpness in the treated than the untreated forearm (**$P < .001$). Error bars represent standard errors.

**Changes in Forehead Sensations to the Capsaicin**

As shown in Fig 3, heating the capsaicin-treated skin altered forehead sensitivity to pressure pain [Side × Time × Heating $F(4,52) = 3.00, P = .027$]. Investigation of this interaction revealed that PPTs were unchanged across sessions when sensory assessments were performed without the application of heat (main effect for Time $F(3.09,40.21) = 1.40, P = .256$), although a slight increase in PPTs was apparent on both sides of the forehead. However, when the pain was rekindled by heat, a significant interaction between time and side tested emerged $F(4,52) = 4.51, P = .003$. After 48 hours of capsaicin, participants reported a significant increase in PPTs in the ipsilateral forehead compared to baseline $t(13) = 2.94, P = .011$ [main effect for Time (ipsilateral forehead) $F(2.94,38.26) = 4.74, P = .007$]. This resulted in significantly higher PPTs in the ipsilateral forehead compared with the contralateral forehead at this time $t(13) = 3.12, P = .008$. PPTs were also higher in the ipsilateral than contralateral forehead 24 hours after the first capsaicin application $t(13) = 2.22, P = .045$.

Sharpness sensations decreased in the forehead after 6 hours of capsaicin $t(13) = 2.87, P = .013$ and remained at this level for the duration of the study [main effect for Time $F(2.63,34.13) = 6.11, P = .003$] (Fig 4). This occurred irrespective of heat stimulation [Heating × Time interaction $F(4,52) = .71, P = .591$] and to the same extent on both sides of the forehead [Heating × Time × Side interaction $F(1.83,23.84) = .88, P = .418$].

**Were Changes in Forehead Sensitivity Related to Pain Intensity, Distress or Forearm Hyperalgesia?**

Individual changes in forehead sensitivity to pressure pain from before until after 48 hours of capsaicin were unrelated to pain, distress, or sensations in the capsaicin-treated forearm (Table 1). However, the development of bilateral analgesia to sharpness, which persisted after 48 hours of capsaicin treatment, appeared to be related to greater capsaicin-evoked pain and distress, especially during heat stimulation. In addition, the development of greater ipsilateral than contralateral forehead analgesia to sharpness was associated with less pressure hyperalgesia in the treated forearm irrespective of heat stimulation.

**Discussion**

We expected that persistent unilateral inflammation in the forearm would evoke hyperalgesia in the ipsilateral forehead. Contrary to expectations, we detected greater analgesia to pressure-pain stimuli on the ipsilateral side of the forehead when the forearm was heated after 48 hours of capsaicin treatment. We also...
detected bilateral forehead analgesia to sharpness after 6 hours of treatment which persisted for the rest of the study.

Capsaicin causes a neurogenic inflammatory response by releasing vasoactive peptides such as substance P and calcitonin gene-related peptide (CGRP) from the peripheral endings of primary afferent fibers.\textsuperscript{29,43,58} It initially excites\textsuperscript{33,64} and sensitizes C nociceptors,\textsuperscript{5,63} leading to central sensitization,\textsuperscript{34} then results in desensitization of primary nociceptive afferents due to block of C-fiber conduction and axonal degeneration.\textsuperscript{10,42} Consistent with inflammation, a red flare,\textsuperscript{10,15,47} burning pain, and primary hyperalgesia to sharp stimulation\textsuperscript{34} developed in the capsaicin-treated forearm. However, hyperalgesia to pressure pain was absent in the treated area after 48 hours of treatment, possibly because the capsaicin did not penetrate to nociceptors in deeper tissue or because of C-fiber desensitization to the capsaicin treatment.\textsuperscript{42,50,53} In support of the second possibility, hyperalgesia to heat decreased across the period of capsaicin treatment. Capsaicin-induced sensitivity to heat is primarily mediated by sensitization of C fiber mechano-heat nociceptors,\textsuperscript{37,39} and C fibers mediate capsaicin-induced pressure hyperalgesia.\textsuperscript{15} Interestingly, secondary hyperalgesia to punctate stimuli in response to capsaicin injection was absent when A-fiber conduction was blocked,\textsuperscript{78} suggesting that heat nonresponsive A-fibers primarily signal sharpness hyperalgesia.\textsuperscript{22}

Hyperalgesia to sharpness may have been maintained by central sensitization.\textsuperscript{34}

When triggered by nociceptive stimuli, DNICs inhibit the activity of wide dynamic range neurons in the dorsal horn\textsuperscript{40,48} and trigeminal nucleus caudalis\textsuperscript{17,49} via a supraspinal loop.\textsuperscript{9,41} This effect has been demonstrated to a range of conditioning stimuli (eg, thermal, mechanical, electrical, and ischemic)\textsuperscript{7,20,23,35,38,52,54,62,68,74} and sometimes, but not always, to capsaicin-induced pain.\textsuperscript{16,25,59} The inhibitory action of DNIC is widespread rather than localized. For instance, bilateral DNIC effects were recorded from wide dynamic range neurons in the spinal cord and trigeminal nucleus caudalis of rats following hot-water immersion of tail, muscle, and paws.\textsuperscript{6,8} In humans, analgesia developed bilaterally to pressure in the thighs during tourniquet-induced arm pain\textsuperscript{68} and to sharp sensations in the forehead during cold-induced hand pain.\textsuperscript{35} Separate intramuscular hypertonic saline injections both in the ipsilateral arm and the contralateral arm reduced pain during electrical stimulation of the left leg.\textsuperscript{62} Thus, DNIC probably played a part in the bilateral forehead analgesia to sharp stimuli in the present study.

Stress-induced analgesia (SIA) may also have contributed to analgesia. The well-documented generalized inhibitory effects of stress and fear\textsuperscript{2,11,24,78} are mediated both by nonopioid and opioid mechanisms.\textsuperscript{61,65,71} Distress was associated with greater forehead analgesia.

### Table 1. Pearson’s Correlations Between Pain, Distress and Hyperalgesia in the Capsaicin-treated Forearm (Compared With the Contralateral Forearm) at 48 Hours of Capsaicin Treatment and Changes in Forehead Sensations (Mean, Asymmetry Between the Side Ipsilateral and Contralateral to Treatment) From Before Until After 48 Hours of Capsaicin Treatment

<table>
<thead>
<tr>
<th></th>
<th>Changes in Forehead Sensations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pressure Pain</td>
</tr>
<tr>
<td></td>
<td>No Heat</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Treated Forearm</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>–.12</td>
</tr>
<tr>
<td>Distress</td>
<td>–.13</td>
</tr>
<tr>
<td>Pressure hyperalgesia</td>
<td>–.18</td>
</tr>
<tr>
<td>Sharpness hyperalgesia</td>
<td>–.17</td>
</tr>
</tbody>
</table>

\* P < .05.

\# P = .07.
to sharpness, providing support for an involvement of SIA in concert with DNIC. Likewise, in a previous study in our laboratory, these 2 mechanisms appeared to operate jointly following cold-induced limb pain, which caused bilateral forehead analgesia both to pressure and sharpness in association with pain and distress.65

Curiously, sensitivity to sharpness did not change in the contralateral forearm during the capsaicin treatment. As both contralateral hyperalgesia59 and contralateral analgesia25,27 were previously reported in response to capsaicin, the lack of change in sensitivity to sharpness in the contralateral forearm might reflect a competitive balance between excitatory and inhibitory influences. Many neurons in lamina VII of the spinal cord respond to noxious stimulation from either side of the body,4 providing a possible location for a convergence between excitatory signals from the treated and contralateral forearm.

Based on findings in an animal model of carageenan-inflammation,67 we expected that hyperalgesia would mask analgesia on the ipsilateral side of the forehead after several hours of capsaicin treatment in the forearm. However, this hypothesis was not supported. Instead, analgesia to sharp stimulation developed symmetrically across the forehead and PPT did not change before the capsaicin site was heated. The basis of this discrepancy is uncertain but is important to clarify because it might provide clues about the mechanism of ipsilateral forehead hyperalgesia in patients with complex regional pain syndrome.59 Possibilities could include the intensity of pain (likely to be greater and more persistent after carageenan injections than topically applied capsaicin), the tissue affected (predominantly muscle in the rat studies and skin in the human studies), or greater tissue injury evoked by the carageenan injection.

The most interesting finding in the present study was the development of ipsilateral forehead analgesia to pressure pain when heat was applied to the capsaicin-treated forearm. A similar response developed acutely during cold-induced limb pain in a previous study.35 The mechanism underlying this transient analgesic response is uncertain, but might involve coeruleospinal pain modulation.35 The locus coeruleus (LC) inhibits nociceptive activity in dorsal horn neurons32 via bilateral noradrenergic projections12,13,21,60,72 to all segmental levels of the spinal cord.55 It does so via actions at a2-adenoreceptors.71,32 During unilateral hindpaw inflammation in rats, noradrenaline was released in the ipsilateral dorsal horn but not contralaterally.56 Tsuuroka et al67 found shorter paw withdrawal latencies to heat not only in the inflamed hindpaw but also in the non-inflamed but hyperalgesic forepaw of rats with bilateral LC lesions compared to sham-operated rats. As this was not observed in the contralateral hind- or fore-paw, coeruleospinal pain modulation appeared to oppose hyperexcitable nociceptive dorsal horn neuron activity ipsilaterally. That is, both an excitatory and a less dominant antinociceptive component were detected hemilaterally during carageenan-induced hindpaw inflammation.67 It is tempting to speculate that the inhibitory component contributed to the development of ipsilateral forehead analgesia to pressure pain in our human studies, both to heat and to transient cold-induced pain.35 Consistent with this, ipsilateral forehead analgesia to sharpness was associated with less pressure hyperalgesia in the treated forearm in the present study, suggesting that an inhibitory mechanism reduced pain sensitivity both in the treated forearm and the ipsilateral forehead.

The dissociation between sharpness and pressure-pain sensations to conditioning stimuli in the present and a previous study35 provides support for different central processing of skin and deep tissue sensibility. Intramuscular capsaicin injections induce a greater area of referred pain than intradermal capsaicin in healthy humans,76 and brief low-frequency input from C fibers in the muscle evokes a prolonged increase in the excitability of the flexion reflex (central sensitization) more effectively than input from cutaneous C fibers.70 In some clinical populations (thalamic lesions, central poststroke pain, complex regional pain syndrome), a loss of cutaneous sensation coexists with the persistence or increase in pain to deep pressure.19,44,57 Noiceptors from cutaneous tissue primarily innervate laminae I and II75 whereas muscle afferents predominantly project to laminae I and V.14,46,51 Moreover, different areas in the brain appear to be activated in response to cutaneous pain versus pain of deeper origin, consistent with distinct cutaneous and deep central pain pathways.28

In contrast to the present findings, sensitivity to pressure pain decreased bilaterally in the forehead during cold-induced limb pain, although the ipsilateral reduction was greater than the contralateral reduction.35 The reason for this discrepancy is uncertain, but may be due to the opposing influences of central sensitization and inhibitory pain modulation processes during capsaicin treatment. A reduction in central sensitization during the later stages of the experiment, in line with desensitization of primary nociceptive afferents, might account for the delayed development of heat-evoked analgesia in the ipsilateral forehead. Alternatively, DNIC may have been stronger during cold-induced rather than heat-induced limb pain because of differences in the modality, intensity, or surface area of stimulation (ie, the entire hand in the cold pressor study versus a small area of skin on the forearm in the capsaicin study). Furthermore, the difference in female-to-male ratio in the 2 studies (1.5:1 in the previous study versus 1:0 in the present study) could explain weaker inhibitory control in the present study because DNIC may be weaker in females than males.26 However, other studies find no support for such assertions.1 Finally, the study relied on self-report measures. Although it is possible that participants changed their rating criterion over the course of the experiment, accommodation is unlikely to account for the changes in sharpness and pressure-pain ratings of the forehead as there was no evidence of accommodation at other sites.

The present study was performed in a young, educated female population and thus may not be entirely representative of the general population. Nonetheless, the results replicate findings of activation of bilateral and ipsilateral pain inhibitory mechanisms following
painful conditioning or inflammatory stimuli.\textsuperscript{35,62,67,68} We detected bilateral analgesia to sharpness after 6 hours of cutaneous limb inflammation, and ipsilateral analgesia to pressure after 48 hours of treatment when the capsaicin-treated site was heated. These findings lend support to an increasing body of research which demonstrates that pain modulation involves hemilateral mechanisms in addition to local and generalized controls.

References

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


42. Lynn B: Capsaicin: Actions on nociceptive C fibres and therapeutic potential. Pain 41:61-69, 1990


64. Szolcsanyi J: Antidromic vasodilatation and neurogenic inflammation. Agents Actions 23:4-11, 1988


