Sympathetic Influence on Capsaicin-Evoked Enhancement of Dorsal Root Reflexes in Rats

Jing Wang, Yong Ren, Xiaoju Zou, Li Fang, William D. Willis, and Qing Lin. Sympathetic influence on capsaicin-evoked enhancement of dorsal root reflexes in rats. J Neurophysiol 92: 2017–2026, 2004. First published May 26, 2004; 10.1152/jn.00145.2004. A series of experiments by our group suggest that the initiation and development of neurogenic inflammation in rats are mainly mediated by dorsal root reflexes (DRRs), which are conducted centrifugally from the spinal dorsal horn in primary afferent nociceptors. In this study, DRRs were recorded in anesthetized rats from single afferent fibers in the proximal ends of cut dorsal root filaments at the L4–L6 level and tested for responses to intradermal injection of capsaicin. Sympathectomy combined with pharmacological manipulations were employed to determine if the capsaicin-evoked enhancement of DRRs was subject to sympathetic modulation. DRRs could be recorded from both myelinated (Aβ and Aδ) and unmyelinated (C) afferent fibers. After capsaicin was injected intradermally into the plantar foot, a significant enhancement of DRRs was seen in C- and Aδ-fibers but not in Aβ-fibers. This enhancement of DRRs evoked by capsaicin injection was almost completely prevented by sympathectomy. However, if peripheral α-adrenoceptors were activated by intra-arterial injection of phenylephrine, the enhancement of DRRs evoked by capsaicin could be restored, whereas no such restoration was seen following pretreatment with an α2-adrenoceptor agonist, UK14,304. Under sympathetically intact conditions, the enhanced DRRs following capsaicin injection could be blocked by administration of terazolol, a δ-2-adrenoceptor antagonist. These results provide further evidence that the DRR-mediated neurogenic inflammation depends on intact sympathetic efferents acting on peripheral α1-adrenoceptors, which augment the sensitization of primary afferent nociceptors induced by capsaicin injection, helping trigger DRRs that produce vasodilation.

INTRODUCTION

Damage to the skin can result in the release of a number of endogenous inflammatory substances from primary afferent terminals, from injured cells, or from the circulation. These include neurotransmitters (glutamate and peptides), prostaglandins, K+ ions, protons, 5-hydroxytryptamine, histamine, adenosine 5'-triphosphate, and bradykinin (Bevan 1999; Brain and Williams 1985; Ferrell and Russell 1986; Kress et al. 1999; Lam and Ferrell 1989, 1991; Levine and Reichling 1999). The consequences are the development of vasodilation (redness, warmth), swelling, and pain. The component of inflammation that depends on release of substances from the terminals of primary afferent fibers is referred to as neurogenic inflammation (Stricker 1876; Szolcsányi 1996). The primary afferents that contribute to neurogenic inflammation are C- and Aδ-nociceptors (Jänig and Lisney 1989; Low and Westerman 1989) that respond to capsaicin (CAP) (Szolcsányi 1996) and therefore contain transient receptor potential vanilloid-1 (TRPV1) receptors (Caterina and Julius 2001). These afferents are peptidergic and release tachykinins, such as substance P (SP), and calcitonin gene-related peptide (CGRP) (Holzer 1988).

Electrophysiological studies have suggested that much of the acute cutaneous neurogenic inflammation that follows intradermal injection of CAP is induced by the centrally mediated triggering of dorsal root reflexes (DRRs) carried by C- and Aδ-afferent fibers (Lin et al. 2000a). DRRs can be evoked when inflammation is induced in either the skin or in a joint, and they have been shown to contribute to the development of neurogenic inflammation (Lin et al. 1999; Rees et al. 1995; Willis 1999). On the other hand, evidence also suggests that the sympathetic postganglionic efferent terminals may be involved in the mediation of the peripheral inflammatory responses by interaction with primary afferent terminals (Jänig et al. 1996; Michaelis 2000). However, the mechanisms by which sympathetic nerves affect the development of neurogenic inflammation still remain obscure. Based on our studies showing that the spread of cutaneous vasodilation (flare) evoked by intradermal injection of CAP is reduced by sympathectomy (Lin et al. 2003), we propose the hypothesis that neurogenic inflammation resulting from the generation of DRRs may depend in part on a sympathetic–sensory interaction in the periphery. In this study, we have further examined electrophysiologically if the generation of DRRs, which has been shown to play an important role in development of neurogenic inflammation when there is tissue injury, is influenced by the presence of sympathetic efferents and have analyzed the possible adrenergic receptor subtypes on which sympathetic efferents exert their action in the periphery. Abstracts reporting some of this work have been published (Lin et al. 2000b,c).

METHODS

A total of 76 male Sprague-Dawley rats, weighing 250–350 g, were used for this study. They were housed two per cage, with free access to food and water, in an animal facility at 25°C with a 12-h alternating light-dark cycle. All experimental protocols were approved by the Institution’s Animal Care and Use Committee and were in accordance with the guidelines of the National Institutes of Health and the International Association for the Study of Pain.

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Animal preparation

Animals were initially anesthetized with sodium pentobarbital (50 mg/kg, ip) to perform surgery. The external jugular vein was cannulated, and anesthesia was maintained by continuous infusion of sodium pentobarbital (5–8 mg/kg/h). Once a stable level of anesthesia was reached, the animals were paralyzed with pancuronium (0.3–0.4 mg/kg/h iv) and ventilated artificially. End-tidal CO$_2$ was kept at 3.5–4.5%. Rectal temperature was monitored using a rectal probe and maintained at $\sim$37°C by a servo-controlled heating blanket.

DRR recordings

Laminectomy was carried out from T$_{12}$ to S$_1$ to expose the lumbar-sacral spinal cord. The dorsal roots and spinal cord were protected from drying and cooling by formation of a mineral oil pool between skin flaps and by circulating heated water through a metal tube placed in the pool. Dorsal roots L$_4$, L$_5$, and L$_6$ were exposed. A rootlet of the L$_4$, L$_5$, or L$_6$ dorsal root was cut distally, and the central end was carefully split into small filaments containing a single active fiber on a mirror plate. Evoked DRRs conveyed by a single fiber of the cut central end of the dorsal rootlet were recorded by placing one of the filaments on a silver unipolar hook electrode. DRRs were amplified and observed on analogue and digital storage oscilloscopes and discriminated from noise using a window discriminator. Digitized signals were processed by an interface (CED 1401) connected to a Pentium PC to construct peristimulus rate histograms for counting the firing rates. Spike-2 waveform software was used to capture the original spikes after subtracting the noise level. DRRs were evoked by applying a series of calibrated von Frey filaments that had graded bending forces to an area on the foot. The sites from which DRRs could be evoked were considered the “receptive fields” for the DRRs. Because the threshold for evoking DRRs by mechanically stimulating peripheral afferent terminals varied with each experiment, an appropriate set of von Frey filaments was chosen for each animal. Care was taken to assure that the same unit was being recorded throughout the experiment by monitoring the size and shape of action potential using the digital oscilloscope.

The fiber types that conveyed DRRs were identified by conduction velocity as A$\beta$-, A$\delta$-, or C-fibers. Conduction velocity was measured with either of the following techniques.

![Figure 1](http://jn.physiology.org/content/92/4/2086/F1.large.jpg)

**Fig. 1.** Evoked dorsal root reflexes (DRRs) recorded from the central end of single C dorsal root fibers of an L$_4$ dorsal rootlet showing the effects of sympathectomy on enhanced DRRs evoked by intradermal capsaicin (CAP) injection. Control group was sympathetically intact (*column A*), and experimental group was sympathectomized (*column B*). Horizontal lines above histograms indicate time of application of von Frey hairs. Bending forces that were used to evoke DRRs are shown above horizontal lines.
1) Extracellular recordings of DRRs were made using two silver unipolar hook electrodes placed on two sites of the central stump of the same cut dorsal root filament with a fixed distance between the recording electrodes. DRRs were evoked by applying von Frey filaments to the “receptive field” on the foot. Conduction velocity was calculated by dividing the conduction distance between two electrodes (2.0 ± 0.5 mm) by conduction delays of the evoked action potential recorded at two locations on the same dorsal root filament.

2) The recordings were also done using one silver unipolar hook electrode placed on the cut dorsal root filament. A bipolar stimulating electrode was placed on the cut dorsal rootlet 15–25 mm proximal to the recording site. Action potentials evoked by electrical stimulation were recorded with a fixed latency. The conduction velocity was calculated by dividing the conduction distance by the latency of the action potential. The shape and size of action potentials evoked by electrical stimulation were always monitored to assure that they were the same unit as ones evoked by mechanical stimulation using von Frey filaments.

**Lumbar sympathectomy**

Surgical sympathectomy at the L2–L6 level was done in the way described by Kim et al. (1993) and previously by our group (Lin et al. 2003; Zou et al. 2002). Briefly, the sympathetic chain was identified through a transperitoneal approach. All ganglia and the chains at L2–L6 were resected bilaterally. Animals were allowed to recover from surgery for ≥1 wk before experiments were performed. At the termination of the experiment, the success of the sympathectomy was confirmed by the absence of noradrenergic axons on the femoral arteries on both sides in preparations stained with the fluorescent glyoxylic acid method (see Lin et al. 2003; Zou et al. 2002). The artery taken from the sham-operated animals has an extensive meshwork of noradrenergic axons, but in the artery in the sympathectomized rats, such axons were not seen at all (see Zou et al. 2002).

**Peripheral administration of α-adrenergic receptor agonists and antagonists**

One branch of the femoral artery on the side of nerve recording was carefully isolated from connective tissue and ligated proximally. The
artery was cannulated distally by a small-sized polyethylene tubing that was connected with a Hamilton syringe. The \( \alpha_1 \)-adrenoceptor agonist, phenylephrine (0.05 \( \mu \)g, Tocris), (Lin et al. 2003) or the \( \alpha_2 \)-adrenoceptor agonist, UK14,304 (0.3 \( \mu \)g, Tocris) (Lin et al. 2003), was administered intra-arterially 10 min prior to CAP injection in sympathetically intact rats. The \( \alpha_1 \)-adrenoceptor antagonist, terazosin (10 \( \mu \)g, Sigma) (Kynch 1986), or the \( \alpha_2 \)-adrenoceptor antagonist, yohimbine (15 \( \mu \)g, Sigma) (Howe et al. 1983), was administered locally by injection of the solution into the artery 10 min prior to CAP injection in sympathetically intact rats. Drugs were dissolved in saline and given in a volume of 10 \( \mu l \) for intra-arterial injection. For control purposes, the same volume of saline was given in other rats. Results from our experiments using blood flow measurements (Lin et al. 2003) indicate that the volume (10 \( \mu l \)) and concentrations of drug solution injected locally would not be enough to produce a systemic effect by spreading into the general circulation.

Experimental protocol

CAP was dissolved in Tween 80 (7%) and saline (93%) to a concentration of 1%. A volume of 10 \( \mu l \) was injected intradermally into the skin of the foot to evoke DRRs. DRRs from C-, A\( \delta \)-, and A\( \beta \)-fibers were recorded in groups of sympathetically intact and sympathetically sham-operated rats before and after intradermal injection of CAP. DRRs from sham-sympathectomized rats were also recorded before and after intradermal injection of CAP as a control. Changes are expressed as a percentage of control values (100%). Statistical comparisons were performed with paired \( t \)-test. A grouped \( t \)-test was used to compare the difference in responses between groups having different treatments. \( P < 0.05 \) was taken as significant.

RESULTS

Effects of CAP injection on evoked DRRs recorded from C- and A\( \delta \)-fibers under sympathetically intact and sympathetically operated conditions

Our first series of experiments was designed to examine if sympathectomy would affect the CAP-evoked enhancement of DRRs. Consistent with our previous reports (Lin et al. 2000a), DRRs evoked by applying a graded series of von Frey hairs and recorded from single C- and A\( \delta \)- (but not A\( \beta \)-) afferent fibers of cut dorsal root filaments were significantly increased following intradural injection of CAP under either sympathetically intact or sympathetically sham-operated (\( n = 4 \)) conditions. Figures 1A and 2A show the examples of the enhanced DRRs recorded from an C - and A\( \delta \)-fiber identified by conduction velocity in sympathetically intact rats. The enhancement reached its peak at around 30 min after CAP injection and lasted \( \geq 60 \) min. A continuous observation was made until 90

\[ \text{Percent Response} \]
After sympathetic postganglionic efferents were removed surgically, CAP injection no longer enhanced DRRs (Figs. 1B and 2B). Under sympathetically intact conditions, the normalized peak values after CAP injection were 243.32 ± 138.52% (control values 100%) in C-fibers (n = 8) and 196.39 ± 72.28% in Aδ-fibers (n = 9) compared with the values before CAP injection, respectively. After sympathectomy, peak values after CAP injection were 122.75 ± 18.5% in C-fibers (n = 6) and 116.65 ± 13.61% in Aδ-fibers (n = 7). The differences between the groups were significant (P < 0.05; Fig. 3). However, there were no differences in the DRRs (P > 0.05) conveyed by Aδ-fibers after CAP injection either in sympathetically intact (125.3 ± 19.6%, n = 5) or in sympathectomized (99.0 ± 12.0%, n = 5) rats (data not shown).

Peripheral administration of α-adrenergic receptor agonists on evoked DRRs recorded from C- and Aδ-fibers under sympathectomized conditions

Under sympathectomized conditions, peripheral α1- or α2-adrenoceptors were activated by intra-arterial injection of phenylephrine or UK14,304 10 min prior to intradermal CAP injection to see if activation of α-adrenoceptors could mimic the conditions when the sympathetic efferents were present. As shown in Fig. 4, there were no obvious changes in DRRs after drug injection. However, the increases in the DRRs evoked by
CAP were restored after the periphery was pretreated with phentylephrine by intra-arterial injection. The peak increases with phentylephrine pretreatment were 193.5 ± 45.8% (control values 100%; P < 0.05, n = 6) in C-fibers and 153.8 ± 41.8% (P < 0.05, n = 7) in Aδ-fibers compared with the DRR response seen with intra-arterial injection of saline, when the grouped responses were 125.48 ± 18.5% in C-fibers (n = 6) and 116.65 ± 13.61% in Aδ-fibers (n = 7). In contrast, pretreatment with UK14,304, an α2-adrenoceptor agonist, by intra-arterial injection did not significantly change the DRR responses induced by CAP injection. The peak increases with UK14,304 were 142.67 ± 23.34% in C-fibers (n = 6) and 140.69 ± 15.29% in Aδ-fibers (n = 6), which were comparable with the DRR responses seen with intra-arterial injection of saline (P > 0.05; Fig. 5; Table 1).

**Effects of blockade of peripheral α-adrenoceptors on evoked DRRs recorded from C- and Aδ-fibers after capsaicin injection under sympathetically intact conditions**

In sympathetically intact rats, we further examined if the blockade of α1- or α2-adrenoceptors affected the CAP-evoked

<table>
<thead>
<tr>
<th>Sympathectomized</th>
<th>Saline</th>
<th>Phenylephrine</th>
<th>UK14,304</th>
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</thead>
<tbody>
<tr>
<td>C-fiber n</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Peak values after CAP injection (%)</td>
<td>125.48 ± 18.5</td>
<td>193.5 ± 45.8*</td>
<td>142.67 ± 23.34</td>
</tr>
<tr>
<td>Aδ-fiber n</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Peak values after CAP injection (%)</td>
<td>116.65 ± 13.16</td>
<td>153.8 ± 41.8*</td>
<td>140.69 ± 15.69</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. saline.

**Table 1. Effects of intra-arterial injections of α1- and α2-adrenoceptor agonists (in sympathectomized rats) on DRRs evoked by capsaicin injection in C- and Aδ-fibers**

**Discussion**

Our previous studies (Lin et al. 1999, 2000a) have provided direct evidence that enhanced DRRs after acute cutaneous inflammation induced by CAP injection are seen in both small myelinated and unmyelinated afferent nociceptors. These results, combined with data obtained by other laboratories showing that inflammatory peptides are released from the peripheral terminals of fine primary afferent nociceptors when they are antidromically stimulated (Holzer 1988; Kress et al. 1999), strongly support the view that DRRs are involved in neurogenic inflammation. This study, using the same acute cutaneous neurogenic inflammatory model, has further found that DRRs enhanced by CAP injection are subject to sympathetic modulation. DRRs are significantly reduced after sympathectomy. In sympathetically intact rats, blockade of peripheral α1-adrenoceptors with terazosin profoundly reduced the enhanced DRRs induced by CAP injection. On the other hand,
when sympathectomized rats were pretreated with an α1-adrenoceptor agonist (phenylephrine) by intra-arterial injection, the reduction in the CAP-enhanced DRRs after sympathectomy could be restored. These findings suggest that sympathetic efferents may participate in modulation of the sensitivity of primary afferent nociceptors in the periphery, which in turn affects the sizes of the afferent volleys evoked by the mechanical stimuli that trigger the DRRs.

Antidromic activity in primary afferent terminals is a major mechanism by which inflammatory peptides are released to produce neurogenic inflammation. This process has been shown to be mediated centrally and can be initiated by intradermal injection of CAP or by induction of experimental arthritis (Lin et al. 1999; Rees et al. 1994; Sluka et al. 1993, 1995). The enhanced afferent discharge activates GABAergic interneurons in the spinal dorsal horn by release of glutamate onto non-NMDA and NMDA receptors (Zou et al. 2001). An increased release of GABA from GABAergic interneurons of the dorsal horn can result in an excessive primary afferent depolarization, which triggers DRRs (Willis 1999; Willis and Coggeshall 2004). CAP sensitivity is considered to be a principal pharmacological trait of a major subpopulation of sensory neurons. CAP-sensitive nociceptors are found mostly among unmyelinated primary afferent fibers (Jancso et al. 1977; Szolcsanyi 1977), but some are small myelinated primary afferent Aδ-fibers (Michael and Priestley 1999; Nagy et al. 1983). Many of these fibers are peptidergic. There was no significant increase in DRRs recorded from Aβ fibers after intradermal CAP injection in these experiments. Therefore it is strongly suggested that DRRs conveyed by C-and/or Aδ-
afferent fibers contribute to the induction of neurogenic inflammation. This result confirms our previous studies (Lin et al. 1999, 2000a).

Postganglionic sympathetic denervation either by surgical or chemical sympathectomy has been suggested experimentally and clinically to be an effective way of reducing pain behaviors in some neuropathic and inflammatory pain models without obviously affecting the functions of other systems (Green et al. 1993; Kim and Chung 1991; Kinnman and Levine 1995; Kinnman et al. 1997; Levine et al. 1986; Moon et al. 1999; Neil et al. 1991; Xie et al. 1995a). For instance, this experimental manipulation has been successfully used in a series of behavioral experiments by Chung’s group in showing the pathophysiological mechanisms by which the sympathetic efferent outflow modulates neuropathic pain (Choi et al. 1994; Kim and Chung 1991; Moon et al. 1999; Xie et al. 2001). Experiments in anesthetized animals done by our group (Lin et al. 2003) have shown that sympathectomy by surgery done at 7–10 days before experiments does not significantly affect the resting blood flow level. Therefore, data both from awake and anesthetized animals do not indicate the possibility that sympathectomy would obviously affect physiological functions, which might interfere with our studies.

Our recent studies suggest that the generation and development of cutaneous neurogenic inflammation (flare) induced by CAP injection depends on intact postganglionic sympathetic efferents. Release of NE and/or neuropeptide Y (NPY) from sympathetic efferents activates α1-adrenergic and/or NPY Y2 receptors, which are believed to be located on the primary afferent terminals (Lin et al. 2003, 2004). Since CAP-induced flare in rats is mediated mainly by DRRs, these experiments further examined if the enhancement of DRRs induced by CAP injection is also sympathetically dependent. We found that either sympathectomy or blockade of peripheral α1-adrenoceptors with terazosin in sympathetically intact rats reduced dramatically the DRRs induced by CAP injection, suggesting that there is an endogenous release of NE from postganglionic sympathetic efferent terminals when tissue injury and NE release might enhance the sensitivity of primary afferent nociceptors to facilitate the process of induction of DRRs. These results are consistent with the data on neurogenic flare induced by CAP injection (Lin et al. 2003). It has been shown that sympathetic efferent activity can enhance ongoing impulse discharges in injured afferents that were previously silent following tissue injury (Shinder 1999). NE and sympathetic stimulation can enhance the activity of primary afferent C-fiber nociceptors innervating inflamed skin (Sato and Kumazawa 1996; Sato and Perl 1991). Cutaneous C-fiber nociceptors in rats that were sensitized by the injection of a mixture of inflammatory mediators into the receptive field responded to sympathetic stimulation and local arterial injection of NE (Hu and Zhu 1989). In an acute cutaneous inflammatory model induced by intradermal injection of CAP, both exogenous and endogenous NE release in the skin produced a prolonged decrease in heat pain threshold at the site where NE was injected.

Table 2. Effects of intra-arterial injections of α1- and α2-adrenoceptor antagonists (in sympathetically intact rats) on DRRs evoked by capsaicin injection in Aδ- and C-fibers

<table>
<thead>
<tr>
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<th>Sympathetically intact</th>
<th>Saline</th>
<th>Terazosin</th>
<th>Yohimbine</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-fiber</td>
<td>n=6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak values</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CAP injection</td>
<td>(%)</td>
<td>206.77±69.61</td>
<td>91.88±20.09*</td>
<td>162.82±22.83</td>
</tr>
<tr>
<td>Aδ-fiber</td>
<td>n=9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak values</td>
<td></td>
<td>186.66±98.94</td>
<td>103.6±23.91*</td>
<td>151.77±21.36</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05, †P < 0.01 vs. saline.
released (Drummond 1995, 1998). Thus activity in sympathetic fibers would help enhance the activity in sensitized nociceptors, which is the key to initiating the induction and development of DRRs. Sympathetic influence on different arthritic models has been shown to be inconsistent. Sluka et al. (1994) reported that sympathetic denervation did not obviously affect the arthritis induced by knee joint injection of kaolin and carrageenan. A series of studies by Green’s group showed that arthritis induced by bradykinin injection into the cavity of knee joint, which was characterized by plasma extravasation, was sympathetically dependent (Green et al. 1993). Also, they found that a neuroendocrine pathway could be activated after bradykinin-induced plasma extravasation developed (Green et al. 1995; Miao et al. 1996). This negative feedback mechanism was also sympathetically dependent and initiated by stimulation of primary afferent C-fibers (Green et al. 1995, 1997). Thus it seems that this sympathetically dependent pathway is actually a self-protection mechanism to prevent tissue from being further inflamed. However, we have not tried to study if such a mechanism also applies to the CAP-induced inflammation.

Another of our findings was that the reduction in the CAP-induced enhancement of DRRs following sympathetic denervation could be rekindled by local activation of $\alpha_1$-, but not $\alpha_2$-, adrenoceptors. Based on this observation, we assume that $\alpha_1$-receptors that are presumably located on the primary afferent fibers are activated by phenylephrine. This process mimics the conditions in sympathetically intact animals, in which NE is released from the sympathetic efferent terminals. The results of the experiment using intra-arterial injection of an $\alpha_1$-receptor antagonist under sympathetically intact conditions were consistent with those after injection of an $\alpha_1$ receptor agonist, implying that the CAP-evoked sensitization of primary afferent nociceptors is normally dependent on the presence of postganglionic sympathetic efferents that would release NE to modulate nociceptive transmission by acting on $\alpha_1$ receptors. This peripheral modulatory mechanism may indirectly influence the induction of DRRs that participate in the pathogenesis of neurogenic inflammation. So far, a variety of observations about the subtype of $\alpha$-adrenergic receptors involved in sympathetic modulation of pathological pain transmission have been reported in clinical studies and also in experimental studies, mostly on neuropathic pain models. In contrast, our previous and present studies have been done in the CAP-induced neurogenic inflammatory pain model. Hyperalgesia induced by intradermal CAP injection is mediated by $\alpha_1$-adrenergic receptors (Kinnman and Levine 1995). Lee et al. (1999) showed that the subtype of $\alpha$-adrenergic receptor mediating the neuropathy induced mechanical allodynia and ec-topis discharges of dorsal root ganglion cells is the $\alpha_2$-adrenergic, not the $\alpha_1$-adrenergic, receptor. Their group has also shown an increased expression of the $\alpha_1$-adrenergic receptor subtype in a neuropathic pain model (Xie et al. 2001). In addition, some other data suggest that $\alpha_2$ or both $\alpha_1$ and $\alpha_2$ receptors are involved in various types of neuropathic pain models (Chen et al. 1996; Hord et al. 2001; Sato and Perl 1991; Xie et al. 1995b). One possible explanation could be that different $\alpha$-adrenergic receptor subtypes might participate in mediation of different types of neuropathic pain. Combined with our recent studies with CAP-evoked neurogenic flare (Lin et al. 2003, 2004), our data support the hypothesis that the induction and development of neurogenic inflammation in rats are mediated mainly by DRRs, which are modulated by postganglionic sympathetic efferents in the periphery by an action on $\alpha_1$-adrenoceptors.

In conclusion, DRRs conducted by C-and A$\delta$-primary afferent fibers following CAP play a major role in the induction and development of neurogenic inflammation, which are suggested to be sympathetically dependent. This sensory–sympathetic interaction seems to be mediated by an $\alpha_1$-adrenergic mechanism in the periphery. The sympathetic postganglionic terminals are essential for nociceptive signal transmission under pathological conditions, such as tissue injury. A positive feedback loop mediated by a dorsal horn circuit is activated following CAP injection to trigger DRRs, which helps induce and develop neurogenic inflammation.

**REFERENCES**


**GRANTS**

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