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Reflex Neurogenic Inflammation

I. Contribution of the Peripheral Nervous System to Spatially Remote Inflammatory Responses That Follow Injury[1]

JON D. LEVINE,*§[2] SAMUEL J. DARDICK,* ALLAN I. BASBAUM,‡ AND EBENEZER SCIPIO§

*Departments of *Medicine, ‡Anatomy, and §Stomatology, University of California, San Francisco, San Francisco, California 94143*

Abstract

Recent studies of the mechanism of neurogenic inflammation have focused on the contribution of neuropeptides released from peripheral terminals of primary afferent sensory neurons. In this study we addressed the contribution of humoral and neural factors to the hyperalgesia and swelling that are produced contralateral to an injured hindpaw, a phenomenon which we refer to as reflex neurogenic inflammation. The contralateral inflammatory response develops gradually, over a period of hours, and shows no tachyphylaxis with repeated application of the same stimulus. Denervation of either limb significantly attenuated the contralateral responses. Selective lesions of small-diameter, presumed nociceptive afferent fibers with capsaicin, or of sympathetic postganglionic efferents by immunosympathectomy, also reduced swelling and hyperalgesia of the uninjured paw. Interruption of venous circulation to the injured limb by vein ligation did not alter the response in the contralateral paw. Taken together, these data suggest that reflex neurogenic inflammation is neurally mediated, via connections across the spinal cord.

Swelling and hyperalgesia or tenderness, two characteristic signs of acute inflammation, are the result of activity in a coordinated group of physiological systems which, in response to injury, produce vasodilation, increased vascular permeability, and sensitization of nociceptive afferents. The former two underlie the swelling and the latter the hyperalgesia. Although numerous studies have addressed the mechanisms underlying sensitization of primary afferents (Moncada et al., 1978; Dubner and Bennett, 1983), few have examined the neural mechanisms underlying the other components of acute inflammation, specifically vasodilation and increased permeability. We have developed a method to reliably elicit and quantify remote inflammatory responses. Our studies were influenced by the reports of Chahl and Ladd (1976) and Denko and Petricevic (1978) that injury to one hindlimb produces swelling of the opposite limb. In this report we describe the time course of the contralateral limb swelling and hyperalgesia produced by unilateral hindlimb injury. We also provide evidence that this spread of acute inflammation involves a spinal cord-mediated connection between the injured and remote sites.

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[2] To whom correspondence should be addressed.

Materials and Methods

The experiments were performed on 250- to 300-gm male Sprague-Dawley rats (Bantin and Kingman, Fremont CA). The standard injury stimulus consisted of a subcutaneous injection of 0.15 ml of normal saline, through a 30 gauge hypodermic needle, into the footpad on the plantar surface of the midfoot. In one group of rats, capsaicin (Sigma Chemical Co., St. Louis, MO) in a vehicle of 50% by volume dimethylsulfoxide (DMSO) in normal saline was injected in place of the standard injury stimulus. The injection of either solution elicited a flexion reflex and, occasionally, a vocalization response. After injury, rats were somewhat less active; however, they ate food, moved about the cage, and interacted with other rats. They did not appear to favor the injured paw. Thus, we consider discomfort elicited by the standard injury stimulus as mild.

In a pilot study we determined that our standard injection in a naive rat did not elicit significant swelling or hyperalgesia in the contralateral paw. However, an injection into the same paw for three consecutive days produced a progressive increase in the magnitude of both the crossed hyperalgesia (Fig. 1*A*) and crossed swelling (Fig. 1*B*) responses over the 3 days. Therefore, rats were routinely "primed" with the standard injury stimulus, on three consecutive days prior to the start of experiments.

Hyperalgesia or tenderness has generally been inferred from decreased thresholds of withdrawal reflexes. In this study, we measured the threshold to withdraw from linearly increasing pressure applied to the dorsum of the foot (Randall and Selitto, 1957). The pressure required to elicit withdrawal was measured before (i.e., base line) and 1, 3, 5, and 7 hr after test injury. In a separate group of animals with no test injury, measurements were also taken at 0, 1, 3, 5, and 7 hr. Hyperalgesia was calculated as a percentage decrease in pressure required to elicit withdrawal, relative to base line. Withdrawal thresholds were based on the average of seven measurements for base line values and four for each time point thereafter. The time course of hyperalgesia was measured in both injured and uninjured paws. The Randall-Selitto (1957) test has been shown to correlate well with hyperalgesia evoked in humans, in response to intradermal injections of algesic agents (Ferreira, 1983).

In separate groups of rats we measured the time course of the remote swelling response (i.e., change in paw thickness in response to injury). Swelling was measured with a constant pressure caliper (Mitutoyo, Tokyo), positioned perpendicular to the paw, with the plantar contact of the caliper placed in the space between the footpads. This is a standard technique used by immunologists to detect intradermal cellular infiltration in studies of delayed-type hypersensitivity reactions (Schwartz et al., 1977; Bach et al., 1978; Sy et al., 1981). It is a reliable and reproducible method to detect changes in paw and ear thickness in the mouse, which are smaller than those which occurred in the present experiments. Paw thickness was measured before, and 1, 3, 5, 7, and 9 hr after injury. In a separate group of animals with no test injury, measurements were also taken at 0, 1, 3, 5, 7, and 9 hr. The swelling response was also calculated as a percentage change from base line, again from the average of seven measurements for base line values and four for each time point thereafter. To assess the accuracy of the

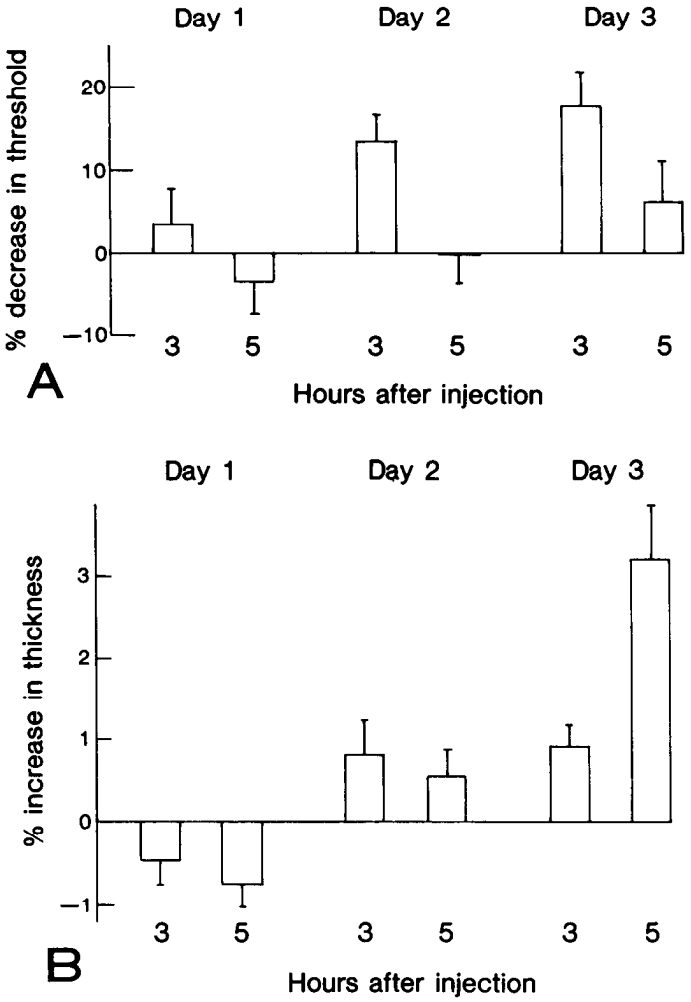

Figure 1. This figure illustrates that significant change in nociceptive threshold and paw thickness in the contralateral hindlimb are only produced after priming injury stimuli. Change, in the uninjured paw, of nociceptive threshold (*A*, $n = 6$) and paw thickness (*B*, $n = 11$) at 3 and 5 hr, respectively, after saline (0.15 ml) injection, on three consecutive days, in previously naive rats. For hyperalgesia, the peak response on day 1 differed significantly from the normal peak of 18.3 ± 1.0% in primed animals, $p < 0.001$. The peaks on days 2 and 3 did not differ significantly from this value. For swelling, both the day 1 and day 2 peaks differed significantly from the normal peak in primed animals of 3.7 ± 0.19%; for both, $p < 0.001$. The day 3 peak, however, did not differ significantly from that of the normal primed animals.

paw thickness measurements, a representative sample of 33 base line values were examined, showing an average paw thickness of 3.43 mm. The average standard error over these 33 base lines was 0.0126 mm, or 0.37% of the total paw thickness.

Groups of rats underwent a variety of peripheral nerve lesions before the effects of injury on the remote hyperalgesia and swelling responses were tested. The various nerve lesions were designed to test three major mechanisms which might underlie the contralateral responses to injury.

1. Neural mediation. First, the responses may be mediated by spinal reflexes. In this case, denervating the injured or uninjured limb would eliminate the remote response. (Hyperalgesia cannot, of course, be tested in the denervated limb.) To selectively address the possible contribution of somatic and autonomic nervous system components in these reflexes, capsaicin, a neurotoxin that is relatively selective for unmyelinated afferents (Jansco et al., 1977; Ainsworth et al., 1981), or guanethidine, which produces an immune-mediated sympathectomy (Burnstock et al., 1971; Jensen-Holm and Juul, 1971), were used.

In the capsaicin group of rats, the sciatic and femoral nerves of one hindlimb were treated 3 days before testing. Under deep anesthesia, a proximal segment of the sciatic and femoral nerves was exposed bilaterally and wrapped with a piece of cotton. On one side, the cotton was soaked with a solution of 1.5% capsaicin (Sigma) in a vehicle of 50% by volume DMSO in normal saline. In the other hindlimb, the cotton was soaked in vehicle only. The cotton was removed after 15 min and the excess fluid in the area was absorbed with a dry piece of cotton (Wall and Fitzgerald, 1981). The effectiveness of the neurotoxin was confirmed by demonstrating, in a separate group of rats, an increase in response latency to noxious heat in the paw of the capsaicin-treated hindlimb (Levine at al., 1984) 3 days after treatment with capsaicin.

Another group of rats was sympathectomized by injecting them with guanethidine (5 mg/day for 6 weeks). In the rat, this produces an immune-mediated degeneration of postganglionic sympathetic efferents, depleting norepinephrine stores from peripheral tissues and from sympathetic ganglia with no significant regeneration for at least 4 months (Burnstock et al., 1971; Jensen-Holm and Juul, 1971). We used a radioenzymatic microassay of tissue norepinephrine (Roizen et al., 1974; DaPrada and Zurcher, 1976) with a sensitivity of 5 pg and found no detectable norepinephrine in the sciatic or femoral nerves. This represented a greater than two order of magnitude decrease in norepinephrine concentration from the same nerves in control animals.

2. Humoral mediation. A second possible mechanism which might underlie contralateral responses to injury is release, at the injured site, of humoral factors which would then act via a systemic route. This could occur completely independent of the nervous system, and thus denervation should have little effect. Chahl and Ladd (1976) suggested that the changes in vascular permeability and C-fiber threshold observed in the contralateral paw following antidromic stimulation of the saphenous nerve are mediated by systemic transport of substances released from the stimulated hindlimb. We have tested this hypothesis directly in our model. A suture placed loosely around the saphenous vein of the hindlimb to be injured was tightened immediately before the injury stimulus. This occludes blood flow and should eliminate the systemic circulation of humoral factors between the two limbs (Chahl and Ladd, 1976).

3. Neurohumoral mediation. Finally, some combination of neural and humoral factors may mediate the contralateral responses. Following injury, for example, a variety of substances could be released from peripheral nerve terminals. These may circulate, via a vascular route, and interact with neural and non-neural cells at the uninjured site. Acute denervation in either limb would eliminate a spinal reflex pathway but would transiently leave peripheral nerve terminals intact. Thus, a neural source of humoral mediator (e.g., neuropeptides released from the intact terminals) may still be present. Chronic denervation, however, of either the injured site or the uninjured site should distinguish between the "pure neural" and "pure non-neural" hypotheses. Thus, in two groups of rats, a unilateral section of the sciatic nerve at the level of the sciatic notch and femoral nerve, where it joins the femoral artery in the thigh, was made under deep pentobarbital anesthesia. To ensure complete denervation, a 5-mm section of nerve was removed. One group (chronic denervation) was studied a minimum of 6 days after the nerve section, at which time the peripheral terminals of the severed nerve would have degenerated (Dubowitz and Brooke, 1973). A second group (acute denervation) was studied within 2 days of nerve section, at which time local injury might still activate the peripheral terminals, resulting in release of inflammatory and hyperalgesic mediators.

Finally, we tested the possibility that there was a self-sustaining central neural component. To test this possibility an additional group of rats received an acute nerve block immediately *following* the injury stimulus. This study tested whether maintained "injury" input to the spinal cord is necessary or whether once the relevant spinal circuits are activated they can sustain the contralateral response. The rats first received a block of the sciatic and saphenous nerves, in the injured paw, with 2% lidocaine. The nerves were then acutely sectioned distal to the pharmacological block, so as to ensure its completeness and duration. Acute nerve block, in the absence of a self-sustaining central neural component, should interrupt the developing remote response.

All values in the text and in figures are given as mean ± 1 SE. Statistical comparisons were by the two-tailed Student's *t* test, except as noted in the text.

Results

Crossed hyperalgesia response

Injection of 0.15 ml of saline into the footpad of one hindpaw of primed rats (i.e., those that had received 0.15 ml of saline on the previous 3 days) elicited hyperalgesia in both the injured and uninjured paws (Fig. 2). The time course of the hyperalgesia in the uninjured paw closely paralleled the response in the injured paw.

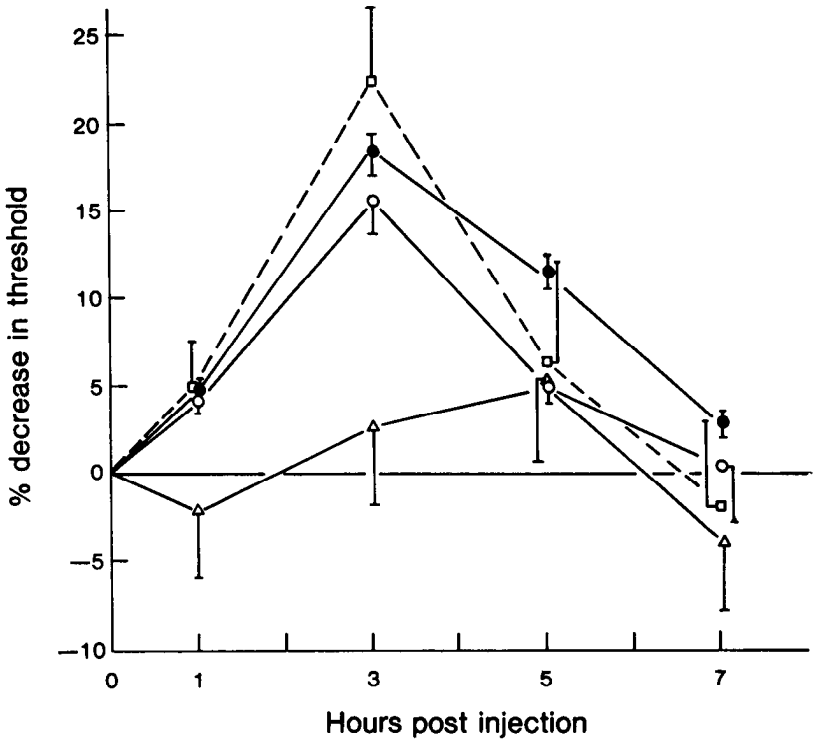

Figure 2. The time course of the change in nociceptive threshold in the uninjured paw, after needle stick (Δ, $n = 7$) and injection of 0.02 ml (○, $n = 7$) and 0.15 ml (●, $n = 79$) of saline into the footpad of the hindpaw of primed rats. The time course of the change in nociceptive threshold in the injured paw after the standard injection of 0.15 ml of saline (□, $n = 10$) is also shown for comparison. A significant positive correlation between magnitude of injury and response was shown by Spearman rank order correlation ($r = 0.344$, $p < 0.001$).

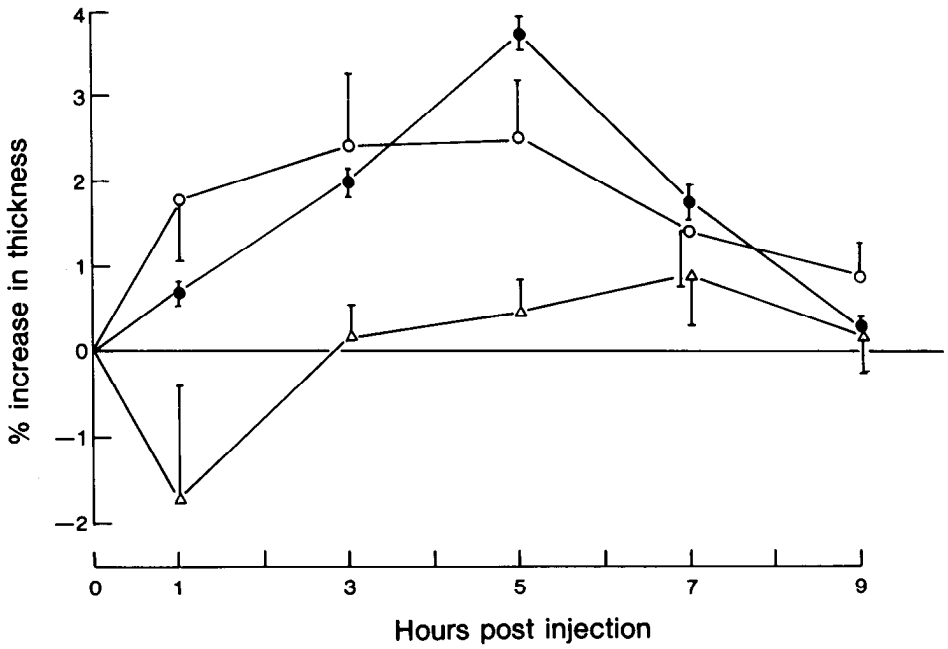

Figure 3. The time course of the change in paw thickness in the uninjured paw, after needle stick (Δ, $n = 11$) and injection of 0.02 ml (○, $n = 8$) and 0.15 ml (●, $n = 82$) of saline into the footpad of the hindpaw of primed rats. A significant positive correlation between magnitude of injury and response was shown by Spearman rank order correlation ($r = 0.484$, $p < 0.001$).

Maximum hyperalgesia (i.e., decrease in threshold) was observed at 3 hr after injury. Paw withdrawal threshold returned to base line by 7 hr. Injection of a smaller volume (0.02 ml) of saline elicited a smaller hyperalgesic response in animals primed as above with 0.15 ml of saline on the previous 3 days. The threshold in the contralateral paw dropped by 15.3%, in comparison to a decrease of 18.3% in response to the standard injury stimulus. Needle puncture alone, although mildly injurious, did not produce a significant hyperalgesia. Nor did repeated measurements in animals with no test injury. These last animals actually showed a slight and insignificant increased threshold of 2.2 ± 2.2% at the 3-hr measurement ($n = 10$). In contrast, 3 hr after unilateral paw injection of 30 μg of capsaicin (in 2 μl), a potent activator of primary afferent nociceptors (Coleridge et al., 1964), there was a 31.0 ± 5.8% decrease in withdrawal threshold of the uninjured paw ($n = 6$).

Crossed swelling response

In addition to hyperalgesia, injection of saline into a hindpaw of primed rats elicited swelling of the uninjured hindpaw. The swelling increased gradually, peaked at 5 hr, and returned to base line between 7 and 9 hr (Fig. 3). The peak swelling produced by a smaller volume of saline (0.02 ml) also occurred at 5 hr but was less than the swelling elicited by the standard injection. In primed rats, puncture of the skin by a 30 gauge needle, without saline injection, did not produce significant swelling in the contralateral paw. Neither did repeated measurement over time in animals with no test injury (0.42 ± 0.54% at the 5-hr measurement, $n = 12$). Injection of

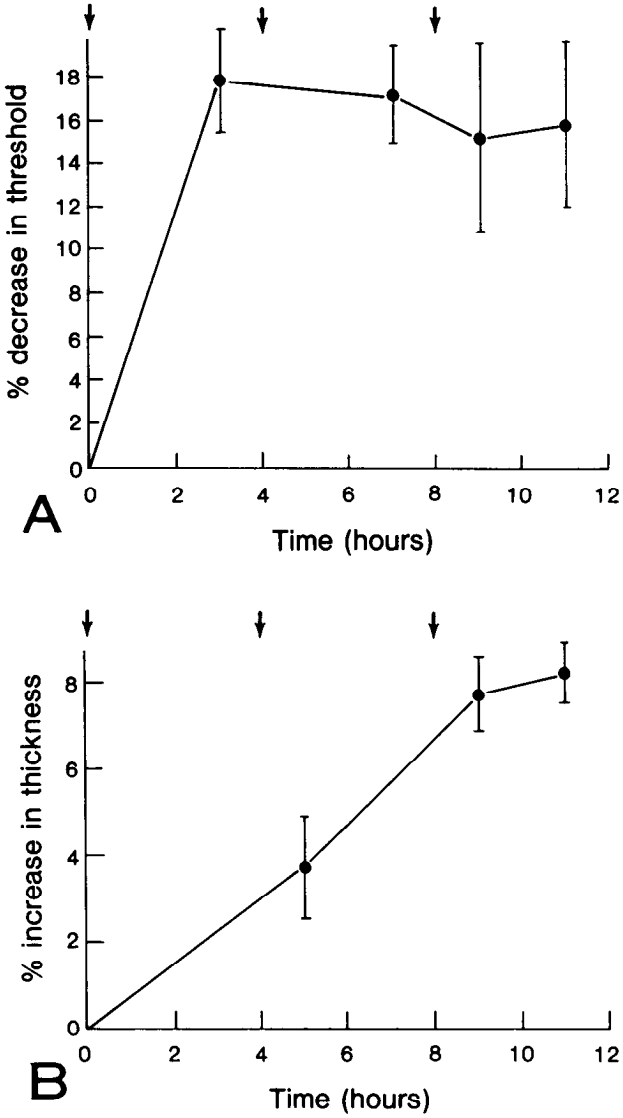

Figure 4. The time course of the decrease in nociceptive threshold (*A*) and the increase in paw thickness (*B*) of the uninjured paw after a series of three standard saline (0.15 ml) injections in primed rats. The time of the three injections (t = 0, 4, and 8 hr) is indicated by *arrows* (*A*, n = 6; *B*, n = 6).

capsaicin produced an increase in paw thickness of 6.2%. Because of the volume changes introduced by the injury stimulus itself, we did not attempt to evaluate the changes produced in the injured paw.

Repeated stimulation

To test whether repeated injury produces tachyphylaxis in the hyperalgesia or swelling responses of the uninjured paw, three injections of saline, separated by 4 hr, were administered to primed rats (Fig. 4). This injection protocol produced a more prolonged swelling and hyperalgesia in the uninjured paw than was produced in the group of primed rats that received the standard (single) injury stimulus. The differences at 9 hr were significant, both for swelling and hyperalgesia (both $p < 0.001$). In fact, both the swelling and the hyperalgesia responses, in this experiment, were still at peak levels at 11 hr. Indeed, not only was there no tachyphylaxis, but the swelling response in multiply injected animals at 11 hr was also significantly greater than the peak (3 hr) response in control animals (8.2 ± 0.70 versus 3.7 ± 0.19%; $p < 0.001$).

Peripheral nerve and vascular lesions

Neurectomy. In primed rats, combined sciatic and femoral nerve section in the limb of the paw to be injured, either 6 days (chronic denervation) or 2 days (acute denervation) before injury, significantly attenuated the development of swelling and hyperalgesia of the contralateral, uninjured paw (each $p < 0.001$) (Fig. 5). The response in the uninjured paw of acutely denervated rats was not, however, significantly different from the response in chronically denervated rats. Sham operation (i.e., anesthesia, skin incision, and nerve exposure) 6 days before injury did not alter the subsequent development of swelling in the uninjured limb.

Acute or chronic denervation of the hindlimb contralateral to the paw to be injured also significantly reduced the development of swelling in the uninjured limb (both $p < 0.001$), and these operations again did not differ significantly from each other. Not surprisingly, chronic bilateral denervation also significantly reduced the swelling in the uninjured limb ($p < 0.001$), but no more so than unilateral denervation of either limb (Fig. 5).

Selective nerve lesions. When the sciatic and femoral nerves of either hindlimb were treated with capsaicin 3 days before injury (Fig. 5), the crossed swelling and hyperalgesia responses were also significantly attenuated (*hyperalgesia:* control 18.3 ± 1.0%, capsaicin treatment on injured side 8.8 ± 4.3%, $p < 0.01$; capsaicin on uninjured side 5.9 ± 5.2%, $p < 0.005$; *swelling:* control 3.7 ± 0.19%, capsaicin on injured side 1.0 ± 0.65%, $p < 0.001$; capsaicin on uninjured side 1.2 ± 0.56%, $p < 0.001$). Treatment of rats with the vehicle for capsaicin had no effect on the development of hyperalgesia in the uninjured paw. It did, however, produce a small, although statistically significant, attenuation in the crossed swelling response (vehicle, 2.4 ± 0.71%; control, 3.7 ± 0.19%; $p < 0.05$). Interestingly, capsaicin treatment of the sciatic and femoral nerves in the uninjured hindlimb also produced a significant decrease in the peak hyperalgesic response in the paw of the *injured* hindlimb (capsaicin, 4.8 ± 5.0; control, 22.4 ± 4.6%; $p < 0.05$). However, application of capsaicin in a muscle belly did not produce significant attenuation of the hyperalgesia (capsaicin, 19.6 ± 1.2%; control, 18.3 ± 1.0%; p = not significant) or swelling (capsaicin, 3.5 ± 0.45%; control, 3.7 ± 0.19%; p = not significant) responses in the injured limb.

Immunosympathectomy with guanethidine had no significant effect on base line (i.e., pre-injury) nociceptive thresholds in either paw. It did, however, attenuate the hyperalgesia ($p < 0.001$) and swelling ($p < 0.001$) responses of the uninjured paw (Fig. 5). Hyperalgesia of the injured paw was also decreased (sympathectomy, 6.6 ± 1.2%; control, 22.4 ± 4.6%; $p < 0.005$).

Post-injury nerve block

In the group of rats that received a nerve block with lidocaine followed by neurectomy, 10 min after the second of two injury stimuli spaced 4 hr apart, the expected further development of swelling and hyperalgesia in the uninjured paw was interrupted (Fig. 6).

Venous ligation

In two groups of rats the saphenous vein was ligated just prior to an injury stimulus. This intervention did not significantly attenuate the development of swelling and hyperalgesia in the contralateral paw, in comparison to sham-operated controls.

Discussion

The present study has demonstrated that injury to one hindpaw of the rat produces characteristic signs of acute inflammation, specifically swelling and hyperalgesia, in the contralateral paw. The magnitude and duration of the remote response in the uninjured paw are similar to those in the injured paw. Both swelling and hyperalgesia can be elicited in the contralateral paw by a similar injurious stimulus and various interventions similarly affect the two components of the remote inflammatory response. The present data

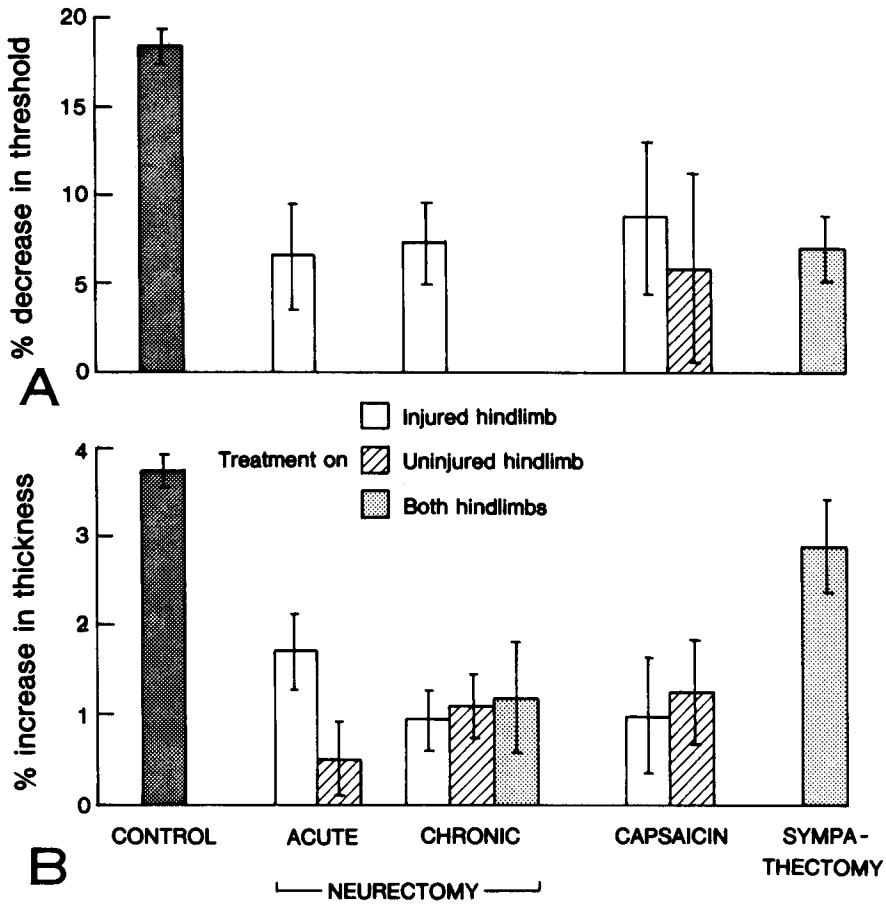

Figure 5. *A*, The effect of lesions of the peripheral nervous system on changes in nociceptive threshold in the *uninjured* paw, 3 hr after standard injury (control, $n = 79$; acute neurectomy, $n = 13$; chronic neurectomy, $n = 10$; capsaicin on injured side, $n = 8$; capsaicin on uninjured side, $n = 8$; sympathectomy, $n = 12$). *B*, The effect of lesions of the peripheral nervous system on changes in paw thickness in the *uninjured* paw, 5 hr after standard injury (control, $n = 82$; acute neurectomy on injured side, $n = 16$; acute neurectomy on uninjured side, $n = 6$; chronic neurectomy on injured side, $n = 16$; chronic neurectomy on uninjured side, $n = 15$; chronic neurectomy on both sides, $n = 18$; capsaicin treatment on injured side, $n = 8$; capsaicin treatment on uninjured side, $n = 8$; sympathectomy, $n = 15$.

provide evidence for a predominantly neural mechanism in the development of the crossed swelling and hyperalgesia responses.

Our data differ from previous studies which demonstrated a contribution of humoral mechanisms. For example, tissue damage can sensitize polymodal nociceptors that innervate neighboring (Fitzgerald, 1979) or remote (Chahl and Ladd, 1976) undamaged tissue, but intact neural connections between the injured and uninjured sites are not necessary for these effects to occur. Furthermore, the study of Chahl and Ladd (1976) demonstrated that activation of nociceptive afferents in one hindlimb of the rat increased vascular permeability in the contralateral hindlimb, even when the injured limb was acutely denervated.

The above findings implicate the "neurohumoral" mechanisms described earlier. In this study, we found that acute and chronic denervation produced comparable attenuation of swelling and hyperalgesia in the uninjured paw. Thus, it is unlikely that a "neurohumoral" mechanism contributes to the remote response to injury. In fact, in both acutely and chronically neurectomized rats there were only small, not statistically significant, contralateral responses. These observations suggest that, in our model, "pure humoral" mechanisms do not significantly contribute to the development of the contralateral swelling and hyperalgesia responses. The apparent difference in mechanism between this study and that of Chahl and Ladd (1976), in which neurogenic inflammation at spatially remote sites was produced by "antidromic" nerve stimulation, may be related to the time course of the changes studied or to the nature of the stimulus used. In the study of Chahl and Ladd (1976), the remote response did not last past 1 hr, at which time our response is not yet detectable.

Since immediate post-injury denervation of the injured hindlimb prevented the development of the contralateral swelling and hyperalgesia, it appears that a self-sustaining central neural component, activated by the injury stimulus, is not sufficient to produce the remote inflammatory response. This conclusion is also supported by the observation of a parallel time course of the hyperalgesia in the injured and uninjured paws. Thus, maintained input from the injury site is necessary to elicit a response at a remote site. This conclusion differs from that of Woolf (1983) who failed to block hyperalgesia with nerve block in the injured paw *following* injury. In that study, however, excitability testing was only performed for 10 min following induction of nerve block.

It is of particular significance that chronic denervation of *either* the injured or uninjured limb markedly attenuated the contralateral swelling and hyperalgesia responses. Local tissue injury apparently activates crossed spinal neural reflexes that release proinflammatory mediators at remote sites. That bilateral nerve section produces no greater reduction in swelling or hyperalgesia than unilateral nerve section further suggests that the innervation of the injured and uninjured limbs are part of a single circuit. The data are best explained by crossed spinal reflexes, but they do not rule out a supraspinal contribution to the reflex. They do, however, provide information about the specific peripheral neural pathways involved.

The effects of capsaicin and guanethidine indicate that both afferent (probably nociceptive) and efferent postganglionic sympathetic neurons contribute to the remote response. Capsaicin treatment of the nerves in either hindlimb attenuated the crossed responses, indicating that the afferent innervation of both hindlimbs contributes to the development of crosed responses. This presumably means that once a response in the uninjured paw is established, it will, in turn, exacerbate the development of swelling and hyperalgesia in the injured paw. The fact that the capsaicin vehicle also produces a small reduction in crossed swelling may have been due to the ability of vehicle to transiently increase the nociceptive threshold (Fitzgerald and Woolf, 1982).

Immunosympathectomy, of course, simultaneously affects both injured and uninjured limbs. Thus, we cannot determine the relative

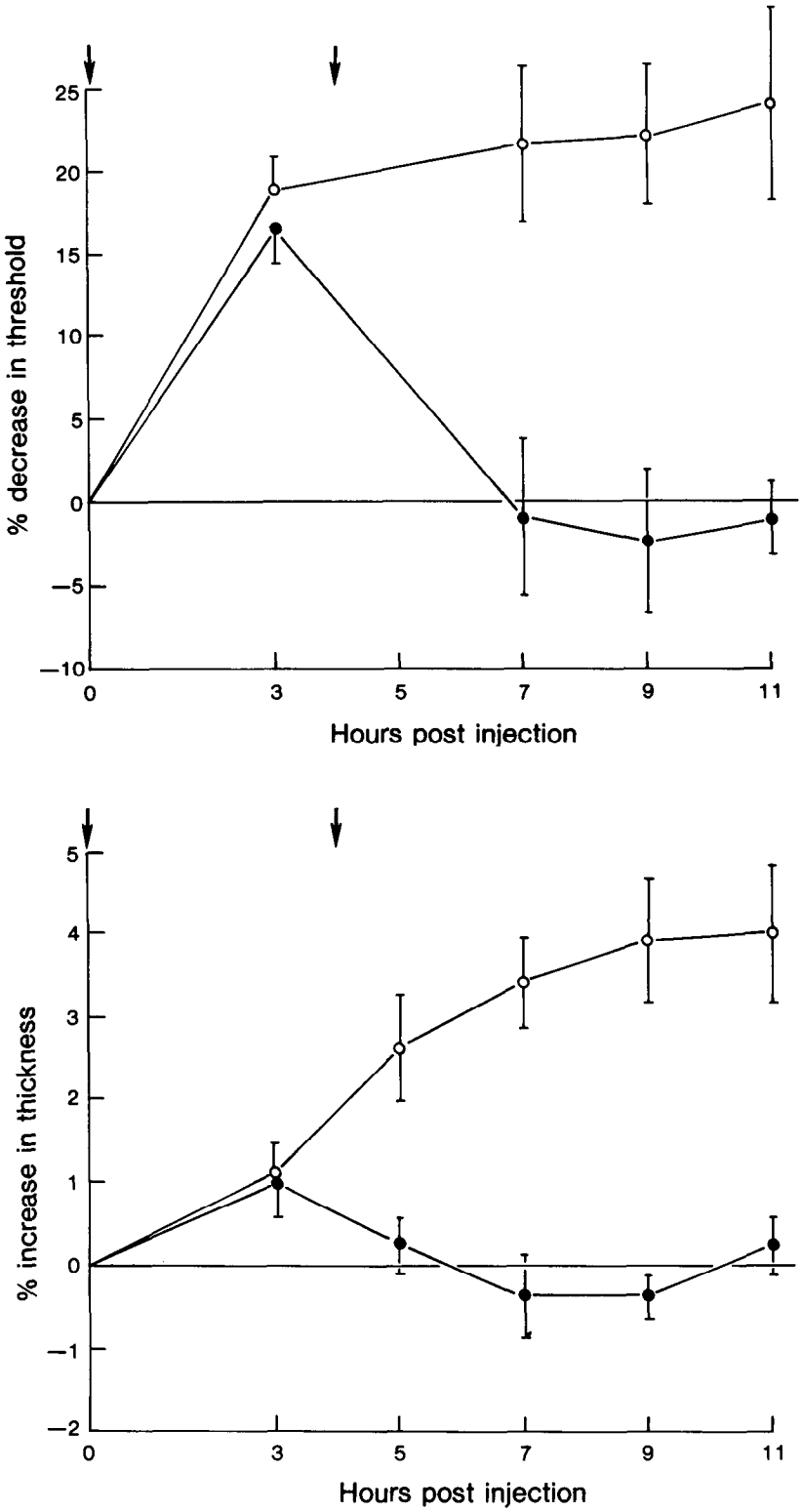

Figure 6. The time course of the change, in the uninjured paw, of nociceptive threshold (*A*) and paw thickness (*B*), in control (○, $n = 7$ and 7, respectively) and acutely neurectomized (●, $n = 9$ and 8, respectively) rats, after a series of two standard (0.15 ml) injections in the same paw of primed rats. The timing of the two injections is indicated by *arrows*. Nerve block was performed at 4 hr, just after the second injection. In both hyperalgesia and swelling the time course of the response in the acutely neurectomized groups is significantly less than that in the sham-operated control groups by a repeated measures analysis of variance ($p < 0.001$).

contribution of postganglionic sympathetic efferents in the injured and uninjured hindlimbs. However, since both sides interact to produce the maximal response, it is likely that the remote responses are secondary, in part, to sympathetic innervation of both limbs. This hypothesis is further supported by the finding that sympathectomy decreased the hyperalgesia in the injured as well as the uninjured paw.

It could be argued that the remote responses to injury, rather than resulting from topographically organized spinal connections, reflect a general increased arousal, somewhat comparable to the increased excitability of gamma efferents that are seen when a subject is aroused. If arousal were a factor, however, the first injurious stimulus would be expected to elicit the greatest remote response; habituation to subsequent stimuli would produce a diminished response. In fact, a limb must be primed by repeated injurious stimulation before a response can be elicited. In addition, there is an augmented response with repeated stimulation; tachyphylaxis was not seen.

The biological significance of the remote responses is suggested

by their magnitude, duration, and failure to develop tachyphylaxis. Both the magnitude and the duration of the hyperalgesic response in the uninjured paw were similar to those in the injured paw. This suggests that crossed swelling and hyperalgesia responses can contribute to remote inflammatory responses that, in many ways, are indistinguishable from those elicited at the site of injury. The fact that even minor injury was able to elicit remote changes suggests that a specific and physiologically significant pathway mediates these effects. As might be expected, however, more severe injury (e.g., capsaicin injection) does generate more intense and widespread physiological changes. In addition, the hyperalgesia and swelling responses in the uninjured paw did not show tachyphylaxis with repeated stimulation. Thus, repeated injury to one paw was able to produce a sustained and enhanced inflammatory response at a distant site. This type of response might allow the seeding of other cellular and humoral components of acute and chronic inflammation at widespread, and possibly somatotopically organized, sites in the body.

The results of these experiments have important implications for the practice of using one side of an experimental animal or subject as a control for manipulation on the opposite side. These results may also bear on the clinical phenomena of allochiria and allochesthesia (Noordenbos, 1959). In allochiria, a painful site that is treated by contralateral cordotomy reappears in a mirror focus on the opposite side of the body. In allochesthesia, the patient misperceives a stimulus and locates it instead at the same point on the opposite side of the body. These phenomena may also be mediated by topographically organized crossed spinal connections. Finally, the model used in this study, in which hyperalgesia is referred to a site different from the location of the injury, may provide a useful tool for the study of referred pain.

In summary, we have demonstrated that, under certain conditions, a predominantly neural basis underlies the spread of acute inflammation from a site of injury to a remote uninjured site. Both nociceptive afferent and sympathetic efferent components are involved. Since the contralateral response is "reflexively" elicited by injury, we propose that this phenomenon be referred to as reflex neurogenic inflammation. The involvement of the spinal cord in reflex neurogenic inflammation suggests that focal application of pharmacological agents to the cord could be used to modulate these effects. In a subsequent report we will describe the contribution of central neural circuits to the development of remote responses. We will also provide evidence that reflex neurogenic inflammation could contribute to the development of experimentally induced arthritis in the rat.

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