

ABSTRACT: This review addresses the issue of how axotomy of peripheral nerve fibers leads to pain and hyperalgesia. The point of axotomy (the nerve injury site), the dorsal root ganglia, and the dorsal horn of the spinal cord are candidate sites for generation of the pain signal that is likely to be critical for maintaining the neuropathic pain state. This review considers neuropathic pain from a "systems" perspective, tracing concepts of neuropathic pain from the work of Henry Head to the present. Surprisingly, the nerve injury site and the dorsal root ganglion belonging to a transected spinal nerve do not give rise to spontaneous activity in putative C-fiber nociceptors. The intact nociceptor belonging to adjacent uninjured spinal nerves, however, does acquire abnormal spontaneous activity and a chemical sensitivity to catechols. It is suggested that partially denervated tissues in the nerve, skin, and other locations may release substances that, in turn, sensitize the intact nociceptors. These abnormalities in the intact nociceptor, which arise in the context of Wallerian degeneration, probably play a role in creating or maintaining the abnormal pain state. These considerations probably also apply to the understanding of pain arising in other neuropathies. The findings relative to the "intact" nociceptor provide a rationale by which to understand how therapies distal to the nerve injury site may diminish pain.

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NERVE LESIONS AND THE GENERATION OF PAIN

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Accepted 3 May 2001

Practitioners interested in the treatment of neuropathic pain face a multitude of therapeutic choices. Drug therapies, electrical stimulation of the nervous system, nerve reconstruction operations, and nervous system lesions constitute a wide array of approaches. At the basis of these choices is the question of mechanism—what is the generator of pain and how are these generators affected with interventions that we offer? In this review a "systems" approach is taken in considering how pathology of the peripheral nerve gives rise to pain. The emphasis here is on traumatic neuropathy. Neurologists may argue that this emphasis is misplaced and that consideration of traumatic neuropathies is irrelevant to an understanding of pain from other more common neuropathies, e.g., diabetic neuropathy. This is not the case, however. Neuropathies (perhaps often) en-

tail an axotomy. Thus, the simple axotomy, surgically induced, is a logical starting point for understanding neuropathic pain.

In a little noticed study published in 1970, Kirk and Denny-Brown determined that lesions of the spinal nerve evoked hyperalgesia.³² The importance of this finding became more fully appreciated after a study by Bennett and Xie in 1988, in which it was determined that creation of a constriction lesion of the sciatic nerve led to behavioral signs of pain in rats.⁶ Seltzer et al. noted that partial ligation of the sciatic nerve induced a similar degree of hyperalgesia.⁷⁹ Kim and Chung determined that merely severing and ligating the L5 and L6 spinal nerve in rats created a similar degree of hyperalgesia (spinal nerve ligation model, similar to the Kirk and Denny-Brown model).³¹ This rediscovery by Kim and Chung that axotomy by itself was sufficient to induce hyperalgesia has proven seminal in current approaches to neuropathic pain. From where does the signal for pain arise after axotomy? Several suspects have undergone scrutiny: the nerve injury site (the neuroma), dorsal root ganglia, and the central nervous system. The Chung lesion is of particular

Abbreviations: CNS, central nervous system; DRG, dorsal root ganglion; NGF, nerve growth factor; SMP, sympathetically maintained pain

Key words: complex regional pain syndrome; neuropathic pain; nociceptors; peripheral neuropathies; sympathetic nervous system; Wallerian degeneration

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value for purposes of this review as this model allows separate elements in the nervous system to be considered to some extent separately. In this review, we consider these targets and, in particular, the point of axotomy, the dorsal root ganglion (DRG), the central nervous system (CNS), and another less scrutinized fourth target—the uninjured nociceptor that, at distal points along the nerve trunk, shares pathways with the axons that have undergone Wallerian degeneration as a result of the spinal nerve axotomy. As will be seen, this fourth target accounts for some aspects of the puzzle of neuropathic pain that heretofore have resisted understanding.

NERVE INJURY AND PAIN: A MATTER OF BALANCE?

It is immediately understandable that lesions of the nervous system create deficits. However, even early conceptions of how the nervous system operates considered the concept of balance, and led the groundwork for considering how lesions of one part of the nervous system might lead to overactive function of another. One example of this is in the writings of Hughlings Jackson, the noted English neurologist of the 19th century. Hughlings Jackson, though more preoccupied with motor function than sensory function, laid the seeds for early conceptions of neuropathic pain.⁸⁴

With his interest in seizures, Hughlings Jackson was no stranger to the concept that lesions of the nervous system could lead to “positive” phenomena, rather than simply creating passive deficits. He noted that “positive” symptoms appeared with lesions of the motor system. Reflexes and motor tone are increased after lesions of upper motor neurons. He conceived of the spinal motor system being under control of the brain, and he viewed the motor symptoms that emerge from rostral lesions as being release phenomena. Henry Head, strongly influenced by the Jackson school, noted that with neuropathic pain, as with the motor system, “positive” symptoms evolved from certain nerve diseases.²⁹ A lesion of the nervous system paradoxically led to increased pain sensibility. This appeared to follow the pattern with motor systems, and Head developed the concept that this increased pain sensibility was again a release phenomenon. He suggested that the epicritic and protopathic pathways served sensibility, where epicritic represented the sensory/discriminative pathways and protopathic represented the more primitive pain pathways. Epicritic sensibility normally governs protopathic sensibility. In the case of neuropathic pain, lesions of the epicritic system result in release of protopathic pain. Head suggested in a

sense that what was felt with a given stimulus was an outcome of the balance between the epicritic/protopathic sensibilities. A peripheral nerve lesion led to a loss of epicritic control and spinal cord mechanisms for pain took control, leading to uncontrolled pain. Epicritic sensibility came to be associated with A-fiber function, whereas protopathic sensibility came to be associated with C-fiber function.

The Head conceptualization dominated much thinking about pain for several decades, but there were many challenges. One observation was that small fibers exclusively innervated the cornea and it was hard to reconcile this with the concept of epicritic/A-fibers and protopathic/C-fibers. Noordenbos gave the Head theories a major boost in his work on the histopathology of postherpetic neuralgia.⁵⁷ He biopsied the intercostal nerves and identified what he interpreted to be a preferential loss of large fibers. As it turns out, there is no preferential loss of a fiber type and the predominance of small fibers simply reflects the pathological changes in fibers of all types. Nevertheless, this clarification came much later and the Nordenbos findings energized the Head concepts of neuropathic pain.

Though the historical roots are often not appreciated, the famous “Gate Control Theory” published in *Science* in 1965 by Melzack and Wall was really a direct and more articulate expression of Head’s ideas.⁴⁷ Melzack and Wall contended that the presence of pain depended on the balance of inputs of A- and C-fibers. Predominant inputs of A-fibers blocked pain and predominant inputs of C-fibers favored pain. Melzack and Wall argued that this “gating” occurred in the dorsal horn. Some psychophysical studies in normal human volunteers have lent direct support to this conceptualization. Except for chemically evoked sensations, cutaneous senses are served by two sensory channels: a pain channel and a nonpain channel. Each channel is served by a separate set of afferent fibers: fibers associated with the innocuous channel and the pain channel.⁹ Compression and ischemic blocks of peripheral nerves lead to blockade of neural activity first in large fibers, then in small fibers. These block techniques allow the nonpain channel to be blocked preferentially. For example, cooling sensation is served by A- δ fibers. As this A- δ fiber activity is blocked, mild cooling stimuli evoke a subtle burning pain sensation presumably served by C-fibers.^{90,99} In preliminary studies from our laboratory (Silvers and Campbell), we further determined that mechanical stimuli evoke burning sensations as tactile sensation is lost, and that warming stimuli may evoke burning sensations as warm fibers are blocked. Whether these dissociations of

the innocuous and pain channels play a role clinically in neuropathic pain remains unclear.

Despite this evidence, many of the underpinnings of the Gate Control Theory have come under challenge. After publication of the Gate Control Theory, further correlative psychophysical/neurophysiological research made it increasingly clear that nociceptors by themselves account for heat-evoked pain.³⁶ Coactivation of large fibers has little effect on normal pain sensibility.^{15,40,41} Moreover, it turns out that in neuropathic pain large fibers acquire the capacity to signal pain. The stroking-induced pain (allodynia), prominent in many patients with neuropathic pain, is served by large fibers normally concerned with tactile sensibilities. Blocking these fibers selectively, rather than making pain worse, actually relieves tactile pain (for Wall at least, not an unwelcome finding given that this argued against a strict specificity formulation in which pain signaling is relegated exclusively to the domain of nociceptors).¹³ Price et al. determined that stimulation of large-diameter afferents evoked pain in neuropathic pain conditions.⁶⁴ Perhaps the most telling argument regarding the relevance of gate control to neuropathic pain arose from the consideration that large-fiber neuropathies as a rule are not associated with pain.⁵⁴ Painful neuropathies appear typically to entail pathological abnormalities in small fibers.

LARGE-FIBER STIMULATION: INDUCTION OR PROVOCATION OF PAIN?

Neurosurgical interest in pain was strongly stimulated by the proposal of Melzack and Wall.⁴⁷ As a direct test of the Gate Control Theory, Wall and Sweet,⁹³ stimulated the infraorbital nerve in a case of neuropathic facial pain and noted relief of symptoms. Soon, neurosurgeons developed techniques to apply electrical stimulation directly to the spinal cord, and this technique endures today as a means to treat neuropathic pain.⁵⁹ Techniques to stimulate the peripheral nerve were also developed as treatments of pain.¹² The underlying strategy with both techniques is the same, and that is to induce non-painful paresthesias in the area described by the patient as being painful. The parameters used clinically for electrical stimulation activate large fibers. A paradox becomes apparent. How can stimulation of large fibers both provoke and relieve pain?

A possible explanation emerges from consideration of the parameters used for electrical stimulation. Lindblom and Meyerson noted that dorsal column stimulation normalizes the pain threshold in cases of hyperalgesia, but does not create hypalge-

sia.^{40,41} The threshold for touch is, however, elevated. In a preliminary study, we studied the effects of high- (50 Hz) and low-frequency (5 Hz) dorsal column stimulation.¹¹ The low-frequency stimulation evoked pain whereas the higher-frequency stimulation (50 Hz) relieved pain. To account for these findings, we assume first that large fibers acquire the capacity to evoke the pathological pain as discussed above. These large fibers destined for the dorsal columns likely have collateral inputs to pain signaling neurons of the dorsal horn. Branch points are known areas of vulnerable conduction safety.^{3,8,27,81,82} This vulnerability is frequency dependent. Thus, at 5 Hz, both branches may be entrained. This frequency hypothesis of dorsal column stimulation suggests that the collateral branch to dorsal horn fails to conduct at high frequencies of stimulation. Accordingly, recently developed computer models suggest that large asymmetries in the size of the daughter axons at branch points may lead to selective filtering depending on the frequency of stimulation.¹⁰⁰ This hypothesis may explain why dorsal column stimulation has little effect on normal nociception, but rather blocks the abnormal pain mediated by inputs of large fibers.^{40,41} Thus, large-fiber stimulation can both induce pain and relieve pain. This conception also is in keeping with the work in movement disorders where stimulation and lesions of identical targets provide similar therapeutic benefits.⁵

SOURCES FOR PAIN FROM NERVE INJURY

The study of neuropathic pain has been guided to some extent by studies of the primary and secondary hyperalgesia that accompanies cutaneous injury. In brief, these studies indicate that sensitized nociceptors account for primary hyperalgesia, whereas secondary hyperalgesia is mediated by central sensitization.^{67,86,89} *Sensitization* refers to the enhanced response evoked by a particular stimulus. In Cartesian terms, sensitization is a leftward shift of the stimulus-response function that relates neural activity to stimulus intensity. This matches the definition of *hyperalgesia*, which is defined as a leftward shift of the stimulus-response function that relates magnitude of pain to stimulus intensity. Peripheral sensitization refers to the augmented responsiveness of primary nociceptive afferents. *Central sensitization* represents the enhanced output of central neurons concerned with pain to inputs of tactile and nociceptive afferents. Central sensitization (particularly the tactile component, sometimes referred to as allodynia or dynamic hyperalgesia)⁶⁰ to a considerable extent is plastic, meaning that its maintenance de-

depends on the ongoing inputs of the sensitized nociceptors in the zone of primary hyperalgesia.⁸⁶ These studies of experimental hyperalgesia implicate important CNS mechanisms for pain, but also emphasize the importance of nociceptive inputs from the periphery.³⁷ From where, then, do the abnormal nociceptive inputs arise that lead to neuropathic pain (Fig. 1)?

Spontaneous Activity and Ectopic Excitability at the Point of Nerve Injury. An obvious candidate for nerve injury pain is the site of nerve injury itself (site D in Fig. 1). The injury site may contribute to pain in two ways. First, nociceptive afferents normally concerned with signaling pain may acquire spontaneous activity. Secondly, nociceptive afferents may acquire heightened sensitivity to stimuli at the point of axotomy. Devor and colleagues have noted large amounts of spontaneous activity in mixed sensory/motor nerve neuromas.^{21,22,91,98} The spontaneous activity appears to occur predominantly in large fibers in the case of mixed sensory/motor nerves, and much of this could be from muscle afferents.⁶⁶ Muscle afferents are normally spontaneously active and thus it is not clear that this spontaneous activity represents abnormal input to the spinal cord. Spontaneous activity in C-fibers belonging to cutaneous nerve neuromas is uncommon.^{7,48} Both the Jänig (Liu et al.)⁴² and the McMahon (Boucher et al.) groups⁹ identified A-fiber but no C-fiber spontaneous activity in recordings from dorsal root fibers after a spinal nerve division distal to the dorsal root

ganglion. This would argue for an important role of A-fibers in neuropathic pain or, alternatively, may argue that spontaneous activity from the nerve injury site (site D) does not play a critical role in neuropathic pain.

Spontaneous activity arising ectopically along the injured nerve can be distinguished from the related property of *ectopic excitability to natural stimuli*. The trunk of a nerve is normally mechanically insensitive. At points of nerve injury, however, mechanical stimuli evoke neural activity. Evidence suggests that mechanical-to-electrical transduction molecules are transported via fast axonal transport along mechano-sensitive afferents.^{34,35} At points of nerve injury, these molecules are expressed ectopically and confer mechanosensitivity to both A and C fibers.⁴⁹ Several studies support the concept that mechanosensitivity is prominent in neuromas.^{66,83} A neuroma located in a location such that it is subject to tethering and other mechanical stresses is commonly a source of pain. This formulation puts emphasis on neuroma location rather than merely the existence of a neuroma, and constitutes the rationale for neuroma excision operations. The operation, whereby a neuroma is said to be removed, is conceptually flawed to the extent that the neuroma reforms as long as the nerve endings are connected to the cell bodies in the dorsal root ganglion. The neuroma removal operation is in actuality a “neuroma relocation” operation. Evidence indicates that neuroma relocation does help many patients.¹⁰ Thus, ectopic mechanical excitability is one of the important mechanisms for pain after nerve injury.

An extensive literature considers the possibility that spontaneous activity in the dorsal root ganglion gives rise to neuropathic pain (sites B and C in Fig. 1). Physiological studies substantiate the concept that axotomy may induce spontaneous activity, but again this spontaneous activity occurs predominantly in A-fibers, and thus the relevance to pain is unclear.⁵¹

Central sensitization (enhanced responses to peripheral inputs in central pain signaling neurons) undoubtedly plays an important role in neuropathic pain (site A in Fig. 1). Prominent tactile pain served by low-threshold mechanoreceptors is one manifestation of central sensitization.¹³ As with hypersensitivity from cutaneous injury, there appear to be two forms of hyperalgesia. One is pain to light tactile stimuli (allodynia or dynamic hyperalgesia). This, as we noted, is due to sensitization to the inputs of low-threshold mechanoreceptors. Another form is manifest as heightened pain to punctate stimuli and has been termed punctate hyperalgesia (also static

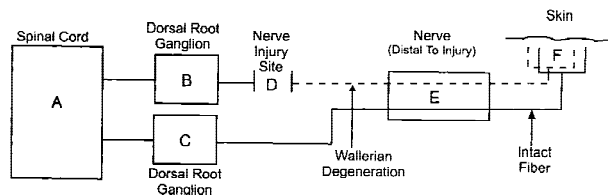


FIGURE 1. Potential sites for generation of signals relevant to pain in the spinal nerve ligation model. (A) Nerve injury induces central sensitization and other changes of pain-signaling neurons of the dorsal horn. Some of these changes could become independent of peripheral inputs. (B,C) Ectopic spontaneous activity and abnormal nerve fiber interactions could occur in the dorsal root ganglion of the injured (B) spinal nerve, and/or in the dorsal root ganglion adjacent to the injured nerve (C). (D) The nerve injury site may be a source of abnormal spontaneous activity in nociceptive afferents and may as well be associated with ectopic mechanosensitivity of nociceptive afferents. (E) The intact nociceptor is exposed to Schwann cells that are either completely or partly denervated which, in turn, may induce spontaneous activity in the intact nociceptive fibers that arise from the adjacent uninjured spinal nerve. (F) Partial denervation of the skin may induce spontaneous activity in the intact nociceptor and catechol sensitization.

hyperalgesia and high-threshold allodynia).^{33,60,65} This form of hyperalgesia is likely due to sensitization to the inputs of mechano-sensitive nociceptors.^{16,87} If neuropathic pain follows the rules of hyperalgesia with cutaneous injury,³⁷ it would be expected that touch-provoked pain would be more plastic (i.e., highly dependent on ongoing nociceptor input), whereas punctate hyperalgesia would be more resilient and less easily modified by blocking the abnormal input of nociceptive afferents. This discussion has direct clinical bearing. Should the target in treating neuropathic pain be the original peripheral lesion, or would this be futile because of enduring central changes? The answer probably varies with the particular lesion and phenotype of the individual. In general, it can be said that peripheral nerve blocks decrease pain substantially if done proximal (or even distal) to known points of injury.⁵⁸ This argues that the central mechanisms are not immutable. Then again, the relative contributions of the nerve injury site, the dorsal root ganglion, and the CNS likely vary from patient to patient. Acutely anesthetizing the peripheral nervous system appears to reduce pain substantially in most cases. The tendency for the pain to recur after procedures such as dorsal rhizotomy supports the idea that the CNS mechanisms for pain perceived in the denervated body part are tenacious.⁴³ Possibly, dorsal rhizotomy relieves pain by one mechanism and generates pain by another. My experience as a neurosurgeon is that dorsal rhizotomy does not create pain (at least on an enduring basis) in patients who do not have pain prior to the rhizotomy. For example, dorsal rhizotomy performed to treat spastic disorders appear not to be related to pain. Pain after dorsal rhizotomy (for treatment of pain) might relate to mechanisms similar to those that account for phantom pain.

Phantom pain is an example of a centralized pain state. Peripheral inputs may affect the phantom, but phantom pain survives dorsal rhizotomy, and in fact may be induced by spinal anesthesia.⁸⁵ Conceptions of phantom pain tend to center on the situation where the phantom is felt in a missing body part. In actuality, however, phantom pain is operative whenever pain is felt in a body part that has lost its innervation. That the body part is still there from the brain perspective is to some extent incidental (actually the visual image of the body part probably reinforces the phantom). Therefore, we greatly underestimate the importance of phantom pain mechanisms if we only consider cases of amputation. Knowing when these centralized phantom mechanisms assume primacy as the pain generator in a

given patient is difficult information to acquire, but obviously of crucial importance. Unfortunately, animal models to date give us little insight into understanding the basis of phantom pain.

ROLE OF THE INTACT NOCICEPTOR: A RATIONALE FOR DISTAL THERAPIES

Thus far, we have considered four sites as generators of pain after nerve injury: the point of injury, the dorsal root ganglia of the injured nerve, the adjacent uninjured nerve, and the CNS. Several compelling lines of evidence, however, point to another candidate generator, viz., the intact nociceptor (sites E and F in Fig. 1). Insight into this proposed mechanism arose from experiments in our laboratory in which we partly denervated the dorsum of the monkey foot by severing the L6 spinal nerve.² The remaining innervation to this area of skin arises from the adjacent roots. We studied the intact nociceptors that reach this partly denervated skin by the adjacent uninjured root(s) utilizing an *in vitro* skin-preparation. Two abnormalities were evident. First, 17 of 25 nociceptors displayed spontaneous activity, compared to 3 of 24 in control experiments ($P < 0.001$). Secondly, nociceptors that served denervated skin displayed sensitivity to alpha-adrenergic agonists (15 of 35), in particular the alpha-1 agonist, phenylephrine (9 of 17, $P < 0.02$), whereas adrenergic sensitivity in control experiments was infrequent (3 of 30). In these experiments, the injury is remote to the nociceptors that display these abnormalities. The abnormalities in the intact nociceptors likely result in some way from the Wallerian degeneration. Neighboring intact nociceptors are exposed to degenerating fibers. The hypothesis is that the molecules associated with this degeneration affect the intact fibers. This interaction could be in the nerve where nerve fibers from the two lumbar roots co-mingle, or possibly in the skin. In favor of the latter is that anesthetizing the cutaneous receptive field appears (at least in some cases) to abolish temporarily the spontaneous activity.⁹⁷ Moreover, the catechol sensitization is present in the cutaneous terminals.

Our work in a primate *in vitro* model evolved from seminal studies of Sato and Perl⁷⁷ who determined that nerve injury may lead to catechol sensitization of nociceptors belonging to the partly injured nerve. Similar to the Ali et al. study discussed above, Nam et al.⁵³ studied the properties of L4 afferents in rats after an L5 and L6 spinal nerve resection. About 12% of the nociceptors developed adrenergic sensitivity mediated by alpha-1 receptors. The site of sensitivity was at or near the receptive field in the skin. The finding of catechol sensitiza-

tion of intact nociceptors serves as a basis for understanding the physiological basis of sympathetically maintained pain. In this condition, patients have pain that is relieved by blocking the sympathetic supply to the skin or by systemic administration of the alpha adrenergic blocking drug, phentolamine.^{68,88}

Li and colleagues in the pain laboratories at Johns Hopkins University did a series of lesion operations in rat that offer important insights into the importance of the intact nociceptor.³⁹ The results, summarized in Figure 2, indicate, firstly, that lesion of the L5 spinal nerve distal to the DRG produces

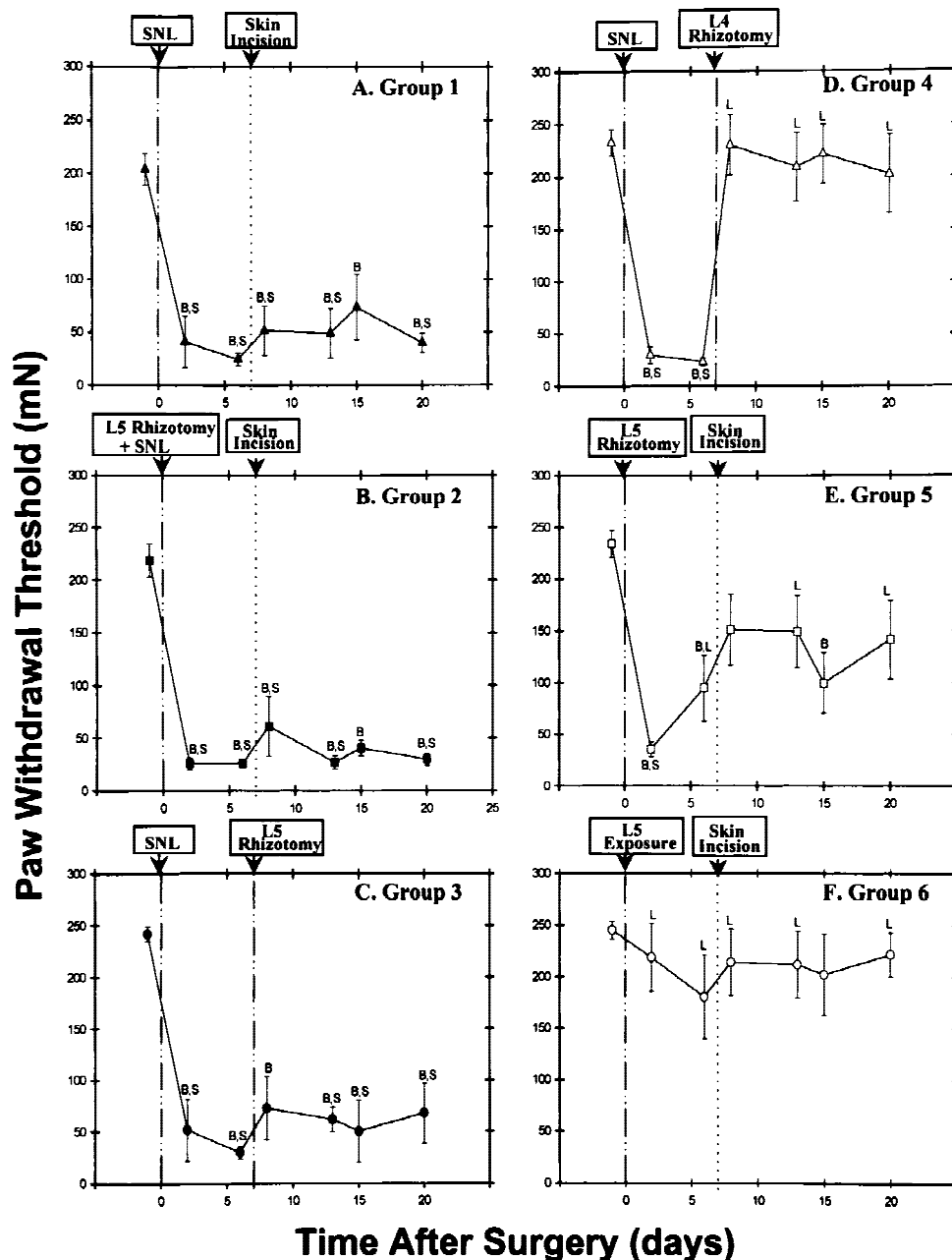


FIGURE 2. Mechanical withdrawal thresholds for stimuli applied to the lateral side of the paw ipsilateral to the side of the lesion as a function of time. (A) Spinal nerve ligation (SNL) was applied to the L5 spinal nerve distal to the dorsal root ganglion. A pronounced decrease in threshold was evident for the duration of the experiment. (B) An L5 dorsal rhizotomy done at the same time as the SNL lesion did not prevent hyperalgesia. (C) The hyperalgesia produced by the SNL was not reversed by an L5 rhizotomy on day 7. (D) L4 rhizotomy on day 7 did eliminate hyperalgesia. (E) An L5 dorsal rhizotomy led to a transient hyperalgesia. (F) A sham operation on the L5 dorsal root did not alter withdrawal thresholds. The labels B, L, and S indicate significant ($P < 0.05$) differences from baseline, SNL, and sham, respectively. (Modified from Li et al., 2000,³⁹ with permission.)

the expected lowering of the withdrawal threshold for punctate mechanical stimuli (Fig. 2A). Lesion of the L5 dorsal root prior to the distal lesion failed to prevent the hyperalgesia (Fig. 2B). Thus, the hyperalgesia from the distal L5 lesion was not due to the inputs from the L5 DRG or the L5 neuroma distal to the DRG. Similarly, severance of the L5 dorsal root days after the distal L5 spinal nerve lesion failed to attenuate hyperalgesia (Fig. 2C). An L4 rhizotomy did reverse the hyperalgesia presumably by denervating the plantar surface of the foot nearly completely (Fig. 2D). Dorsal rhizotomy of the L5 spinal nerve by itself created a short-lasting hyperalgesic state (Fig. 2E). These results emphasize that the inputs of the injured L5 root are not critical to the hyperalgesia, and offer further support for the concept that intact nociceptors serving the partially denervated tissues play a critical role in generating neuropathic pain.

SUPPORT FOR THE "INTACT NOCICEPTOR HYPOTHESIS" FROM PATIENT STUDIES

The "intact nociceptor hypothesis" provides a rationale by which to understand the otherwise perplexing efficacy of distal therapies. North and colleagues noted that sciatic nerve anesthetic blocks, well distal to the spinally located site of nerve root compression from lumbar disk herniation, often relieve radicular pain.⁵⁸ Further evidence derives from the observation that capsaicin applied to the skin alleviates pain associated with nerve injuries.^{26,73,95} Capsaicin is a selective toxin for cutaneous nociceptors when applied topically to the skin.^{56,80} Topical capsaicin could only work for nerve injury pain if the nociceptors in the skin targeted by the capsaicin are playing an active role in the ongoing pain. Other topical therapies appear to work in nerve injury pain.^{20,44}

INTACT NOCICEPTOR AND SYMPATHETICALLY MAINTAINED PAIN

One of the clearest lines of evidence indicating the importance of the intact nociceptor stems from research on sympathetically maintained pain (SMP). By definition, pain and hyperalgesia are reduced substantially or even completely in patients with SMP by blocking the function of the sympathetic ganglia that serve the painful area. The suggestion has been made that norepinephrine released by sympathetic terminals at the point of nerve injury or at the DRG may account for this effect.

Indeed, sympathetic sprouting into the DRG and basket formation around large-diameter cells has been determined to occur in rats consequent to axotomy distal to the DRG.⁴⁵ Because the sprouting is associated with large-diameter cells, the likely af-

ferents that would be activated by sympathetic stimulation would be A- β tactile (or muscle afferent) fibers. Furthermore, sympathetic stimulation may actually suppress activity in these A-fibers.⁵⁰ It would seem unlikely that sympathetically mediated activation of these tactile afferents would explain SMP, given that activation of tactile fibers in the painful skin under the influence of a sympathetic block no longer creates pain.

Though a role for sympathetic interactions in the DRG and nerve injury site cannot be dismissed, evidence favors the concept that sympathetic interactions with intact nociceptors in the skin account for SMP. As noted above, injury to one spinal nerve evokes catechol sensitization of nociceptors that belong to another nerve root, when the nerve fibers normally share the same cutaneous innervation zone. The clinical corollary of this relates to the effects of norepinephrine delivered intracutaneously. Wallin et al. determined that after a sympathetic block or surgical sympathectomy, epinephrine injected into the skin evoked pain.⁹⁴ We repeated this work using physiological doses of norepinephrine in a blinded vehicle-controlled protocol.¹ An example of the results for one subject is shown in Figure 3. Pain and hyperalgesia were first relieved by performance of a standard anesthetic block of the relevant sympathetic ganglia. Norepinephrine was then in-

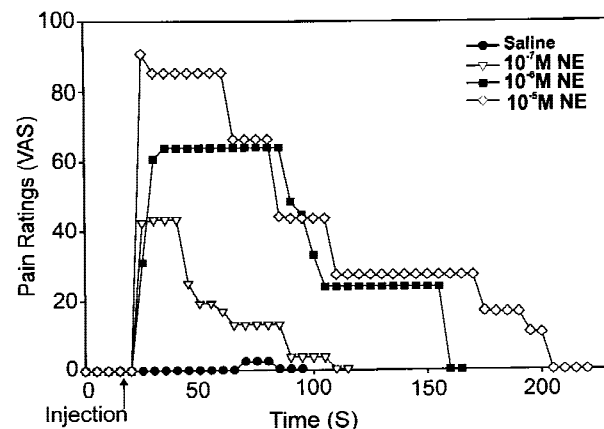


FIGURE 3. Pain induced by intradermal injection of norepinephrine in a patient with sympathetically maintained pain. A camel's hair brush was used to map the zone of tactile hyperalgesia (allodynia). The patient then underwent a sympathetic ganglion block with a 0.25% bupivacaine solution. Intradermal injections of saline and incremental concentrations of norepinephrine (NE) were made at different sites first on the unaffected extremity (doses unknown to patient). The patient rated the pain induced by the injection continuously using a computerized visual analog scale with descriptive markers. Norepinephrine evoked pain in a dose-dependent manner in the affected extremity but not the unaffected contralateral extremity. (Adapted from Ali et al., 2000,¹ with permission.)

jected into homologous areas of the contralateral uninvolved limb and the affected limb. No pain was felt from injection into the contralateral limb. The pain evoked by the norepinephrine in the affected limb varied with dose, and the effective doses were in the physiological range associated with vasoconstriction effects. In normal subjects, these doses of norepinephrine were painless. The results in this patient are representative of what was seen in a group of patients with SMP. Choi and Rowbotham have noted that patients with postherpetic neuralgia also have pain with injection of epinephrine in the skin.¹⁸

To explore further the nature of the catechol sensitivity in patients with SMP, we also applied clonidine topically.²⁰ Clonidine is an alpha-2 adrenergic agonist. In our primate *in vitro* studies, we determined that the nociceptors were sensitized to the alpha-1 adrenergic agonist, phenylephrine, and had little sensitivity to a highly specific alpha-2 agonist.² Clonidine applied topically to patients with SMP not only did not evoke pain but instead relieved hyperalgesia locally. One possible explanation for this is that clonidine activates alpha-2 receptors located on the terminals of sympathetic fibers. Activation of these "auto" receptors blocks norepinephrine release and hence would be expected to decrease activation of nociceptors.³⁰ The sensitization of nociceptors is believed to provide the tonic input needed to perpetuate cutaneous hyperalgesia.⁸⁸ Clonidine applied remote to the painful area had no effect. Thus, sympathetic interactions with intact nociceptors in the skin are probably critical in SMP.

That nociceptors acquire functional alpha-1 adrenergic receptors is supported further by work of Drummond et al.²⁴ A radioligand for alpha-1 adrenergic receptors (¹²⁵I-hydroxyphenyl-ethyl-aminomethyl-tetralone) was administered to skin biopsies from patients with reflex sympathetic dystrophy (complex regional pain syndrome). Quantitative autoradiography demonstrated higher concentrations of these receptors in the epidermal and dermal layers in the painful limb as opposed to the nonpainful limb and limb of other normal/control subjects.

A further link is provided from work of Ruocco et al.⁷⁵ Somatic innervation to the lower lip is provided through the mental nerve, whereas sympathetic innervation is provided through the superior cervical ganglion. These investigators lesioned the mental nerve and observed for changes in sympathetic innervation of the lower lip. They observed sprouting of sympathetic fibers to the upper dermis, an area normally devoid of sympathetic innervation. This

sprouting would increase the likelihood of nociceptor/sympathetic coupling.

MECHANISM OF ALTERATIONS IN THE PROPERTIES OF THE INTACT NOCICEPTOR

The evidence above strongly supports a role for the intact nociceptor in neuropathic pain. Wallerian degeneration of the axotomized fibers appears to provide the basis for this change in the behavior of the intact nociceptor. Indeed, in mice with delayed Wallerian degeneration, hyperalgesia is attenuated after nerve injury.⁷⁰ It is likely that signals from the denervated target (the skin, for example), or even "denervated" Schwann cells may express molecules that in turn alter the physiological properties of the intact nociceptors.

Some studies hint that nerve growth factor (NGF) may be one of the culprits. Metabolic neuropathies have been shown to increase levels of NGF in the skin.²³ NGF administration in humans produces hyperalgesia to heat and local tenderness and sensitizes nociceptors.^{25,62} Neutralization of endogenous NGF reduces sensitivity to heat stimuli.⁴⁶

Application of high doses of exogenous NGF has been shown to sensitize primary afferent nociceptors to heat (but not mechanical stimuli). Several investigators^{69,74} have studied the effects of systemic anti-NGF therapy and noted a partial reversal of hyperalgesia in the Chung spinal nerve ligation model. Ro et al.⁷² demonstrated attenuation of hyperalgesia by local application of anti-NGF treatment at the site of nerve injury. Whether anti-NGF at the level of the skin attenuates hyperalgesia remains unanswered. Clearly, many other cytokines, growth factors, or other molecules may play a role as well.

ARE ALL NERVE LESIONS BAD?

The mainstay of therapies for one of the best known neuropathic pain disorders is lesion-surgery. Trigeminal neuralgia has been successfully treated by neurectomy, radiofrequency thermal lesions of the Gasserian ganglion, and other lesion operations. Infrequently, these operations lead to increases in pain, but in the great majority the procedures induce at least short-term pain relief. Thus, at least in patients (as opposed to rats), lesion operations are not necessarily bad.

What Nerve Fibers Must Be Lesioned to Get Neuropathic Pain?

We can consider the liability of pain from a nerve lesion from the perspective of generalized neuropathies. Large-fiber neuropathies are not ordinarily associated with pain.⁵⁴ Neuropathies that affect small fibers do have a liability for pain. Classic

examples include diabetes, postherpetic neuropathy, and other small-fiber neuropathies. This liability is still incompletely understood, however. One puzzle is that destruction of the terminals of nociceptive fibers in the skin can be achieved by application of capsaicin and this does not cause pain (not counting the pain from the initial application).⁸⁰ This seems to suggest that small-fiber lesions may cause pain only when there is a lesion of large fibers as well. Another possibility is that neuropathic pain occurs when there is a lesion of nociceptive afferents that do not contain the VR1 receptor (the receptor activated by capsaicin).

Do Genetic Factors Affect the Liability for Neuropathic Pain? The liability for pain seems to vary substantially from one patient to the next. Different strains of animals differ substantially in proneness to hyperalgesia after nerve injury.⁵² An obvious explanation is that these differences between strains reflect the influence of genetic factors on pain-proneness. These genetic factors likely influence the liability for developing neuropathic pain in humans.

Role of Injury Location. Proneness to pain most assuredly relates to injury location as well as the type of lesion. Li et al. noted in rats that dorsal rhizotomy creates less hyperalgesia than a lesion of the same root distal to the dorsal root ganglion.³⁹ One explanation for this could be that dorsal rhizotomy does not create Wallerian degeneration in the peripheral nerve. Conventional neurosurgical wisdom is that dorsal rhizotomy (as may be done to treat spasticity, or aid in removal of a tumor) does not create pain (in patients without preexisting pain). Contrariwise, root avulsion (as with brachial plexus lesions) carries a high liability for pain. Avulsion injury is clearly more than a rhizotomy and really constitutes a lesion to the dorsal horn. We have collected preliminary data that the manner in which the nerve is lesioned also affects the magnitude of hyperalgesia in rat models of pain.⁴ Specifically, a crush lesion in rats is associated with less hyperalgesia than a ligation/cut lesion.

Location of injury along the peripheral nerve likely plays a role in neuropathic pain in other ways as well. Neuromas may be removed, but of course when done distal to the dorsal root ganglia a new neuroma forms. To excise a neuroma for purposes of ridding the patient enduringly of the neuroma is conceptually flawed. However, neuromas may be relocated and relocation of neuromas does help some patients.¹⁰ That “*neuroma relocation surgery*” works at all testifies to the importance of ectopic mechano-

sensitivity as one of the important pathophysiological mechanisms that produce pain.

Role of Restorative Surgery If a nerve is large and has important function, neuroma relocation surgery should not be the intervention of choice. Though not proven, substantial anecdotal evidence dating to the writings of Leriche indicates that nerve repair may help decrease neuropathic pain.³⁸ Thus, when possible, nerve lesions should be repaired rather than reexcised.

Role of Other Lesions Dorsal rhizotomy might be argued to be a means to abolish abnormal inputs not only from the injured nerve, but from the “intact nociceptors” that serve the denervated skin as well. Though short-term benefits are common, long-term results may be unsatisfactory.⁶¹ The reason that dorsal rhizotomy fails needs more scrutiny. Clearly, phantom pain mechanisms of central origin may ultimately be a dominant pain mechanism. Quite possibly, central neurons deprived from their normal inputs may develop enhanced spontaneous activity. These central neurons may also recruit collateral inputs from other intact afferents and in this way develop increased activity.⁹⁶ Another source of alternative inputs from the nerve injury site could be ventral root afferents.¹⁹

Selective destruction of the pain signaling peripheral neurons with molecular techniques may offer hope in some clinical situations. This needs to be pursued. Such approaches have been entertained centrally where internalization of substance P receptors allows toxins to be introduced selectively into putative dorsal horn nociceptive neurons.⁵⁵ The caveat here is that surgical destruction of the dorsal horn (the DREZ operation) appears to relieve pain in cases of pain arising from preganglionic lesions (avulsion injury of the brachial plexus),^{14,71,76} but does not relieve pain in cases where pain arises from postganglionic lesions.⁶³

A special case regarding lesion operations concerns the role of the sympathetic nervous system. As noted, lesions of the peripheral nerve induce catechol sensitization of the nociceptors that remain. Therapies directed at blocking norepinephrine activation of nociceptors will be expected to relieve pain to the extent that catechol sensitization is the culprit with regard to abnormal nociceptor activation. The lesion operation, sympathectomy, thus relieves pain in some patients with disorders such as complex regional pain syndrome.^{28,78} A major frustration relates to individual variability. Many lesion operations work, but in only a percentage of patients. More

knowledge about phenotypes may allow more precise utilization of interventions.

CONCLUSIONS

That lesions of nerve should have the capacity to create pain rather than simply inducing a deficit is at once a paradox. Early investigators struggling with this perplexing enigma suggested that warring neural circuits battled for supremacy. Under normal situations, the epicritic (later, large-fiber) system prevails. With lesions, the protopathic (small-fiber) system takes over and pain results. With time, these early views have given sway to the contemporary evidence that nociceptors signal pain in the epicritic sense. Nociceptors provide the central nervous system information regarding location, intensity, and even the quality of noxious insults. Moreover, in pathological pain states, the large-fiber systems, namely the afferents that normally provide tactile sense, actually are recruited as signalers of pain.

Creation of animal models of neuropathic pain has led to an explosion of interest and knowledge of this condition. It is now established that simply severing a peripheral nerve (axotomy) creates a hyperalgesic state. However, the liability for hyperalgesia appears to be less for preganglionic than postganglionic lesions. If this in fact is true, then *deafferentation pain* is a misnomer to the extent that deafferentation refers to a loss of inputs to the central nervous system. The spinal nerve ligation model (where a postganglionic lesion is made in a spinal nerve near the spinal foramen) has allowed independent assessments to be made of specific sites of abnormal impulse generation. Two candidates for generation of abnormal nociceptor activity are the injury site ("neuroma pain") and the DRG. Though abnormal A-fiber spontaneous activity appears to arise from the DRG of the injured nerve, there has been a failure to find spontaneous activity in C-fibers arising from either the DRG or injury site. Where abnormal nociceptive C-fiber activity has been identified, however, is from the uninjured fibers from the intact roots adjacent to the nerve injury site. The (partly) denervated tissues (e.g., skin, denervated Schwann cells) may express factors that trigger these abnormalities.

Investigators of the 19th and early 20th centuries struggled with whether pain had its own nervous system in the way vision, hearing, smell, touch, and proprioception have theirs. Now it is clear that it does. It is also clear that lesions of the somatic nervous system produce pain and hyperalgesia, viz., neuropathic pain. It remains uncertain how precisely this happens. Paradoxes remain. Lesions of nocicep-

tors may easily be accomplished with capsaicin applied topically or intradermally, but neuropathic pain seems not to follow. Large-fiber neuropathies do not lead to pain generally. What about an axotomy does cause pain, then? Of note, nerve injury at once sets to work biological processes directed at regeneration. The molecules of regeneration (and the prerequisite degeneration) may have much to do with the positive symptoms of pain that accompany nerve injury.

The symptoms of patients that present with neuropathic pain, at one time considered by many to have problems more in the realm of psychiatry than neurology, are finally becoming more understandable. From molecules to circuits, we finally are coming to understand these fascinating disorders and learning techniques to treat them. For the interventionist, a peril is faced. The very lesions intended to relieve pain carry the liability to create pain as well. Very soon perhaps we will acquire the skill to carry on these therapies more intelligently. Or even better, we may learn how to correct the neuropathy and thus directly address the underlying generators of pain.

This review was made possible by many richly stimulating interactions with Richard A. Meyer, Matthias Ringkamp, Srinivasa Raja, Allan Belzberg, and John Griffin. Sylvia Horasek assisted with the figures. This work was supported by NIH grant NS-14447.

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