Mechanisms and Management of Neuropathic Pain

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The focus of this brief review is treatments that are effective for patients with neuropathic pain. We will discuss these treatments in the context of neural mechanisms that are thought to contribute to pain following peripheral nervous system injury or dysfunction. Although some mechanisms come into play only when the nervous system is damaged others are operative under physiological conditions and contribute to pain even when there is no neural damage or dysfunction. Regardless of whether pathological or physiological, each mechanism offers a potential point for treatment. In this chapter, we will relate therapeutic interventions to particular pain mechanisms, and review the available clinical evidence for the efficacy of such treatments. Finally, current therapeutic options will be discussed in the context of a treatment trials algorithm for peripheral neuropathic pain.


MECHANISMS OF NEUROPATHIC PAIN

Table 1 lists some of the neural mechanisms thought to contribute to neuropathic pain. More than one pain generating mechanism is likely to be operative in an individual patient. It is also likely that even in patients with the same diagnosis, different pain generating mechanisms contribute to different degrees. For example, some patients with postherpetic neuralgia (PHN) have lancinating pain, minimal sensory deficit, cutaneous hyperalgesia and allodynia. Other PHN patients have constant pain, virtually complete cutaneous anesthesia and no cutaneous hypersensitivity. While many PHN patients may have a mixture of these two types of sensory abnormalities it seems likely that the pain associated with each type of abnormality has a distinct mechanism. In support of this concept, PHN associated with profound sensory loss appears to be less responsive to currently available treatments.

If there are multiple mechanisms involved in generating neuropathic pain, it is likely that a variety of pharmacologically distinct drugs, targeted upon these different mechanisms will be effective. The challenge that confronts both the clinician and the clinical scientist is to match specific treatments to different pain generating mechanisms.

| TABLE 1 |
| NEUROPATHIC PAIN |
| Potential contributing mechanisms |
| Nervi nervorum activation |
| Spontaneous ectopic activity in damaged primary afferent nociceptors (PAN) |
| Increased mechanical or thermal sensitivity of PAN |
| Adrenergic receptor mediated sensitization of PAN |
| Neurogenic inflammation |
| Loss of central inhibitory effect of myelinated primary afferents |
| Reorganization of spinal cord connectivity |
| Spontaneous activity in deafferented spinal pain transmission neurons (SPTNS) |
| Prolonged excitation of SFTNs |
Primary afferent nociceptor activity in neuropathic pain.

Any pathological process that leads to increased discharge in primary afferent nociceptors (PANs) should produce pain, provided their central connections are intact. Although loss of function is the more frequent correlate of nervous system injury or disease, there are two distinct classes of nerve pathology that could cause increased PAN activity: physiological activation of nociceptive nervi nervorum and abnormal activity in damaged primary afferent nociceptors.

Nervi nervorum.

Peripheral nerves have an extrinsically derived innervation via the neurovascular bundle and some of the innervation appears to be by unmyelinated nociceptors. Assuming that this is correct an inflammatory process involving the nerve could activate chemosensitive PANs that normally innervate the connective tissue sheath. Acute inflammatory demyelinating neuropathy (Guillain-Barre syndrome) is an example of a condition that could elicit pain through activity in the nervi nervorum. Guillain-Barre syndrome is commonly painful. The pain these patients report is usually deep and has an aching quality more typical of pains of musculoskeletal origin. Although anti-inflammatory agents would be expected to relieve the pain in Guillain-Barre Syndrome, this has not been systematically studied.

Damaged PANs: spontaneous and/or ectopic impulse generation.

A second set of mechanisms for nociceptor activation are brought into play when PAN axons in the nerve trunk are directly damaged. In patients, damage to unmyelinated and small diameter myelinated fibers is usually revealed by a sensory deficit to thermal and noxious stimuli. This may be confusing to evaluate clinically because hyperalgesia and hypoesthesia may coexist in many patients.

Although evidence of clinical damage to PANs is one of the most ubiquitous features of patients with neuropathic pain, this correlation does not prove that activity in the dysfunctional PANs generates the pain signal. The evidence that favors this idea is derived primarily from studies in a variety of animal models. These studies show that some damaged PAN axons exhibit spontaneous activity, sensitization and increased mechanical sensitivity.

Extensive but anecdotal clinical experience indicates that similar phenomena occur in patients. Thus, spontaneous pain is present in a variety of axonal polyneuropathies that affect unmyelinated axons. Although persistent pain is not the rule following nerve trauma, unpleasant mechanical hypersensitivity is very common particularly near neuromata or sites of entrapment. In two patients with postamputation phantom limb pain, Nystrom and Hagbarth demonstrated by microneurography that there was spontaneous ectopic activity in primary afferents innervating the painfully sensitive neuroma. That a pain signal can be generated in or near a neuroma is supported by Chabal's demonstration in patients that local perfusion of a neuroma with lidocaine can provide significant relief.

Direct clinical evidence that dysfunctional PANs can generate a pain signal in the absence of a noxious stimulus has been provided by Ochoa and his colleagues. They have described a small number of patients who complain of burning cutaneous pain and have a reduced threshold to heat pain. This pain appears to be C fiber mediated because it persists during compression block of myelinated axons and, importantly, spontaneous C fiber discharge has been recorded in primary afferents innervating the painful region. Interestingly, the skin of these patients is painful and hyperalgesic primarily in regions that are objectively warmer than surrounding normal skin. The authors propose that the pain and warmth in these patients are due to spontaneous activity in sensitized PANs with peripheral release of vasodilating peptides such as substance P. The fact that moderate cooling of the skin relieves the burning pain is consistent with the notion that spontaneous activity in nociceptors sensitized to thermal stimuli is crucial.
to pain generation in these patients. We have also observed that some patients with postherpetic neuralgia (PAN) have coextensive regions of spontaneous pain, mechanical hyperalgesia and objective warmth.

The idea that spontaneously active C mechanothermal nociceptors are generating a pain signal in some PHN patients is supported by several other clinical observations. First, PHN patients often volunteer that icing their skin provides relief. Second, we have recently completed a controlled clinical trial demonstrating that cutaneous application of lidocaine produces relief in PHN patients with cutaneous hyperalgesia. Finally, some PHN patients are relieved by topical application of capsaicin, a neurotoxin which selectively inactivates unmyelinated primary afferents, primarily nociceptors. These clinical observations support the idea that, in some patients with neuropathic pain, spontaneous activity arising in the peripheral terminals of dysfunctional PANs is critical for generating a pain signal.

The clinical and experimental evidence reviewed above indicates that when a peripheral nerve is damaged the PANs develop spontaneous activity and can become sensitized to both thermal and mechanical stimulation. Clinically relevant sites along the dysfunctional PAN where abnormal impulses can be generated include its axon just proximal to an interruption (usually in a neuroma) and at its terminals in the tissue that it normally innervates.

Spontaneous ectopic impulses in damaged primary afferents are sensitive to blockade by use dependent blockers of voltage sensitive sodium channels. Prominent drugs of this class are the local anesthetics and their congeners. Oral and parenteral administration of these drugs are most commonly used to treat cardiac arrhythmias. The proven efficacy of such drugs in defined patient groups such as diabetic neuropathy, traumatic neuropathy and postherpetic neuralgia is consistent with an etiological role of spontaneous ectopic activity in damaged PANs in these diseases. However, it should be pointed out that parenteral use of 'local' anesthetics appears to have broad analgesic efficacy including painful conditions unassociated with obvious PAN damage. Furthermore, there is some evidence that parenteral lidocaine can inhibit spinal cord nociceptive neurons.

Sympathetically maintained pain.

Since Leriche reported the efficacy of surgical sympathectomy in the treatment of causalgia (1939) an immense clinical and experimental literature has accumulated that supports the view that in certain patients sympathetic postganglionic neurons, through the release of noradrenaline, can activate or sensitize PANs either in peripheral tissues or at a site of damage in a peripheral nerve.

The key clinical observations are those demonstrating pain relief by a variety of sympatholytic procedures or adrenergic blocking agents. These include perivascular or paraspinal surgical sympathectomy or local anesthetic block, regional intravascular perfusion with guanethidine, bretylium or reserpine, intravenous phentolamine and oral phenoxybenzamine and prazosin.

In addition to the vast literature on sympathetic block, there are clinical observations that support the idea that sympathetically maintained pain involves a change in the stimulus response function of PANs. Thus Walker and Nulsen (1948) observed that following sympathectomy, stimulation of the decentralized sympathetic chain reproduced the pain in patients who had had causalgia prior to surgery. Such stimulation did not produce pain in patients undergoing sympathectomy for vascular insufficiency. In patients who had obtained relief of pain by sympathetic block, Wallin et al were able to reproduce the pain by injecting norepinephrine into formerly affected areas of skin. A similar result with the alpha-1 agonist phenylephrine was reported by Davis et al. Norepinephrine does not produce pain when injected into normal skin. In a related study, Chabal demonstrated that infiltration of epinephrine, but not saline, into the area around a postamputation neuroma produces...
pain with a burning and shooting quality.

These clinical studies provide critical support for the concept that in patients with sympathetically maintained pain, PANs in damaged peripheral nerve acquire increased sensitivity to \(\alpha\)-adrenergic agents. This phenomenon has been documented in animal models of SMP\textsuperscript{21,72,73,82}. It is possible that pain could arise in sympathetically denervated tissues if circulating catecholamines were in sufficient concentration to sensitize nociceptors. The clinical syndrome of post-sympathectomy neuralgia might be an example of such a phenomenon\textsuperscript{63-}. 

In summary, there is a wealth of clinical and experimental evidence to support the hypothesis that some neuropathic pains are maintained by increased activity in dysfunctional PANs. Factors such as sensitization, spontaneous ectopic impulse generation and increased alpha adrenergic sensitivity may contribute to this increased activity. Positive results in controlled clinical trials with treatment approaches such as topical application of the PAN neurotoxin capsaicin, and lidocaine, have provided important evidence supporting a contribution to pain by these mechanisms.

To the extent that PAN activity contributes to neuropathic pain it follows that neuropathic and non-neuropathic pain share an essential neural mechanism. It also leads to the prediction that some centrally acting analgesic drugs, such as opioids, should also relieve PAN mediated neuropathic pain, though perhaps to a different degree than non-neuropathic pain. This issue is controversial\textsuperscript{4,49} but we and others have demonstrated significant opioid efficacy for relief of neuropathic pain\textsuperscript{33,60,68}.

Loss of the central inhibitory action of myelinated primary afferents.

Most natural stimuli to the skin activate a broad range of primary afferents. Selective blockade of myelinated afferent axons in a peripheral nerve leads to a loss of fine spatiotemporal discrimination of skin stimuli. In addition to this loss of function under conditions of myelinated afferent axon block, activation of intact unmyelinated primary afferents even by normally innocuous cold and pressure stimuli produces a severe usually burning pain that outlasts the stimulus\textsuperscript{39}. Clearly, activation of myelinated afferents has a significant inhibitory effect on the intensity of pain produced by concurrently active PANs. Importantly, some innocuous stimuli are capable of eliciting pain mediated by unmyelinated afferent axons when myelinated afferents innervating the same cutaneous region are blocked. Observations such as these contributed to the Gate Control Hypothesis of Melzack and Wall\textsuperscript{52} which postulated that myelinated afferents activate an inhibitory interneuron in the substantia gelatinosa (the "Gate") which modulates the pain transmission neuron receiving input from unmyelinated PANs.

Although the Gate Control Hypothesis gave rise to a number of clinical studies of selective myelinated fiber activation the question of whether such a mechanism does contribute to any clinical syndrome remains open. Furthermore, despite promising anecdotal reports, analgesic efficacy has not been proven for any treatment method based on this concept. The most extensively studied methods using this approach are transcutaneous electrical nerve stimulation (TENS)\textsuperscript{88} and dorsal column or spinal stimulation\textsuperscript{47,56}. Although occasional patients report dramatic relief, the efficacy appears to wear off over time in many patients. Furthermore, because stimulation produces a characteristic sensation it has been difficult to study this type of method in a truly double blind manner\textsuperscript{48}. Patient selection may also be a significant problem. On the other hand, TENS is safe and virtually without side effects so there is little harm in using it.

Increased excitability of central pain transmission neurons.

A variety of changes are known to occur in central somatosensory neurons as a result of damage to primary afferent neurons. Some of these are listed in Table I. Because of the obvious difficulty in determining the relevance of such mechanisms to painful
human disease, this subject will not be reviewed in detail in this chapter. Two mechanisms, deafferentation hyperactivity and central 'sensitization' will, however, be considered here because there are relevant therapeutic options.

**Deafferentation hyperactivity.**

Experimental studies have shown that some deafferented dorsal horn neurons, including putative somatosensory projection neurons, develope high levels of spontaneous activity following dorsal rhizotomy. Whether this actually occurs in patients is unclear, however, one of the best examples of a human deafferentation syndrome is brachial plexus avulsion. The majority of patients with this condition have significant pain. Consistent with the idea that hyperactive dorsal horn neurons are generating a pain signal is the observation that dorsal root entry zone lesions which destroy most of the dorsal horn appear to be one of the few consistently effective treatments for this condition.

**Nociceptor induced prolonged central excitation.**

It is well established that prolonged or repetitive input from unmyelinated PANs produce progressive increases in dorsal horn neuronal and subjective responses to subsequent cutaneous stimuli. Wind-up is a well established example of this phenomenon. Wind up refers to the observation in dorsal horn nociceptive neurons that repeated identical inputs from unmyelinated PANs is associated with a progressive increase in the discharge produced by each stimulus. Wind up can be suppressed by opioids, substance P antagonists and NMDA channel blockers. A phenomenon similar to wind up has been observed in the responses of human subjects to repeated near threshold noxious thermal stimuli. The increased excitability of dorsal horn neurons by volleys in unmyelinated PANs may represent a prolonged depolarization due to both peptides and Calcium entry via the NMDA channel. There is some evidence that nitric oxide also contributes to this prolonged increase in excitability.

Although this phenomenon is probably a normal consequence of any prolonged noxious input it could play a major role in the maintenance of neuropathic pain, particularly if there is a persistent peripheral source of input via unmyelinated PANs. As discussed earlier in this chapter there is reason to believe that this is indeed the case for many patients with neuropathic pain. If substance P and excitatory amino acids acting at the NMDA receptor contribute significantly to neuropathic pain, antagonists for these actions could represent a significant advance for the management of neuropathic pains.

One area of active clinical investigation is the study of drugs acting at the NMDA channel (see above). Ketamine is of particular interest because it has an NMDA channel blocking effect, is currently in clinical use and has been shown to have analgesic actions. At the present time the issue of the analgesic efficacy of NMDA blockers for neuropathic pain is under active investigation.

**CURRENT TREATMENT OF NEUROPATHIC PAIN**

The evidence reviewed above clearly demonstrates that neuropathic pain is not a unitary phenomenon. Just as there are multiple etiologies for neural injury, there are multiple pain generating mechanisms. Each different mechanism provides a potential opportunity for a pain relieving intervention by the clinician. The current armamentarium for the treatment of neuropathic pain includes a variety of procedures and drugs, some with established efficacy and others whose efficacy is unsupported by empirical proof. Each of these therapies targets a particular pain generating or pain modulating mechanism. Unfortunately, it is usually not possible to determine with certainty the pain generating mechanism in a particular patient. Clearly, the current challenge for the clinician is to provide help for patients in the face of diagnostic uncertainty and a limited range of proven therapies.

Our current approach is the algorithm outlined in the figure. This flow diagram is meant as a general guide for a treatment oriented clinical evaluation of
neuropathic pain. It is not necessary to use this approach in patients who have a clear cut diagnosis for which well-accepted and effective treatments are available. For example, an elderly otherwise healthy and neurologically intact patient with shooting pains in the lower trigeminal divisions may be presumed to have trigeminal neuralgia and should be treated immediately with Carbamazepine. A patient with hypoth- enar pain, progressive loss of sensory and motor function in the ulnar distribution and conduction slowing of the ulnar nerve at the elbow should be considered for early decompressive surgery. On the other hand, if the clinical features do not suggest a diagnosis that has an established effective treatment, this algorithm can provide a useful framework for reducing the time and degree of suffering. The goal is to achieve optimal therapy in the minimum time.

Phase I: local treatments.

In the initial phase of evaluation the emphasis should be on uncovering pain generating factors that are potentially reversible or can be effectively managed with local therapies. The goal of this approach is to avoid, where possible, committing the patient to a longterm course of systemic drugs, all of which have significant and/or occasionally dangerous side-effects.

In patients with extremity pain associated with swelling, temperature change and cutaneous hypersensitivity the diagnosis of sympathetically maintained pain should be considered and rapidly assessed with a diagnostic sympathetic block. A positive response calls for a program of physical therapy, repeated blocks and possibly oral sympatholytic drugs. Surgical approaches to peripheral nerve pain such as neurolysis, decompression, transposition or neurontomy should be considered in patients with traumatic or entrapment neuropathies that are exacerbated by movement. TENS is most effective for traumatic and compressive mononeuropathies when the stimulating electrodes can be placed on a relatively normal stretch of nerve that is proximal to the site of injury. However, because it is harmless, a short trial of TENS is warranted in any patient.

Patients with significant cutaneous hypersensitivity, especially with thermal hyperalgesia and warm skin are the most likely to benefit from topical therapy. Capsaicin preparations are occasionally of benefit if the patients can put up with the burning sensations that are common early in treatment. Clinical trials suggest that some patients with postherpetic neuralgia, diabetic neuropathy and postmastectomy pain achieve benefit with capsaicin, especially the 0.075% preparation. Topical preparations of aspirin and NSAIDs and others containing lidocaine and prilocaine/lidocaine are currently commercially available.

Phase II: Oral Medications.

Although some patients achieve satisfactory relief with local therapies, most are left with significant residual pain. Our next step is to initiate therapy with a tricyclic antidepressant. Tricyclics have been clearly established as effective for the two most common forms of neuropathic pain, diabetic neuropathy and post herpetic neuralgia. A variety of other pain syndromes also respond. Our own experience is that, in addition to those conditions, many patients with chronic pain due to traumatic mononeuropathies have a good response to tricyclics. Amitriptyline, desipramine and imipramine are the most extensively studied of the antidepressant drugs. Unfortunately, these drugs have a variety of pharmacologic actions (blockade of 5HT and norepinephrine uptake, antagonism of histamine, alpha adrenergic and muscarinic cholinergic receptors). Their mechanism of analgesic action is uncertain. There is some evidence that antidepressants which are relatively selective for the blockade of 5HT reuptake are ineffective for the treatment of chronic neuropathic pain.

Because of the broad range of side effects, tricyclic antidepressants are often unpleasant for patients and are associated with sedation, orthostatic hypotension,
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Cardiac conduction block, urinary retention and memory disturbance. Patient compliance is a significant problem. Warning the patients about the side effects and initiating therapy with a very low dose is essential.

If, following dose optimization with tricyclics, patients continue to experience significant pain we proceed to a lidocaine infusion. Intravenous lidocaine provides significant relief for postherpetic neuralgia and other neuropathic pains. With a positive response to the lidocaine infusion we proceed to a therapeutic trial of Mexiletine. We will push the dose of oral mexiletine up to 1200 mg/day, provided plasma levels are within the therapeutic range. Gastrointestinal side effects are common but can be handled with symptomatic treatment in most patients. It is often the case that the relief obtained with mexiletine is disappointing despite a dramatic response to lidocaine. In these patients we may add an anticonvulsant such as carbamazepine or switch to an alternative antiarrhythmic such as tocainide.

A significant number of patients continue to have pain despite fully exploiting the approach outlined above. We offer these patients the option of long term opioid therapy. There is no question that some patients with neuropathic pain obtain significant relief with opioids. This is not surprising considering the likelihood that for many patients with neuropathic pains there are shared neural mechanisms with non-neuropathic pains (see above). It must be admitted that the long term efficacy of opioids in neuropathic pain has not been tested rigorously in a prospective clinical trial.

**SUMMARY AND CONCLUSION**

This is an exciting time for those of us who manage patients with neuropathic pain. There has been steady progress in our understanding of mechanism of pain generation and in the availability of good quality clinical trials that establish efficacy for certain drugs. It is clear that a large number of patients with neuropathic pain have hyperactive, dysfunctional PANS and there is clinical evidence that therapies expected to reduce such activity (PAN neurotoxins and both systemic and topical local anesthetics) effectively reduce neuropathic pain. The role of more traditional analgesic therapies such as opioids, tricyclics, anticonvulsants and sympatholysis are becoming more clearly defined. Finally, new therapies, rationally targeted upon recently discovered mechanisms (e.g. NMDA channel activation, spinal neurokinin release) are on the horizon.

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