Pain

Neuropathic pain: aetiology, symptoms, mechanisms, and management

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We highlight current theories about peripheral neuropathic pain and show that progress in management is contingent on targeting treatment not at the aetiological factors or the symptoms but at the mechanisms that operate to produce the symptoms. This approach will require substantial progress in our understanding of the pathophysiology of neuropathic pain, the development of accurate diagnostic tools to discover what mechanisms contribute to the pain syndrome in an individual, and effective treatments aimed specifically at the mechanisms.

Neuropathic pain is a pathological pain

The capacity to experience pain has a protective role: it warns us of imminent or actual tissue damage and elicits coordinated reflex and behavioural responses to keep such damage to a minimum. If tissue damage is unavoidable, a set of excitability changes in the peripheral and central nervous system establish a profound but reversible pain hypersensitivity in the inflamed and surrounding tissue. This process assists wound repair because any contact with the damaged part is avoided until healing has occurred. By contrast, persistent pain syndromes offer no biological advantage and cause suffering and distress. Such maladaptive pain typically results from damage to the nervous system—the peripheral nerve, the dorsal root ganglion or dorsal root, or the central nervous system—and is known as neuropathic pain. Such syndromes comprise a complex combination of negative symptoms or sensory deficits, such as partial or complete loss of sensation, and positive symptoms that include dysaethesia, paraesthesia, and pain.

Apart from trigeminal neuralgia, which responds well to carbamazepine,[1] pharmacotherapy for neuropathic pain has been disappointing. Patients with neuropathic pain do not respond to non-steroidal anti-inflammatory drugs and resistance or insensitivity to opiates is common. Patients are usually treated empirically with tricyclic or serotonin and norepinephrine uptake inhibitors, antidepressants, and anticonvulsants that all have limited efficacy and undesirable side-effects.[2] Neurosurgical lesions have a negligible role and functional neurosurgery, including dorsal column or brain stimulation, is controversial, although transcutaneous nerve stimulation may provide some relief. Local anaesthetic blocks targeted at trigger points, peripheral nerves, plexi, dorsal roots, and the sympathetic nervous system have useful but short-lived effects; longer lasting blocks by phenol injection or cryotherapy risk irreversible functional impairment and have not been tested in placebo-controlled trials. Chronic epidural administration of drugs such as clonidine, steroids, opioids, or midazolam is invasive, has side-effects, and the efficacy of these drugs has not been adequately assessed.

There is no treatment to prevent the development of neuropathic pain,[3] nor to adequately, predictably, and specifically control established neuropathic pain.[2,4] The aim of treatment, therefore, is often just to help the patient cope by means of psychological or occupational therapy, rather than to eliminate the pain. Thus, there is an unmet clinical need and a challenge to develop more effective therapy can be achieved only if the relation between the aetiology, mechanisms, and symptoms of neuropathic pain are understood.

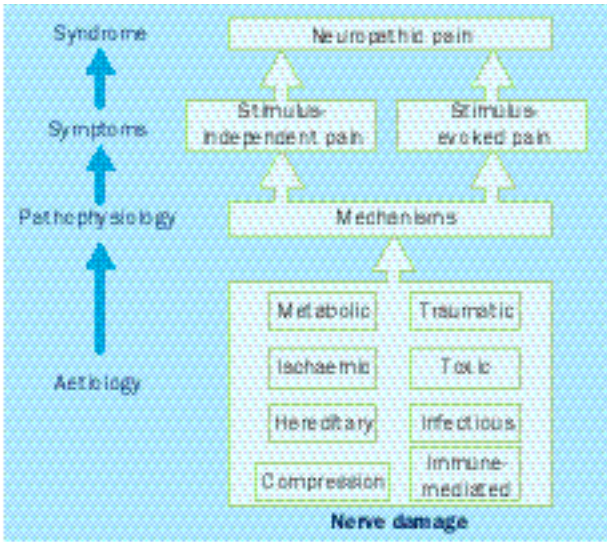

Figure 1: **Aetiology, mechanisms, and symptoms**

Aetiology of neuropathic pain

Neuropathic pain is currently classified on the basis of the aetiology of the insult to the nervous system or the anatomical distribution of the pain. Although this classification has some use for the differential diagnosis of the neuropathy, and for disease-modifying treatment if available, it offers no framework for clinical management of the pain. The relation between aetiology, mechanisms, and symptoms in this condition is complex (figure 1). The pain that manifests in diverse diseases may operate through common mechanisms. No pain mechanism is an inevitable consequence of a particular disease process; only a few patients are affected and there are no predictors to indicate which patient will develop neuropathic pain. One mechanism could be responsible for many different symptoms. Furthermore, the same symptom in two patients may be caused by different mechanisms. Finally, more than one mechanism can operate in a single patient, and these mechanisms may change with time. Thus, in patients with neuropathic pain it is impossible to predict

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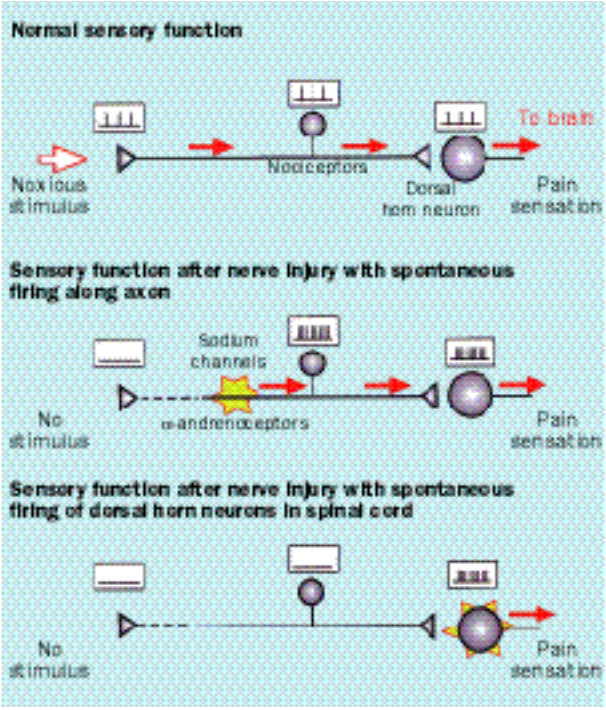

Figure 2: **Stimulus-independent pain**

the mechanisms responsible for their pain on the basis of only the aetiology of the neuropathy or on the distribution and nature of the symptoms. Without identification of the mechanisms, the optimum treatment strategy for the patient's pain cannot be selected. A further confounding issue is that the extent to which common pain syndromes such as low back or myofascial pain have a neuropathic component is not known, because of the absence of specific diagnostic tools. This review only looks at peripheral neuropathic pain. The pain that results from spinal cord, brain stem, or thalamic/cortical damage is less common and may have different mechanisms.

Why does nerve injury cause pain?

Pain is normally elicited only when intense or damaging noxious stimuli activate high-threshold nociceptor primary sensory neurons. Peripheral neuropathic pain manifests as spontaneous pain (stimulus-independent pain) or pain hypersensitivity elicited by a stimulus after damage to or alterations in sensory neurons (stimulus-evoked pain). Normal neuronal function is contingent on the neuron itself, its supporting glial cells, and the environment with which it interacts. For example, the chemicals that surround the peripheral terminals of nociceptors in the skin determine baseline sensitivity and activation threshold; inflammatory mediators and cytokines can sensitise nociceptor terminals such that they begin to respond to normally innocuous thermal and mechanical stimuli. Inflammation within the nerve or ganglion may also alter neurons by introducing new chemical messengers that alter the function, chemistry, or even survival of cells. Loss of cells or axons reduces sensibility and induces changes in the surrounding neurons that survive. Indeed, loss of sensory axons within the epidermis of patients with postherpetic neuralgia has been positively correlated with sensory deficits[5] and pain.[6]

Constitutive availability of growth factors in normal skin is needed to maintain neuronal phenotype. Nerve growth factor is retrogradely transported from innervation targets to sensory neuron cell bodies where it regulates concentrations of neuropeptide transmitter.[7] Traumatic injury to axons or axonal transport blockade from the use of cytostatic drugs (eg, vincrisitine or taxol) will initiate profound phenotypic changes through the disruption of the constant communication that a cell body maintains with its target. The local axon environment is also a key determinant of sensory neuron phenotype. Schwann cells not only insulate axons, but also control sensory neuron function,[8] for example, through sodium-channel expression and distribution along the axon.[9,10] Schwann cell dedifferentiation initiated by nerve injury causes a switch away from the production of myelin to the synthesis of growth factors, which have profound effects on neighbouring intact and injured neurons.

Many examples of activity-dependent gene expression have been described within the nervous system, and insults that cause changes in activity or sensory input to the spinal cord are likely to have long-term effects on neuronal phenotype and function. Normal sensory function is the product of an actively maintained equilibrium between neurons and their environment. Any disruption of this equilibrium that results from changes in sensitivity, excitability, transmission, growth status, and survival can initiate profound changes in sensory function, which explains why diverse diseases can manifest as pain.

A genetic component probably contributes to the diverse phenotype of individuals with apparently similar lesions, and would explain, for example, varied susceptibility to developing postherpetic neuralgia after an attack of shingles. Experimental models show enormous strain differences in pain behaviour and analgesic sensitivity,[11] and is an area ripe for further genomic research (eg, quantitative trait locus analysis). Ophoff and colleagues[12] discovered that a familial migraine syndrome was a channelopathy with a mutation in a calcium channel and similar changes may underlie some neuropathic pains.

Symptoms of neuropathic pain

Many patients with neuropathic pain exhibit persistent or paroxysmal pain that is independent of a stimulus. This stimulus-independent pain can be shooting, lancinating, or burning and may depend on activity in the sympathetic nervous system. Spontaneous activity in nociceptor C fibres is thought to be responsible for persistent burning pain and the sensitisation of dorsal horn neurons. Similarly, spontaneous activity in large myelinated A fibres (which normally signal innocuous sensations) is related to stimulus-independent paraesthesias and, after central sensitisation, to dysaesthesias and pain. Stimulus-evoked pain is a common component of peripheral nerve injury or damage and has two key features: hyperalgesia and allodynia. Hyperalgesia is an increased pain response to a suprathreshold noxious stimulus and is the result of abnormal processing of nociceptor input. Allodynia is the sensation of pain elicited by a non-noxious stimulus and can be produced in two ways: by the action of low threshold myelinated Aβ fibres on an altered central nervous system; and by a reduction in the threshold of nociceptor terminals in the periphery. Because allodynia as a clinical diagnosis does not implicate a particular mechanism, it may be more useful to subclassify it under the umbrella of hyperalgesia, so that the diagnosis of symptoms can be more suitably aligned with mechanisms.

Stimulus-evoked hyperalgesias are commonly classified into subgroups on the basis of modality—ie, mechanical,

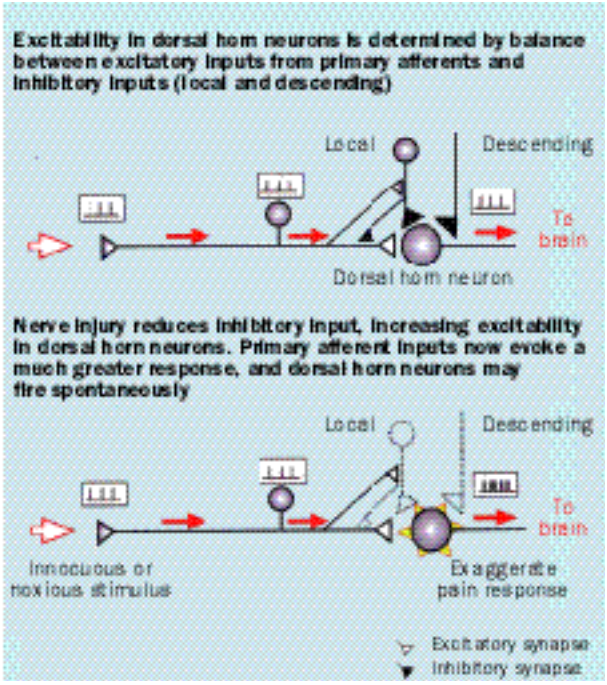

Figure 3: **Disinhibition in which nerve injury reduces inhibition in dorsal horn through various mechanisms**

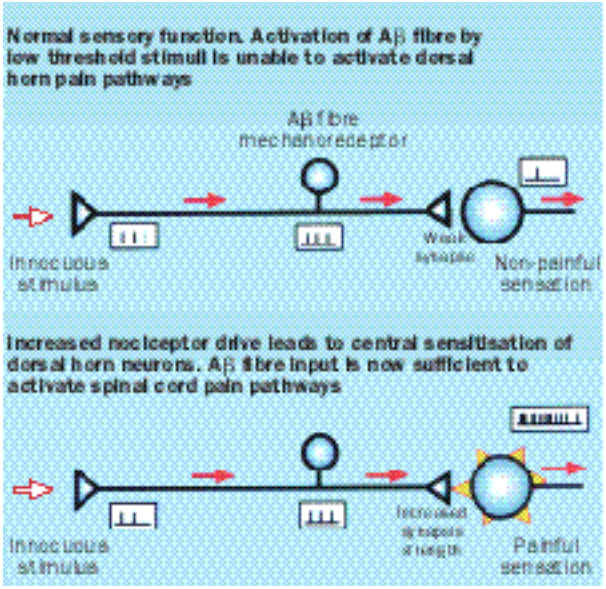

Figure 4: **Brush-evoked mechanical hyperplasia and central sensitisation**

Central sensitisation as a result of increased nociceptor drive or disinhibition after nerve injury leads to exaggerated dorsal horn response to Aβ-fibre input and tactile hyperalgesia.

thermal, or chemical. Mechanical hyperalgesias are further classified as brush-evoked (dynamic), pressure-evoked (static), and punctate hyperalgesias. Abnormal sensitivity is not confined to the periphery. The neuroma, a swelling at the proximal end of the injured nerve which contains regenerative axon sprouts, commonly exhibits exquisite mechanical sensitivity because of altered membrane properties of both C and A fibre axons.

Mechanisms of peripheral neuropathic pain

Stimulus-independent pain

Two types of sodium channel are found in sensory neurons; the first type are sensitive to tetrodotoxin, a potent puffer-fish toxin, and the second type are insensitive to tetrodotoxin. The channels that are sensitive to tetrodotoxin are responsible for the initiation of the action potential and exist in all sensory neurons. By contrast, channels that are insensitive to tetrodotoxin are found only on nociceptor sensory neurons, have much slower activation and inactivation kinetics than the tetrodotoxin-sensitive channels, and are implicated in pathological pain states.[13] After nerve injury, both types of sodium channels begin to accumulate in the axon at the neuroma site and along the length of the axon[14] and result in foci of hyperexcitability and ectopic action potential discharge in the axon and cell body of injured sensory neurons (figure 2). Ochoa and colleagues[15] reported spontaneous firing of C fibre nociceptors and low threshold Aβ fibre mechanoreceptors after nerve injury in human beings. After nerve insult, injured and uninjured sensory afferents may display ectopic discharge properties with the tetrodotoxin-insensitive sodium channels particularly implicated in the latter.[13] Unfortunately, the available sodium-channel blockers are not selective so they act on neural and cardiovascular sodium ion channels and produce central-nervous-system and cardiovascular-system side-effects. Nevertheless, such drugs are the mainstay of much treatment of neuropathic pain, including local anaesthetics, antiarrhythmic and antiepileptic agents, and tricyclic antidepressants.

In a few patients stimulus-independent pain is sympathetically maintained. After partial nerve injury, injured and uninjured axons begin to express α-adreno-receptors, which renders them sensitive to circulating catecholamines and noradrenaline released from postganglionic sympathetic terminals (figure 2). Nerve injury also induces the sprouting of sympathetic axons into the dorsal root ganglion where they form baskets around the cell bodies of sensory neurons[16] and may constitute a mechanism in which sympathetic activity initiates activity in sensory fibres. Sympathetically maintained pain theoretically requires specific treatment, such as sympathetic blocks, guanethidine, or α1 antagonists that would not be appropriate for patients with sympathetically independent pain, although Kingery's meta-analysis[2] shows poor outcome with sympatholytic approaches.

Not all stimulus-independent pain is mediated by spontaneous activity in primary sensory neurons. Neurons in the dorsal horn of the spinal cord receive input from primary afferents. The firing of dorsal horn projection neurons, which process and transfer information about peripheral stimuli to the brain, is determined not only by the excitatory input they receive, but also by inhibitory inputs that can be segmental (restricted to the spinal cord) or descend from the brain. Thus, increased inhibition will reduce activity in dorsal horn neurons and act as a spinal "gate". This process is the basis of transcutaneous electrical nerve stimulation, which activate segmental inhibitory pathways, or brain stimulators, which activate descending inhibitory pathways. Peripheral nerve injury may reduce the amount of inhibitory control—ie, disinhibition—over dorsal horn neurons through various mechanisms (figure 3). GABA, an inhibitory transmitter in the dorsal horn, is reduced, and GABA receptors and opioid receptors, which exist presynaptically on primary sensory neurons and postsynaptically on dorsal horn neurons, are downregulated. The expression of cholycystokinin, an endogenous inhibitor of opiate

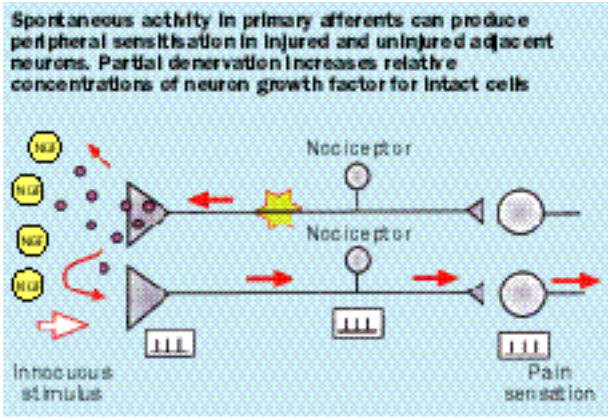

Figure 5: **Mechanical and thermal hyperplasia**
Innocuous stimuli cause pain if peripheral terminals are sensitised such that they have a much lower activation threshold. This sensitisation can result from antidromic activation, neurogenic inflammation, and increased sensory neuron exposure to molecules such as nerve growth factor (NGF).

receptors, is upregulated in injured sensory neurons. Furthermore, interneurons in lamina II, many of which are inhibitory,[17] are thought to die after peripheral nerve injury, possibly through an excitotoxic mechanism.[18] The disinhibition that occurs as a result of these processes increases the likelihood that a dorsal horn neuron will fire spontaneously or in an exaggerated way in response to primary afferent input, and would be sensitive to agents that increase inhibition and use-dependent sodium-channel blockers. An attempt to mimic the action of GABA lead to the development of the antiepileptic gabapentin, which reduces neuropathic pain,[19] but does not act on GABA receptors or any currently known target. Nevertheless, augmenting central inhibition can be a useful therapeutic approach with opiates, GABA-enhancing drugs, or drugs such as clonidine that mimic descending inhibition.

Stimulus-evoked pain

Mechanical hyperalgesias are one of the most common manifestations of neuropathy. Brush-evoked (dynamic) hyperalgesia is the consequence of an increased central response to Aβ fibre input. Continual input to the dorsal horn as a result of spontaneous firing in C fibre sensory neurons causes sensitisation of dorsal horn neurons, which increases their excitability such that they respond to normal inputs in an exaggerated and extended way. Thus, stimuli that would normally be innocuous are now painful.

The main neurotransmitter in primary afferents is the excitatory aminoacid glutamate. Activation of nociceptors causes the release of glutamate from central terminals that acts on the ionotropic glutamate receptor amino-3-hydroxy-5-methylisoxazole-4-proprionic acid postsynaptically to cause a rapid depolarisation in dorsal horn neurons and, if threshold is reached, action potential discharge. Another ionotropic glutamate receptor, N-methyl-D-aspartate (NMDA), is closed at resting membrane potentials, because a magnesium ion blocks the channel pore so that when glutamate binds to the receptor it does not activate the cell. However, depolarisation causes this channel to open. Neuropeptides such as substance P, colocalised in nociceptor central terminals with glutamate, are also released and act on neurokinin 1 receptors, extend depolarisation, and increase intracellular concentrations of calcium. This process activates protein kinase C which phosphorylates the NMDA receptor at serine and

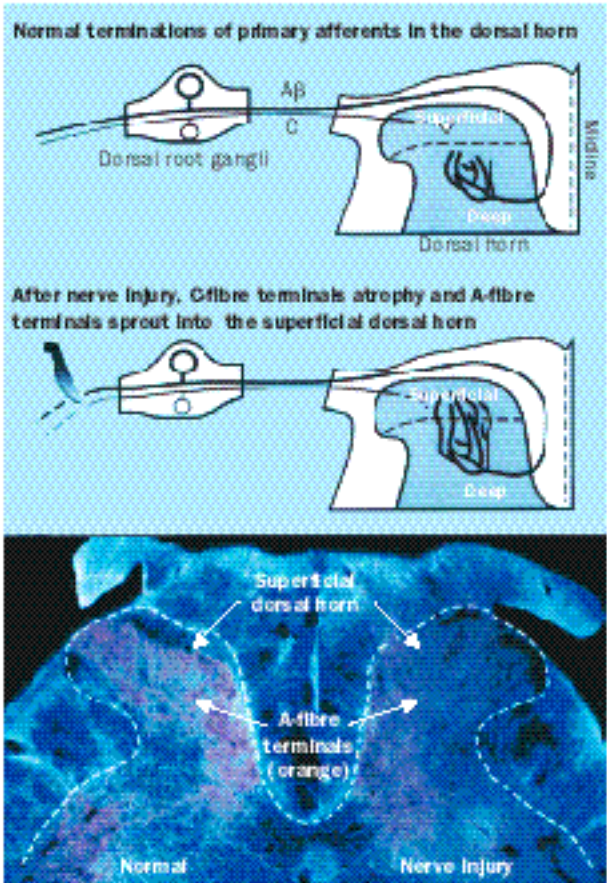

Figure 6: **Sprouting of A fibres**

threonine residues,[20] removes the magnesium block, and thereby increases excitability. Phosphorylation of the NMDA receptor at tyrosine residues by tyrosine kinases also increases excitability by increasing the probability of an open channel. Thus, nociceptive input to the dorsal horn increases the excitability of neuronal membranes—the phenomenon of central sensitisation—which changes the way the neurons respond to subsequent inputs.[21]

Central sensitisation can manifest in three ways: enlargement of the area in the periphery where a stimulus will activate neurons; increased response to a supra-threshold input; and previously subthreshold inputs reach threshold and initiate action potential discharge. These changes manifest as hypersensitivity to pain that spreads from the site of injury and includes tactile Aβ-fibre-mediated hyperalgesia (figure 4).[22,23] Spread of pain beyond the territory of an affected nerve is a common feature, once thought to indicate hysteria but now recognised as the result of central sensitisation. The role that central sensitisation and the NMDA receptor have in pathological pain is highlighted by studies that show blocking of central sensitisation with NMDA antagonists abolishes pain hypersensitivity in patients with neuropathic pain.[24] There is much evidence to support the role of central sensitisation in neuropathic pain. Stimulus-response latencies in psychophysical studies on brush-evoked hyperalgesia indicate activity along fast conducting myelinated axons. Electrical stimulation of A fibres elicits painful dysaesthesias in these patients, and selective Aβ-fibre conduction block with ischaemia or pressure abolishes the allodynic features while leaving thermal and high threshold mechanical modalities intact.[25] Finally, disruption of constant activity in nociceptors by local anaesthetic

Drug treatment of neuropathic pain and new agents under development

Mechanism	Symptom	Target	Drug
Sodium-channel accumulation, redistribution, altered expression	Spontaneous pain, paraesthesia, neuroma sign	Sodium channels sensitive to tetrodotoxin Sodium channels resistant to tetrodotoxin	Sodium-channel blockers Antiepileptic agents (carbamazipine lamotrigine) Antiarrhythmic agents (mexilitine tricyclic antidepressants) Blockers with greater analgesic than anticonvulsant index* Ion-channel selective blockers†
Central sensitisation	Tactile (dynamic) hyperalgesia Cold hyperalgesia Pin-prick hyperalgesia	NMDA-R Neurokinin 1-R Neuronal nitric oxide synthase Protein kinase γ	NMDA antagonists Ketamine, dextramethorphan, amantidine Glycine site antagonists* Subunit specific antagonists† Neurokinin-1-R antagonists* Neuronal nitric oxide synthase, protein kinase C inhibitors
Peripheral sensitisation	Pressure (static) hyperalgesia Thermal hyperalgesia Spontaneous pain Neurogenic inflammation	Vanilloid receptor-1-desensitisation Neurokinin 1 Sodium channels resistant to tetrodotoxin Nerve growth factor	Capsaicin Neurokinin-1-R antagonists* Blockers of sodium channels resistant to tetrodotoxin† Nerve growth factors
α-receptor expression Sympathetic sprouting	Spontaneous pain	α-receptor antagonists Nerve growth factor/trKA	Phentolamine Guanethidine Nerve growth factor antagonists†
Increased transmision Reduced inhibition	Spontaneous pain Hyperalgesia	N-type calcium channels Receptors (MOR, α_2, GABA, neurokinin 1 adenosine, $P2X_3$, kainate, mGluR, CCK, nAChR)	Conotoxin Opiates Gabapentin Clonidine Tricyclic antidepressants SNRIs

*In clinical development. †In preclinical development.

blockers or sympathetic ganglion blockade can abolish mechanical allodynia without blocking activity in large myelinated fibres. This effect indicates that A-fibre-mediated mechanical allodynia as a result of central sensitisation in some patients requires some continual input to maintain the central hyperexcitability.[22,23,26] Cold allodynia and mechanical hyperalgesia to punctate stimuli also are the result of central sensitisation, although in the later case, the symptom is not thought to rely on continual input to the dorsal horn. Jensen[27] suggested a similar mechanism for hyperpathia, in which sensory thresholds are increased yet a suprathreshold stimulus suddenly elicits an explosive response.

Some patients exhibit a brush-evoked allodynia without any signs of persistent or spontaneous pain. Although low-level continual input may occur below the threshold of conscious detection, it is more likely that these patients have an A-fibre-mediated pain mechanism that does not require constant nociceptor drive. These mechanisms include: disinhibition as shown (figure 3), A fibre sprouting in the spinal cord (figure 5), and A fibre phenotypic switching after peripheral nerve injury. A fibre central terminals occur in all laminae of the dorsal horn, other than lamina II in the superficial dorsal horn which receives nociceptor C-fibre innervation exclusively (figure 5). Peripheral nerve injury, however, induces sprouting of A fibre central terminals into lamina II.[28] This sprouting is probably dependent on injury to the peripheral axons of C fibres.[29] Thus, intrathecally supplied neurotrophic factors, which may act as a C fibre "therapy", can prevent A fibre sprouting.[30] The functional importance of A fibre sprouting is that if lamina II, which normally receives only nociceptor information, begins to receive information about non-noxious stimuli, this information may be misinterpreted by the nervous system as noxious—an anatomical substrate for mechanical allodynia.[31] This rewiring of synaptic connections could explain why tactile allodynia occurs in patients with postherpetic neuralgia who have absent nociceptor innervation of the skin.[32]

The nociceptors substance P and calcitonin-gene-related peptide are normally expressed by nociceptor primary afferent C fibres and Aδ fibres, and are strongly implicated in sensory transmission between nociceptors, and the central nervous system, and the generation of central sensitisation. After peripheral nervy injury, the expression of these neuropeptides by these cells is downregulated. However, large myelinated Aβ fibres begin to express these neuropeptides—a phenotypic switch.[33] Thus, low threshold stimuli, activating Aβ fibres, may cause release of substance P in the dorsal horn and thereby generate a state of central hyperexcitability that is normally produced only by nociceptor drive.

The perception of pain in response to innocuous thermal stimuli in a small group of patients with spontaneously firing intact nociceptors has been reported and attributed to a reduction in the activation threshold of nociceptor peripheral terminals—peripheral sensitisation. Action potentials can travel in both directions in sensory axons and ectopic discharge will result in invasion by antidromic action potentials of the peripheral terminal where they elicit the release of neuropeptides, such as substance P and calcitonin-gene-related peptide (figure 6). Release of these substances may lead to the sensitisation of peripheral sensory terminals of injured and uninjured fibres.

A change in the function, chemistry, and structure of neurons (neural plasticity) clearly underlies the production of the altered sensitivity characteristic of neuropathic pain. These changes have been most extensively investigated in sensory and spinal cord neurons, but similar changes occur in the brain, particularly in the cortex and can be measured

experimentally and by functional magnetic resonance imaging or positron-emission tomography. Dramatic alterations in cortical spatial maps can be detected after nerve injury that may contribute to phantom pains.[34]

Mechanisms as the target of management

The relation between the mechanisms responsible for the symptoms of neuropathic pain, the molecular targets that underlie these mechanisms, current drug therapy of neuropathic pain, and the new agents under development are shown in the panel. Knowledge about the mechanisms that produce neuropathic pain has advanced through laboratory investigation and quantitative sensory testing of symptoms in patients, the latter shows whether the pain is mediated centrally or peripherally and which fibre types and modalities are involved. A symptom-based analysis of neuropathic pain is important for assessments of disease progression and treatment outcome. However, as a tool to define treatment strategy, symptoms alone are not useful because they are not equivalent to mechanisms.

Sensitive and specific diagnostic tools are needed to reveal the particular pathological processes that are responsible for pain in an individual. Accurate diagnosis of mechanisms will be of use only if the mechanisms can be adequately targeted with specific therapy. Sodium channels that are insensitive to tetrodotoxin, for example, offer a new target for treatment because their sensory neuron specificity would avoid the side-effects of other membrane stabilisers, such as tricyclic antidepressants, sodium-channel blockers, and anticonvulsants. Such new treatments will require carefully controlled clinical trials, the cohorts of which should be selected not by aetiology, which has no relation to treatment outcome,[2] but according to closely related symptoms, such as stimulus-independent pain or brush-evoked pain, to maximise the chance of discovering mechanism-specific treatments.

Only when we have the tools to identify the mechanism responsible for the pain in a particular individual, and then the capacity to reverse the mechanisms, will the management of neuropathic pain really advance. The onus on the clinician will then be to use the history, examination, investigation, and diagnostic tools as a way to identify the mechanisms that operate in their patients and use this information to select appropriate treatment.

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