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Applied physiology: neuropathic pain

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KEY LEARNING POINTS

- Much information about neuropathic pain models is gleaned from studies in animal models.
- Damage to peripheral nerves causes phenotypic and excitability changes.
- Inflammatory mediators can produce excitation of neurons in the peripheral nervous system (PNS) and central nervous system (CNS).
- Nerve injury can lead to cell death and anatomical reorganization.
- A loss of inhibitory mechanisms and increase in excitatory mechanisms are associated with increased activity in the spinal cord in neuropathic pain.
- Microglia are activated in neuropathic pain and release pronociceptive substances which can activate neurons in the spinal cord.
- Supraspinal sites have increased excitatory influences on spinal nociceptive processing following nerve injury.

INTRODUCTION

Neuropathic pain is a form of chronic pain defined as "Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[1] The spectrum of neuropathic pain is associated with a variety of disease states (**Table 1.1**),[2,3] but it is important to recognize that neuropathic pain is a relatively frequent, but unusual and by no means inevitable, consequence of those disorders.

Various patterns of neuropathic pain are recognized and it may be spontaneous in nature (continuous or paroxysmal) or evoked by sensory stimuli. These patterns may coexist in the same patient and are not necessarily unique to any disease entity. Neuropathic pain is also usually associated with various phenomena associated with disturbances in sensory function and it is possible to broadly classify neuropathic pain patients on the basis of their sensory phenotype, for example in postherpetic neuralgia.[4] Therefore, pain may exist in the context of sensory loss (anesthesia dolorosa) or more unusually in the presence of hypersensory phenomena (e.g. allodynia (**Figure 1.1**), hyperalgesia (**Figure 1.1**), and hyperpathia). Occasionally, a mixed picture of disordered sensory function may be evident depending on which areas are tested.

While the biological advantage to the organism of nociceptive pain is readily identifiable, it is less easy to do so for neuropathic pain and it is probable that, in broad terms, neuropathic pain is a result of a pathological process representing a disordered regenerative response to neuronal damage. For example, in patients with the hyper-sensory subtype of neuropathic pain, the mechanistic implication of allodynia is that elements of the sensory nervous system which normally signal innocuous

Table 1.1 A classification of the more frequent disorders associated with neuropathic pain, with examples.

Cause of neuropathy	Examples
Trauma	Phantom limb
	Spinal cord injury
	Surgical
	Peripheral nerve injury
Infection/inflammation	Postherpetic neuralgia
	HIV
Cancer	Invasion/compression of neural structures by tumor
Drugs	Vinca alkaloids
	Taxols
	Ethanol
	Antiretroviral drugs
Ischemic injury	Poststroke pain
	Metabolic neuropathies, i.e. diabetic neuropathy
Compression	Trigeminal neuralgia
	Sciatica
Demyelination	Multiple sclerosis
	Charcot–Marie–Tooth

sensation have begun to encode painful stimuli, while in hyperalgesia the structures which normally subserve nociception have become hyperexcitable.

Before exploring what is known about the pathophysiology of neuropathic pain, three major caveats as to the nature of the existing literature need to be stated. First, the overwhelming bulk of the literature related to neuropathic pain mechanisms has emerged from rodent studies in which the major outcome measure is hypersensitivity of spinal withdrawal reflexes evoked by sensory stimuli. Thus, in this chapter, it will actually only be possible to discuss the putative mechanisms of evoked hypersensitivity, a relatively minor component of the spectrum of clinical neuropathic pain. Second, since it is also not currently possible to directly measure pain in experimental animals, the putative pain mechanisms which are to be discussed can only be interpreted in the context of responses to nerve injury which are possibly, but not certainly, related to pain. Third, the vast majority of research into neuropathic pain mechanisms has concentrated on changes in the peripheral nerve or spinal cord following peripheral nerve injury. Although knowledge is accumulating regarding alterations in the brain following peripheral nerve injury, much less is known about the significance of these changes. Therefore, this chapter will focus mainly on peripheral and spinal mechanisms of neuropathic pain.

ANIMAL MODELS OF NEUROPATHIC PAIN

Unravelling the mechanisms involved in neuropathic pain requires the use of laboratory animal models that replicate as far as possible, with the above caveats, the different pathophysiological changes present in patients. For reasons of reproducibility and simplicity, most studies of neuropathic pain are based upon animal models of traumatic nerve injury, usually in the rat sciatic nerve (**Figure 1.2**).

Rodent models of neuropathy

The most commonly used nerve injury models are: the chronic constriction injury (CCI) of sciatic nerve,[7] the partial sciatic nerve ligation (PNL) model,[8] the spinal nerve ligation (SNL)/transection model (**Figure 1.2**),[9] and the spared nerve injury (SNI) model.[6] All models are associated with the development of hypersensitivity to thermal (heat and cold), and mechanical stimuli which are used experimentally as correlates of hyperalgesia and allodynia symptoms in neuropathic pain patients.[10] However, the relevance of these measures to the human condition is questionable.

The CCI model consists of the loose ligation of the sciatic nerve with chromic gut sutures. An inflammatory reaction develops and consequentially damage to most A-fibers and some C-fibers. It is likely that there is a significant inflammatory component in the development

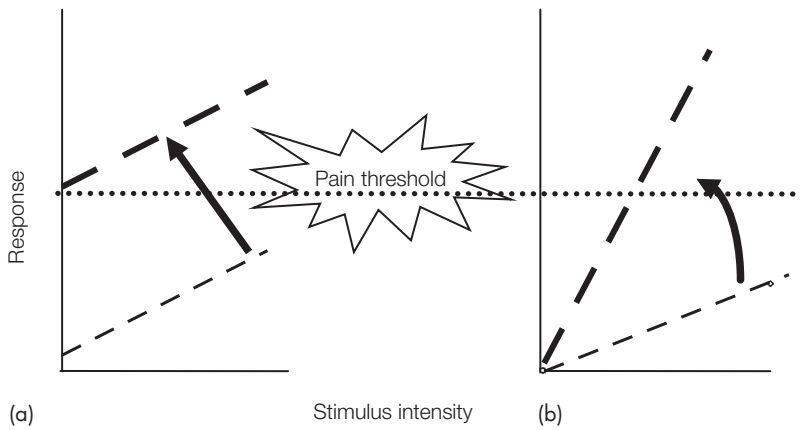

Figure 1.1 Graphical representation of (a) allodynia, a painful response to a normally innocuous stimuli and (b) hyperalgesia, an increased response to a normally painful stimulus. Stimulus intensity versus response relationship for noxious and innocuous stimuli. © The Board of Management and Trustees of the British Journal of Anaesthesia. Adapted from Bridges *et al.*, 2001[5] by permission of Oxford University Press/ British Journal of Anaesthesia.

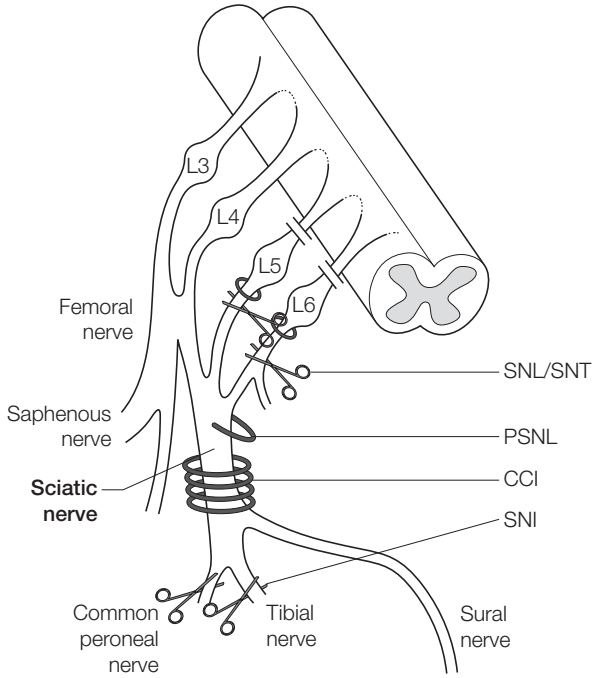

Figure 1.2 Rodent models of nerve injury. Many rodent models are based upon injury to the peripheral, usually sciatic, nerve. Schematic drawing of partial sciatic nerve injury (PSNL), chronic constriction injury (CCI), spared nerve injury (SNI), and spinal nerve ligation or transection (SNL/SNT) of the L5 and L6 spinal nerves. Adapted from Decosterd and Woolf, 2000[6] by permission of the International Association for the Study of Pain.

of the painful neuropathy.[11] In the PNL model, a tight ligation is created around 33–50 percent of the sciatic nerve, leaving the rest of the nerve "uninjured."[8] The SNL model traditionally consists of injury to the L5 and L6 spinal nerves, which contribute to the sciatic nerve.[9] However, a transection of the L5 spinal nerve alone results in comparative symptoms and hence some experimenters now use this as a modified SNL model.[5] This model is favorable to mixed injury models as it allows the examination of cellular responses of injured afferents (with cells in the L5/L6 dorsal root ganglia (DRG)) versus uninjured afferents (in the L4 DRG), and their relative importance in neuropathic pain.[12] The spared nerve injury model involves tight ligation and lesion of the tibial and common peroneal nerves.[6] This model allows testing of distinct regions of the hindpaw which are either innervated by injured or uninjured neurons, as well as separating degenerating neurons from uninjured neurons to a greater level.

Although commonly used and reproducible, there are shortcomings of these animal models which need to be considered. First, while neuropathic pain can be a devastating consequence of nerve injury in humans, the majority do not develop neuropathic pain following nerve injuries,[3] whereas most animals do develop reflex hypersensitivity in response to the above injuries. Therefore, the aforementioned animal models do not precisely mirror the "normal" human response to nerve injury. Second, for good ethical reasons, most animal models of neuropathic pain study the animals for a period of weeks, whereas the clinical course of neuropathic pain presenting to a pain relief clinic is often measured in years. Finally, as with all animal models, it is difficult to know what is actually perceived by the animal. To date, the behavioral manifestation of pain in rodent models of neuropathic pain has relied largely on measuring alterations in cutaneous sensory thresholds via measurement of reflex withdrawal thresholds to stimuli, such as punctuate mechanical (such as von Frey filaments),[13] which are not without their shortcomings, heat (such as the infrared heating device[14]) or cooling (such as the application of acetone) stimuli. Whilst these hypersensory phenomena do occur in a subset of humans with neuropathic pain, they are more usually observed in response to mechanical rather than thermal stimuli. (It must be noted that because the terms hyperalgesia and allodynia are defined in terms of pain, and we cannot yet measure pain in rodents, the use of these terms in the context of animal studies is inappropriate. We will therefore use the term "hypersensitivity" in the context of animal studies.)

Therefore, there is a need for the development of more clinically relevant animal models of neuropathic pain, as well as more complex behavioral tests designed to measure a spontaneous ongoing pain phenotype, and pain comorbidity.

Recent developments in rodent models of neuropathy

In recent years, scientists have worked to rectify the limitations of animal models, including development of models that more closely represent individual disease states. For example, as a model of peripheral diabetic neuropathy, a single injection of streptozotocin induces diabetes in the rat and is associated with the development of reflex hypersensitivity.[15] To model trigeminal neuralgia, chronic constriction injury of the infraorbital branch of the trigeminal nerve has been described.[16] In order to reproduce some features of postherpetic neuralgia, varicella zoster virus-infected fibroblasts are injected into the hindpaw and retrogradely transported to the cell bodies of sensory neurons in the DRG.[17, 18, 19] Similarly, the mechanisms by which the HIV virus could directly interact with the nervous system to produce peripheral neuropathic pain are being investigated by studying the effects of the HIV-envelope protein, glycoprotein 120 (gp120) *in vivo*.[20, 21, 22] Gp120 is thought to be key to the production of neurological disorders associated with HIV infection via the activation of the chemokine receptors CXCR4 and CCR5 expressed by neurons and glial cells.[23] Finally, drug-induced neuropathies are becoming more prevalent clinically with painful peripheral neuropathy presenting as an

unfortunate side effect of treatment with chemotherapeutics, including taxols and vinca alkaloids, or with antiretroviral agents which form part of the highly active antiretroviral therapy (HAART) for the treatment of HIV disease. Rats treated systemically with such drugs develop signs of a neuropathic phenotype and are therefore important, clinically relevant models that are currently being investigated for the understanding of underlying mechanisms.[22, 24, 25, 26, 27] The aforementioned models are important as they model some aspects of the diseases most frequently associated with neuropathic pain.

The majority of neuropathic pain models were originally described in rats, but more recently have adapted to the mouse. The translation of these models from rat to mouse is important as novel transgenic tools, useful for the study of neuropathic pain, are further developed.

Behavioral tests of pain phenotype

In addition to new models, work is being conducted to improve the range of behavioral tests employed *in vivo* (**Figure 1.3**). For example, spontaneous exploratory activity assessed in the open field paradigm is classically used as a measure of anxiety-related behavior in rodents.[28] This test has been used as a measure of locomotor activity in pain models[29] and more recently, additional measures of thigmotactic behavior indicate the presence of altered exploratory behavior in rodent models of pain without the presence of locomotor deficits. This behavior is sensitive to clinically employed analgesics, such as gabapentin and morphine,[19, 27] suggesting the thigmotaxis to be correlated to a nonstimulus-evoked pain-like behavior in rodents be it spontaneous pain or pain comorbidities.

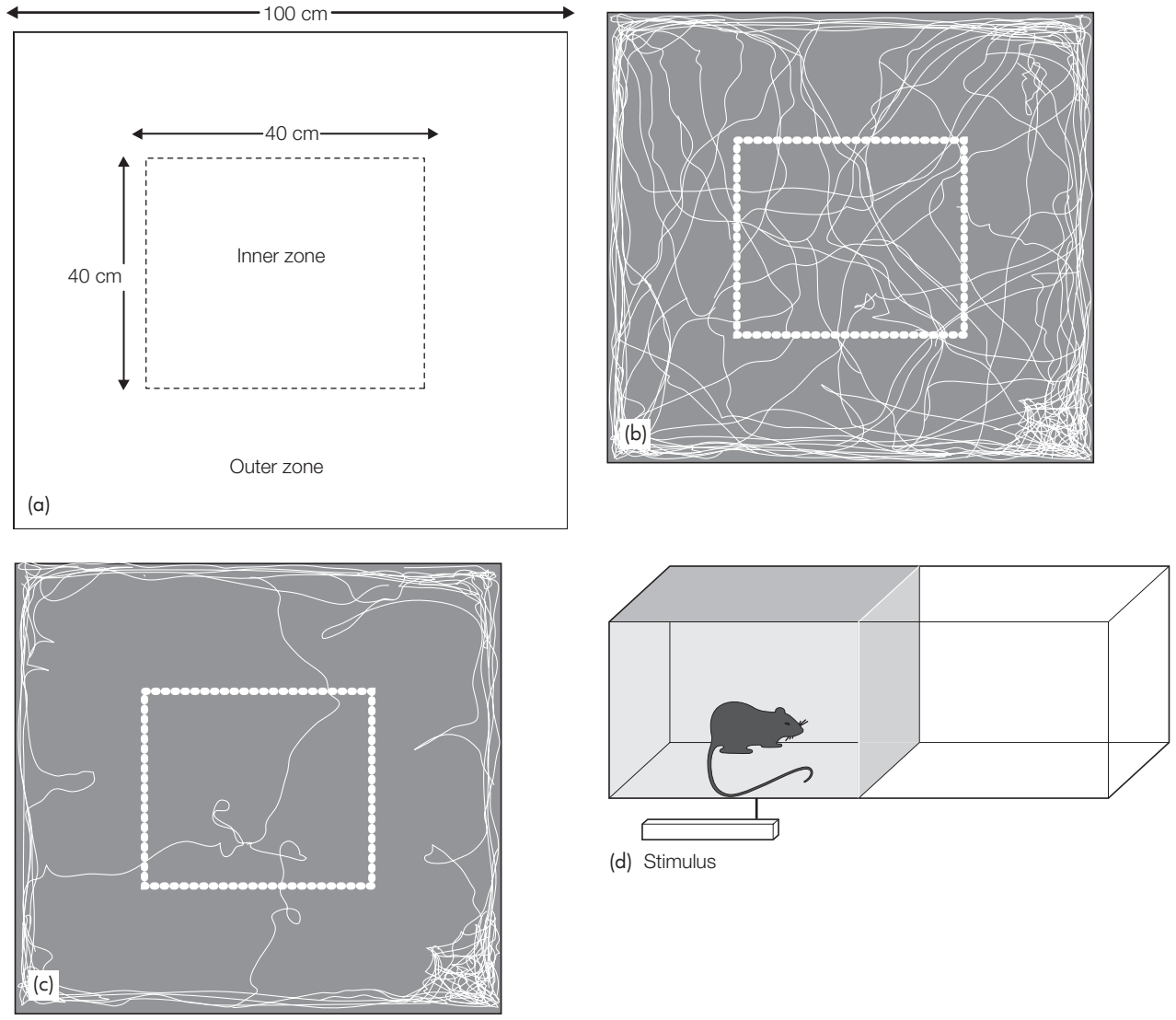

Figure 1.3 Examples of behavioral paradigms adapted for the assessment of pain conditions in rodents. (a–c) The open field paradigm in which neuropathic rats display thigmotactic (wall hugging) behavior: (a) open field arena; (b) naive rat; (c) rat with nerve injury. (d) The dark/light box: place preference paradigm in which rats chose between the aversive noxious stimulus or the aversive light compartment.

Further types of test involve active escape and avoidance of preferred environments (such as a dark versus light arena) in association with noxious stimuli.[30] These tests involve conflicting choices in which the animal must choose an adverse environment over the presence of a noxious stimulus and appear to respond well to analgesic drugs.[31] Alternatively, place preference paradigms associate a place with a preferable treatment such as delivery of an analgesic drug. However, the development of the latter paradigm in relation to neuropathic pain is ongoing and their utility remains to be proven. It is important to remember the effects of species variability[32] and therefore care must be taken to establish the suitability of tests in rodents.

MECHANISMS OF NEUROPATHIC HYPERSENSITIVITY

A variety of pain-related phenomena, both central and peripheral, have been associated with peripheral nerve injury (**Table 1.2**). These are generally not mutually exclusive and it is entirely possible that any one of these (or more likely a combination) contribute to symptomatology in individual patients suffering from neuropathic pain. It is therefore inappropriate to attempt to generate a unifying hypothesis of pathophysiology for all neuropathic pain states. The next challenge is to diagnose which of these phenomena may be operative in an individual patient and to interpret each symptom within the mechanistic framework arising from work with neuropathic pain models. In this regard, neuropathic pain is ideally suited to the mechanistic-based approach to treatment.[33, 34]

Peripheral mechanisms

PRIMARY AFFERENT EXCITABILITY

In normal primary afferent neurons, it is rare for firing threshold to be reached without the input of a stimulus.

Table 1.2 An overview of pathophysiological events which are likely to be related to the generation of neuropathic pain.

Peripheral nervous system	Central nervous system
Sensitization and spontaneous activity in sensory neurons	Central sensitization
Abnormal ion channel expression	Spinal reorganization
Altered neuronal biochemistry	Changes in inhibitory systems
Sensory neuron apoptosis	Glial cell activation
Immune–neuronal interactions	Alterations in descending modulation
Loss of trophic support for neurons	Cortical reorganization

However, following a nerve injury, many injured axons and associated cell bodies in the DRG undergo an increase in their intrinsic electrical excitability. As a result they begin to generate impulse discharge spontaneously or with only minimal stimulation linked to the injury site.[35] This has been termed ectopic discharge[36] and has also been demonstrated in humans, suffering from neuropathic pain.[37] Ectopic discharge originating in the peripheral nervous system (PNS) can result in excess spontaneous and stimulus-evoked electrical impulses feeding into the central nervous system (CNS) (**Figure 1.4**).[39] Ectopic afferent activity may also trigger and maintain central sensitization amplifying the afferent signal from the remaining afferents that innervate the partly denervated skin and deep tissues leading to tenderness to touch ("tactile allodynia").[38]

Furthermore, oscillations in resting membrane potential in primary sensory neurons are thought to contribute to their ectopic potential. A small number of A-fibers (10 percent) exhibit subthreshold membrane oscillations in their resting state or under depolarization conditions. An increase in these oscillations is observed in sensory neurons from axotomized rats.[40] Due to the sensitivity of such oscillations to tetrodotoxin (TTX), a role for changes in sodium channel function in the nerve in DRG has been proposed. Increases in oscillations lead to increased ectopic activity in these neurons that may underlie paresthesiae, dysesthesiae, as well as frank pain.

Abnormal discharges may also arise at the site of nerve injury, at other points along the nerves or in the cell body in the DRG.[41] Myelinated and unmyelinated primary afferent axons may become spontaneously active after nerve injury.[38, 42] Wallerian degeneration of an injured, spontaneously active myelinated fiber allows cross-excitation of neighboring unmyelinated fibers (termed "ephaptic transmission") inducing ectopic discharge even in an uninjured axon.[43, 44] Such ectopic discharge present in both low-threshold mechanoreceptors and in nociceptors may contribute to allodynia and hyperalgesic components of neuropathic pain.

Sodium channels

Sodium (Na^+) channels are critical to the physiology of excitable membranes. There are significant alterations in the expression of Na^+ channels in the cell bodies and the terminal neuroma of peripheral nerves following nerve injury. Such accumulation of Na^+ channels in the neuroma of cut sensory axons[45] are thought to generate ectopic discharge (**Figure 1.5**).[46]

There are many different and distinct voltage-gated Na^+ channels, of which at least six are expressed by primary afferent neurons within the DRG.[47] These can be defined by their sensitivity to TTX. In the DRG, TTX-sensitive channels (TTX-s) are expressed predominantly by A-fibers. In contrast, TTX-resistant (TTX-r) channels are expressed by a subset of primary afferent neurons specifically in the smaller C-fibers associated with

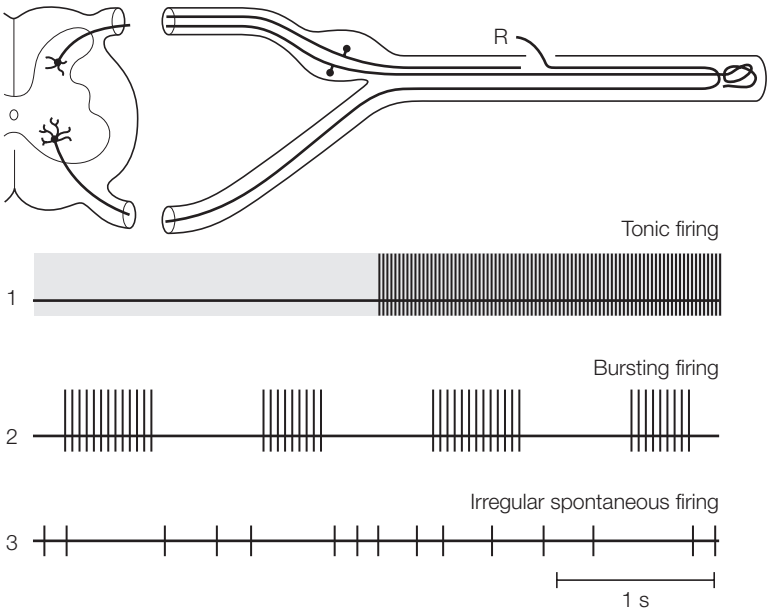

Figure 1.4 Patterns of spontaneous ectopic discharge recorded from sensory neurons ending in a neuroma. Fine axon bundles were microdissected from an injured nerve and placed on a recording electrode (R). Spontaneously active fibers fire tonically (1), in bursts (2), or irregularly (3). Intracellular recording from a dorsal root ganglion neuron with ectopic burst discharge (asterisks, spike height is truncated). One burst is shown in detail below. Bursts are triggered when ongoing membrane potential oscillations reach threshold and are maintained by postspike depolarizing after potentials (DAP). The burst initiates a hyperpolarizing shift which stops firing and resets the oscillations. Reprinted from Devor, *Melzack and Wall's Textbook of Pain*. 2005, 5th Edition © 2005 Elsevier Ltd,[38] adapted from Amir and Devor 1992.[39] Used with permission from The American Physiological Society and Elsevier.

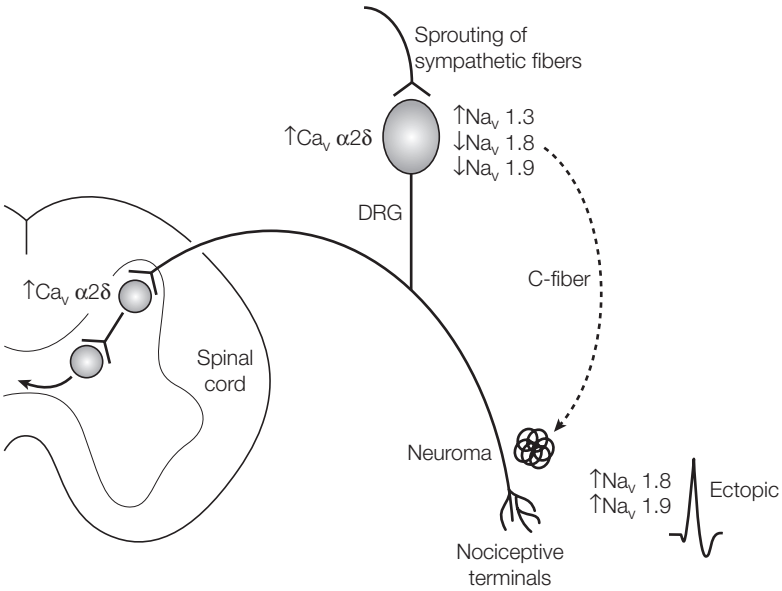

Figure 1.5 Alterations in Na^+ and Ca^{2+} channel subunits in the peripheral nervous system (PNS) following nerve injury. There is an increase in the expression of tetrodotoxin sensitive Nav1.3 channels and the calcium channel α2δ-1 (Cavα2δ-1) subunits in dorsal root ganglion (DRG) neuron cell bodies. The tetrodotoxin-resistant Na^+ channel subunits Nav1.8 and Nav1.9 decrease in the DRG and are also redistributed from the DRG neuron cell bodies to peripheral axons at the site of injury. Sprouting of sympathetic nerve fibers in the DRG also act to sensitize peripheral afferents. These changes are thought to result in spontaneous ectopic discharges and lower the threshold for mechanical activation that leads to hypersensitivity.

nociception.[48] Following peripheral nerve injury, there is a reorganization of ion channel expression in DRG neurons.[36] Some sodium channels subtypes are diminished, whilst others appear *de novo* and others are translocated to different parts of the neuron. For example, there is an up-regulation of the TTX-s channels $Na_v1.3$ (not normally expressed by DRG cells) and $Na_v1.7$, and a down-regulation of the TTX-r channels $Na_v1.8$ and $Na_v1.9$. As $Na_v1.8$ and $Na_v1.9$ produce slowly inactivating currents, their decreased expression may lead to a hyperpolarizing shift in resting potential, increasing the fraction of TTX-s channels available for activation.[47, 49] Electrophysiological studies demonstrate a reduced density of TTX-r currents and a shift in the voltage dependence of activation to a more negative potential in the following nerve injury.[49] In contrast, up-regulation of $Na_v1.3$ results in a switch in the properties of the TTX-s currents in DRG neurons, with the emergence of a rapidly repriming current, which could sustain frequent ectopic discharges and lead to hyperexcitability in the cell.[50] In support of this, TTX produces dose-dependent inhibition of ectopic activity[51] and reduced mechanical hypersensitivity in the spinal nerve transection (SNT) model.[52] In partial nerve injuries, the intact afferent neurons show little or no change in the expression of $Na_v1.8$, although there is a redistribution of these channels from their cell bodies in the DRG to their axons,[53] which may explain the neuroma hypersensitivity. These findings were corroborated in immunohistochemical studies of tissue taken from patients suffering from neuropathic pain following traumatic brachial plexus avulsion[54] and in human sensory nerves localized close to the injury site and within the neuroma.[55]

A Na^+ channel subunit that has received more attention in recent years is the $Na_v1.7$ channel. $Na_v1.7$ is expressed, almost exclusively, in DRG, particularly in small C-fiber nociceptors and to a lesser extent in medium-sized Aδ and large Aβ cells.[56] The $Na_v1.7$ channel underlies a fast TTX-s current with slow repriming kinetics and slow inactivation. Significantly, the $Na_v1.7$ channel has been localized to sensory endings, such that both its distribution and physiology may predispose it to a major role in transmitting painful stimuli. A mutation in the human gene encoding $Na_v1.7$ resulting in sensory neuron hyperexcitability is thought to be associated with the development of neuropathic pain in primary erythermalgia.[57, 58] However, experimentally the role for $Na_v1.7$ in neuropathic pain is unclear as mice lacking this channel develop signs of neuropathic pain as normal.[59]

The mechanism contributing to the changes in Na^+ channel expression in peripheral nerve injury is unclear, but the influence of growth factors appears to be a crucial factor. For example, in the absence of nerve growth factor (NGF), DRG neurons *in vitro* increase $Na_v1.3$ expression and decrease $Na_v1.8$ expression.[60] NGF is a member of the neurotrophin family of polypeptides, which are produced by peripheral target tissue during embryonic development, are required for peripheral sensory neurons for survival and can influence the morphology, excitability, and synaptic plasticity of sensory neurons in adulthood.[61] Additionally, glial-derived neurotrophic factor (GDNF), a member of a second family of growth factors, normalizes $Na_v1.3$ expression, reduces ectopic discharge in A-fibers, and reduces hypersensitivity[62] when delivered to the injured nerve. $Na_v1.9$ expression is similarly reliant on GDNF.

Therapeutic agents that exhibit use-dependent block of sodium channels show efficacy against painful peripheral neuropathy in the clinic. Systemic administration of lidocaine and other sodium-channel blockers relieves painful symptoms of postherpetic neuralgia, painful diabetic neuropathy, idiopathic trigeminal neuralgia, and other conditions.[63] Topical lidocaine also relieves pain in postherpetic neuralgia.[64] Sodium channel blockade is also a likely mechanism through which at least some drugs which also have efficacy in epilepsy (e.g. phenytoin and carbamazepine) might suppress neuropathic pain and the well-established efficacy of tricyclic antidepressants (TCA) may be due, at least in part, to their ability to block sodium channels.[65]

Potassium channels

There is a large variety of K^+ channels[66] and their significance in pain signaling is far from understood. Classic voltage-gated K^+ channels, often called delayed rectifiers, have six transmembrane domains and can be divided into nine gene subfamilies. The K_V1 subfamily is the most explored among subtypes of sensory neurons.[67] $K_V1.1$ and $K_V1.2$ are present in large-diameter sensory neurons, whereas $K_V1.4$ is present in most small sensory neurons that express $Na_V1.8$, making it the candidate nociceptive delayed rectifier. The activation of voltage-gated K^+ channels ultimately decreases the excitability of a cell. Thus, K^+ channels are prime molecular targets for suppressing hyperactive neurons, and might, therefore, prove useful in suppressing hypersensitivity.

Other K^+ channels that figure prominently in excitation of neurons, are the M channel (*KCNQ* gene), the H channel- (*HCN* gene) and calcium-activated K channels. All these channels are thought to be present on some populations of sensory neurons.[68, 69, 70] However, their relevance to pain is largely unknown.

Calcium channels

Activation of voltage-dependent calcium channels (VDCC) is critical for neurotransmitter release. Calcium ion channels have also been shown to influence the generation of hypersensitivity and in particular, a role for N-type Ca^{2+} channels has been shown. N-type, but not P- or Q-type, Ca^{2+} channel antagonists can attenuate hypersensitivity to mechanical and heat stimuli in models of neuropathic pain.[71, 72] Furthermore, cannabinoid receptor agonists, known to have analgesic effect in nerve injury models, attenuate Ca^{2+} flux at N-type channels.[73]

A calcium channel subunit that has received much attention of late is the $\alpha_2\delta$-1 subunit. This subunit is upregulated in rat DRG neurons, on central afferents terminals and on neurons within the spinal dorsal horn following nerve injury (**Figure 1.5**).[74, 75] This is correlated with pain behavior following peripheral nerve injury suggesting that $\alpha_2\delta$-1 may contribute to neuroplasticity in neuropathic pain. In support of this, transgenic mice that constitutively overexpress $\alpha_2\delta$-1 in neuronal tissues demonstrate pain behavior and exaggerated and prolonged dorsal horn neuronal responses to peripheral mechanical and thermal stimulation.[76] Furthermore, the $\alpha_2\delta$-1 subunit is thought to be the site of action of gabapentin[77, 78] and pregabalin,[79] which are effective in relieving signs of hypersensitivity in animal models[80] and neuropathic pain in man.[64, 81]

ALTERATIONS IN SENSITIVITY TO STIMULI

Transient receptor potential ion channels

Transient receptor potential (TRP) ion channels are sensory transducers, many of which are expressed in nociceptive primary sensory neurons where they are involved in generating chemical- and thermal-evoked pain sensations.[82] In particular, TRPV1 responds to noxious heat (temperatures $>43^\circ$C) and the pungent ingredient in hot chilli peppers, capsaicin, producing the classic burning sensation. In contrast, TRPA1 responds to cold temperatures ($<18^\circ$C) and to the irritant, mustard oil, also producing a burning sensation.

Following nerve injury, the phenotype of cells expressing TRP channels fundamentally changes so that TRPV1

and TRPA1 are also expressed by neurons of a non-nociceptive phenotype. Expression of TRPV1 has been shown to decrease in injured nociceptive neurons, while they increase in the neighboring uninjured neurons.[83] This includes novel expression in large diameter, low threshold A-fibers which may indicate a phenotypic switch contributing to symptoms of neuropathic pain. Similarly, TRPA1 expression is increased in a subset of small diameter primary sensory neurons following nerve injury likely inducing cold hypersensitivity.[84] Interfering with TRPA1 channel function using antisense knockdown technology abolishes hypersensitivity to a cold stimulus following spinal nerve ligation in the rat.[85] Therefore, targeting specific TRP channels may prove useful as analgesic strategies in the future.

THE ROLE OF PERIPHERAL INFLAMMATORY MEDIATORS

Nerve injury, trauma, and/or infection evoke a cascade of cellular events in the PNS, including a neuroinflammatory response with the release of chemical mediators, including many proinflammatory cytokines and chemokines.[86, 87] Cytokines and chemokines (small chemoattractant cytokines) are growth factor proteins secreted primarily from leukocytes as part of the immune and inflammatory response[88] and have been demonstrated to play a role in the pathogenesis of pain.[87] These factors can act on neurons to induce changes in gene expression, which in turn lead to the emergence of abnormal electrical activity, known to be essential for the manifestation of neuropathic pain behavior. Following nerve trauma, tumor necrosis factor-α (TNFα) is released from Schwann cells and infiltrating and resident macrophages, and in turn stimulates the sequential production and release of interleukin-1β (IL-1β) and interleukin-6 (IL-6) (**Figure 1.6**).[86] Accordingly, neutralizing antibodies to TNFα and IL-1β reduce behavioral signs of experimental neuropathic pain[90, 91] and IL-6 knockout mice fail to exhibit neuropathic pain after nerve injury.[92]

Intact and injured sensory neurons are known to express receptors which respond to TNFα, IL-1β, and IL-6. However, the direct mechanism of neuronal sensitization remains to be fully determined. Indirect evidence suggests an action of TNFα on neuronal sodium or calcium channels,[93] whereas IL-1β may be involved in a complex signaling cascade that leads to the production of pronociceptive compounds (such as nitric oxide, NGF, and prostaglandins) from immune cells or Schwann cells. Such substances lead to changes in gene expression and neuronal excitability in intact nociceptors.[94] The gp130 cytokines, IL-6 and leukemia inhibitory factor (LIF), have been shown to be crucial in the up-regulation of key modulators of sensory processing, such as brain-derived neurotrophic factor (BDNF), galanin, and substance P following nerve injury.[94] The chemokine CCL2 (MCP-1) is another injury-induced factor that accumulates within sensory neurons in models of neuropathic pain[22] and contributes to macrophage recruitment. CCL2 has been implicated in the maintenance of neuropathic pain and knockout mice for the receptor, CCR2, fail to develop signs of neuropathic pain.[95] Recent developments in the understanding of the importance of nonneuronal cells and inflammatory mediators in the response to damage of the peripheral nervous system has greatly aided the understanding of peripheral mechanisms of neuropathic pain.

CELL DEATH IN THE PNS

Many forms of nerve injury can also produce death of sensory neurons.[96] Apoptosis may be a result of mitochondrial dysfunction[97] and has been associated with a number of neuropathies.[96, 98, 99] Mitochondria-dependent apoptosis is activated by a number of factors including reactive oxygen species, ceramide, and nitric oxide,[100] which have been implicated in the pathophysiology of neuropathies. These factors cause the release of cytochrome C from mitochondria leading to the formation of the apoptosome complex and subsequent activation of effector caspases. Alternatively, apoptotic pathways can be activated via stimulation of death receptors, such as TNFR1[100] which can act via the JNK (c-Jun-N-terminal kinase) pathway to activate effector caspases. In support of this, TNFα is released in response to chemotherapeutic agents that produce painful peripheral neuropathy,[101] following direct nerve injury,[102] and in response to HIV-gp120 *in vitro*[103] and caspases have been shown to be important in neuropathic responses in various models of neuropathy.[20, 96, 104, 105] It is thought that the activation of these pathways may be involved in neuropathic pain even though there may be a prolonged latent phase of apoptosis, before cell death.

Spinal cord mechanisms

The sensory input from primary sensory neurons is transferred, via their central axons, to second-order neurons in the dorsal horn of the spinal cord. The synaptic contacts made between afferent central terminals and dorsal horn neurons are highly organized, both topographically and functionally to maintain accurate transfer of information regarding the peripheral noxious stimuli. Following peripheral nerve lesions, synaptic processing in the spinal cord can be subject to diverse forms of functional, chemical, and structural plasticity that are highly involved in the production of hypersensitivity to sensory input. Increased synaptic efficacy (the phenomenon of central sensitization), loss of inhibitory mechanisms, alterations in synaptic contacts, and the activation of nonneuronal cells all play major roles in producing increased pain sensitivity in neuropathic pain. This chapter will address each of these areas in turn.

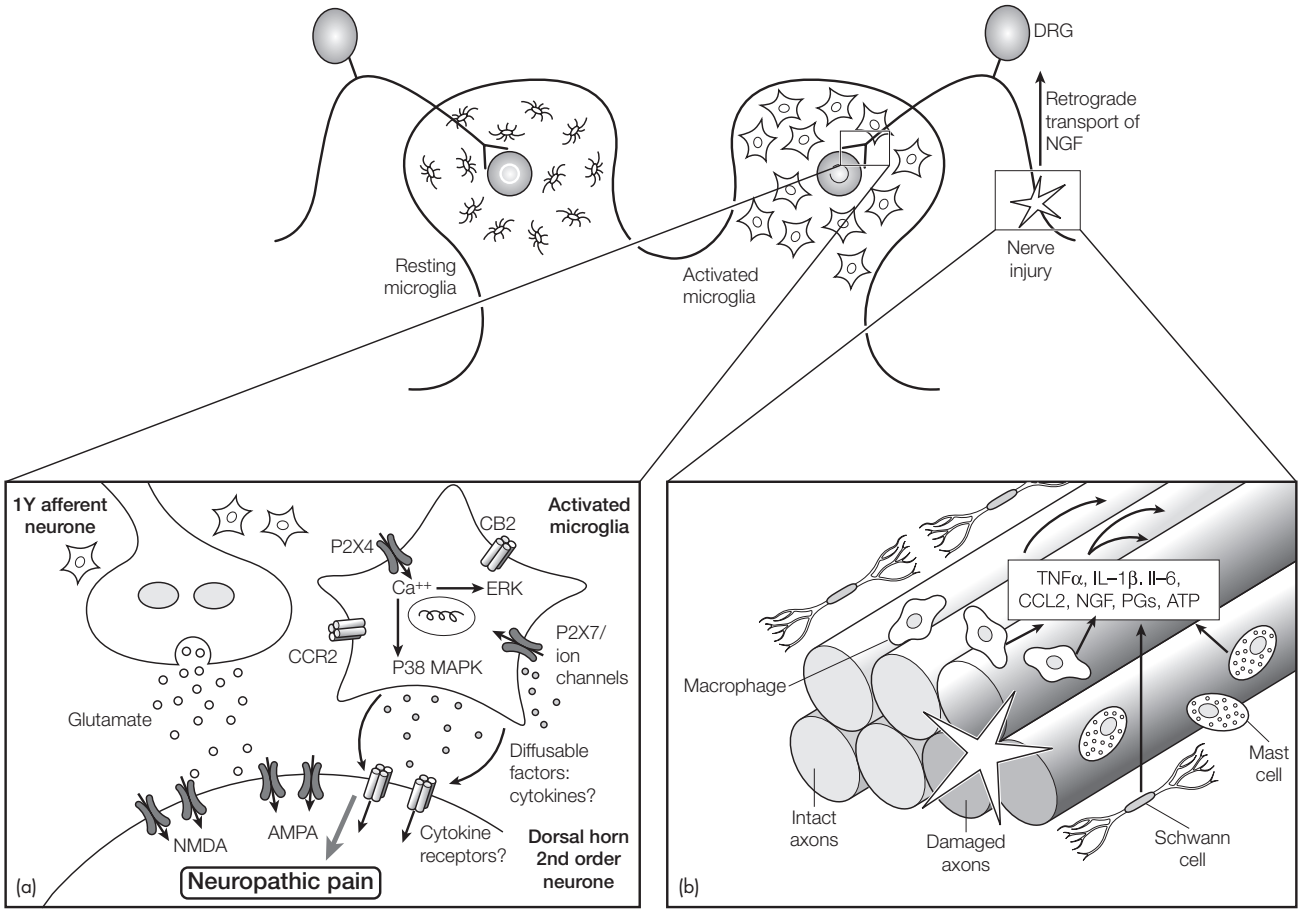

Figure 1.6 The immune system in neuropathic pain. Overview of the effect of the immune system on primary sensory neurons and the spinal cord after peripheral nerve injury. (a) Representation of a mixed nerve injury in which injured and uninjured axons are juxtaposed. The site of injury is typified by the recruitment and proliferation of nonneuronal elements (such as Schwann cells, mast cells, and macrophages), which release factors including the cytokines TNFα, IL-1δ, IL-6, the chemokine CCL2, prostaglandins (PGs) and growth factors, including nerve growth factor (NGF) that initiate and maintain sensory abnormalities after injury. These factors might either induce activity in the axons they act on or be transported retrogradely to cell bodies in the dorsal root ganglion (DRG), where they alter the gene expression of neurons. (b) The effect of the immune system in the spinal cord following peripheral nerve injury with a focus on microglial activation. A primary afferent neuron terminal is flanked by microglial cells that maintain and survey the environment in the spinal cord. In neuropathic pain states, the microglia are activated, probably by the release of transmitters or modulators from primary afferents. The activated microglia release several proinflammatory cytokines, chemokines, and other agents that modulate pain processing by affecting either presynaptic release of neurotransmitters and/or postsynaptic excitability. The release of inflammatory mediators (such as tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), interleukin-6 (IL-6), nitric oxide (NO), ATP, and prostaglandins (PGs) initiates a self-propagating mechanism of enhanced cytokine expression by microglial cells. This leads to an increase in intracellular calcium, and activation of the p38 and MAPK/ERK pathway. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CCR2, CCL2 receptor; CX3CR1, fractalkine receptor; EAA, excitatory amino acids; ERK, extracellular signal-regulated kinase; FPRL1, formyl peptide receptor-like 1; MHC, major histocompatibility complex; NGF, nerve growth factor; NK1R, neurokinin-1 receptor; NMDA, *N*-methyl-D-aspartic acid; P2 × 4, P2 × 7, ionotropic purinoceptors; p38MAPK, p38 mitogen-activated protein kinase. Adapted with permission from Macmillan Publishers Ltd: *Nature Reviews Neuroscience*[86] © 2005 and reprinted from *Trends in Neuroscience*, 28, Tsuda M, Inoue K, Salter MW, Neuropathic pain and spinal microglia: a big problem from molecules in "small" glia, 101–7, © 2005, with permission from Elsevier.[89]

EXCITATORY MECHANISMS

The afferent barrage associated with peripheral nerve injury is associated with the development of a sustained state of hyperexcitability of dorsal horn neurons, a process dubbed central sensitization.[106, 107] In addition to events such as lowering of activation thresholds of spinal neurons, central sensitization is characterized by the appearance of "wind-up."[108, 109, 110] Wind-up is characterized by an increasing response to repeated C-fiber

volleys, and may contribute to hyperalgesia in humans. However, the exact relationship of the relatively short-lived phenomenon of wind-up and the persistent state of central sensitization remains to be fully elucidated.[111]

The excitatory amino acid glutamate is the major excitatory neurotransmitter released at the central terminals of primary afferent nociceptive neurons following noxious stimulation. Glutamate acts at a number of post-synaptic receptors, including metabotropic (mGluRs) and the ionotropic α-amino-3-hydroxyl-5-methyl-4-isoxazole (AMPA), kainate and *N*-methyl-D-aspartic acid (NMDA) receptors. A large body of evidence suggests that the NMDA receptor subtype is the most intimately involved in central sensitization associated with inflammation and nerve injury.[110] For glutamate to exert its effects, receptor phosphorylation and the removal of an Mg^{2+}-dependent ion channel block are critical events in activating the NMDA receptor. NK1 (substance P), AMPA (glutamate), and trkB (BDNF) receptors and the activation of intracellular serine/threonine and tyrosine kinase signalling cascades are all involved in this permissive process.[112, 113]

NMDA receptors are also involved in the maintenance of central sensitization. Nerve injury induces increased release of excitatory amino acids into the spinal dorsal horn which is associated, in an NMDA receptor-dependent manner, with increased intracellular calcium concentration ($[Ca^{2+}]_i$) in dorsal horn neurons.[114] Initial NMDA receptor activation contributes to further increased concentrations of glutamate and aspartate, representing a continual positive feedback loop which maintains sensitization. The increased $[Ca^{2+}]_i$ could also form a positive feedback loop, potentially through indirect activation of protein kinase C (PKC), a hypothesis supported by the antihypersensitivity effect of a PKC inhibitor in the SNL model of neuropathic pain,[115] as well as the evidence that deletion of genes for isoforms of adenylate cyclase, protein kinase A, and protein kinase C all impair the development of pain hypersensitivity in transgenic mice.[116, 117] Activity-dependent central sensitization is displayed by many cells in both the superficial and deep laminae of the dorsal horn. However, in the context of pain hypersensitivity, the effect of sensitization appears to be particularly important for lamina I spinothalamic or spinoparabrachial projection neurons, particularly those expressing the NK_1 receptor.[118, 119]

In addition to Ca^{2+} influx through the NMDA ion channel inducing heterosynaptic potentiation in dorsal horn neurons, activation of voltage-gated calcium channels can enhance excitatory transmission through NMDA receptor-independent mechanisms.[120] For example, neurotrophins such as BDNF, acting through their cognate Trk receptors, facilitate synaptic transmission,[121, 122] partly through a NMDA receptor independent mechanism. Synaptic transmission may also be enhanced by cytokines, such as TNFα, which may be released from glial cells in the dorsal horn.[123] Pharmacological studies support a role for NMDA receptors in neuropathic pain. Pre- and postinjury intraperitoneal administration of the NMDA receptor antagonist MK-801 prevented hypersensitivity in the CCI model[124] and electrophysiological data also demonstrates that MK-801 significantly reduces the hyperresponsiveness to noxious stimulation after peripheral nerve injury.[125]

The agonist action of glutamate at the NMDA receptor can be modulated by glycine.[126] Antagonizing the glycine modulatory site of the NMDA receptor prevents development of hypersensitivity following peripheral nerve injury and attenuates wind-up in isolated spinal cord neurons.[127] Coadministration of a glycine/NMDA receptor antagonist and morphine has also been demonstrated to attenuate pain behavior in an animal model of trigeminal neuralgia.[128]

SPINAL INHIBITORY SYSTEMS

γ-Aminobutyric acid and glycine

The γ-aminobutyric acid (GABA) pathway forms a major inhibitory neurotransmitter system in the CNS. Depression of such spinal inhibitory mechanisms are thought to be important for sustained enhancement of excitatory transmission and central sensitization.[129] In support of this, administration of GABA-mimetics reduces neuropathic hypersensitivity and antagonism of the GABA receptors is associated with hypersensitivity.[130] Moreover, peripheral nerve injury results in a substantial loss of GABA-mediated inhibitory currents,[131] decreased extracellular levels of GABA,[132] a decrease in dorsal horn levels of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD) 65 kDa,[131] and decreased GABA receptor levels in the spinal cord, probably due to degeneration of the primary afferent neuron terminals on which the receptor is localized.[133] Apoptosis in the dorsal horn following nerve injuries may correlate to selective death of GABAergic inhibitory interneurons[131] due to excessive glutamate release or a result of cell death-inducing signals within the spinal cord.[134] All of the above factors likely promote a functional loss of GABAergic transmission in the superficial dorsal horn.

GABAergic and/or glycinergic inhibition are important factors in the maintenance of orderly information processing by preventing the generation of synchronized wave activity in the CNS. Synchronous neuronal activity leading to oscillatory Ca^{2+} waves can be evoked in the spinal dorsal horn network by the potassium channel blocker 4-aminopyridine (4-AP) after pretreatment with blockers of $GABA_A$, glycine, and AMPA/kainate receptors.[135] This may correlate to reduced inhibition and increased neuronal excitability observed in dorsal horns of animals with neuropathic pain.[136] Theoretically, such synchronous activation of larger parts of the dorsal horn network would lead to pain that violates the innervation patterns of peripheral nerves or dorsal roots characterized by violation of sensory modality borders (e.g. allodynia,

where normally nonnoxious stimuli are perceived as painful) and somatotopic borders (radiating pain or mirror-image pain). Therefore, disinhibition as a result of altered GABA and glycine signaling may lead to waves of excitability and could underpin neuropathic pain. However, further studies will be required to evaluate under what physiological and pathophysiological conditions crossing of somatotopic and sensory modality borders occurs in spinal dorsal horn.[135]

Opioid system

The endogenous opioid system is also dysregulated following nerve injury. Evidence supports a loss of μ-opioid receptors in the DRG[137] and in the spinal cord following nerve injury.[40, 138, 139] Spinal opioid receptors are localized predominantly on the presynaptic terminals of primary afferents in the superficial dorsal horn[138] and therefore this may reflect degeneration of primary afferent neurons. Additionally, increased cholecystokinin (CCK) mRNA synthesis by DRG neurons[140] and increased expression of the CCK_B receptor in the superficial dorsal horn following peripheral axotomy may potentially decrease the antinociceptive effects of opioids due to opioid antagonistic properties of CCK.[141] These changes may all contribute to the reduced potency of peripherally or spinally delivered opioids in neuropathic pain (**Figure 1.7**).[142]

Cannabinoid system

The endogenous cannabinoid system has received much interest within the field of neuropathic pain due to the fact that unlike the opioid system, spinally expressed cannabinoid receptors are unaffected following nerve injury.[143] In such, manipulation of the cannabinoid system has been effective in alleviating signs of neuropathic pain in animal models of neuropathic pain[5, 22, 144, 145] representing a possible therapeutic advantage of cannabinoids over opioids in neuropathic pain.

ANATOMICAL REORGANIZATION

Tactile mechanical allodynia is thought to be mediated by Aβ-fiber afferents.[146] However, the mechanisms by which this occurs are yet to be fully understood. Several studies using bulk labeling and single afferent fiber-filling techniques have demonstrated that following a peripheral nerve lesion, the central axons of injured Aβ-fibers sprout from their normal termination sites in the deeper laminae of the dorsal horn (laminae II and IV) into lamina II of the dorsal horn, which is normally restricted to C-fiber and Aδ nociceptors.[147, 148] This synaptic rearrangement means that second-order dorsal horn neurons that normally receive predominantly high threshold sensory input, now receive inputs from low threshold mechanoreceptors. Such misinterpretation of information within the spinal cord may result in low threshold sensory information being interpreted as nociceptive, leading to the emergence of hypersensitivity after peripheral nerve injury. The outgrowth of central Aβ-fiber terminals is prevented by NGF and GDNF treatment, presumably by provision of trophic support for damaged C-fibers, suggesting an important role for neurotrophins in the regulation of this manifestation of structural plasticity.[149] However, some studies have raised concerns about the specificity of bulk-labeling techniques and the sampling of intracellular labeled intact and injured afferents,[150, 151] such that the labeling may actually be due to damaged C-fibers abnormally taking up the label. However, in favor of the sprouting theory, stimulation of Aβ-fibers in injured nerves can produce activation of neurons in lamina II measured electrophysiologically and by expression of c-Fos.[152, 153] Nevertheless, further work is required to resolve the basis for the differences in these anatomical studies, and to determine the extent to which sprouting of Aβ-fibers contributes to tactile hypersensitivity after peripheral nerve injury.

THE ROLE OF NONNEURONAL CELLS

Peripheral nerve injury produces molecular and cellular changes that result in multiple forms of neuronal plasticity and anatomical reorganization at various levels of the peripheral and central nervous systems. Oligodendrocytes, astrocytes, and microglia form a large group of CNS glial cells. Although often underappreciated, a substantial body of evidence has accumulated showing that peripheral nerve injury leads to activation of glia in the spinal cord implicating astrocytes and particularly microglia.[89, 123]

Microglia are immune-derived cells and represent 5–10 percent of glia in the CNS.[154] Microglia are said to be resting under normal conditions and do not actively influence nociceptive processing. However, microglia become activated by events such as CNS injury, microbial invasion, and in some pain states. Following peripheral nerve lesions, spinal microglia appear to migrate to the relevant spinal segments, thus increasing the local microglial population, and become activated involving a stereotypic series of changes including morphological alteration (they become hypertrophic and ameobiod), gene expression, and function. Moreover, activated microglia produce and release various chemical mediators, including proinflammatory cytokines, chemokines, and other potentially pain-producing substances, that can produce immunological actions and can also act on neurons to alter their function (**Figure 1.6**).[89, 155] The status of microglia in the spinal cord has been examined in a variety of nerve injury models and substantial evidence, both direct and indirect, indicates that microgliosis fundamentally contributes to the pathophysiology of neuropathic pain.[20, 22, 156, 157, 158] This is supported by several studies that have shown specific microglial inhibitors and/or modulators, such as fluorocitrate and minocycline block, and/or reverse neuropathic states.[21, 22, 159, 160]

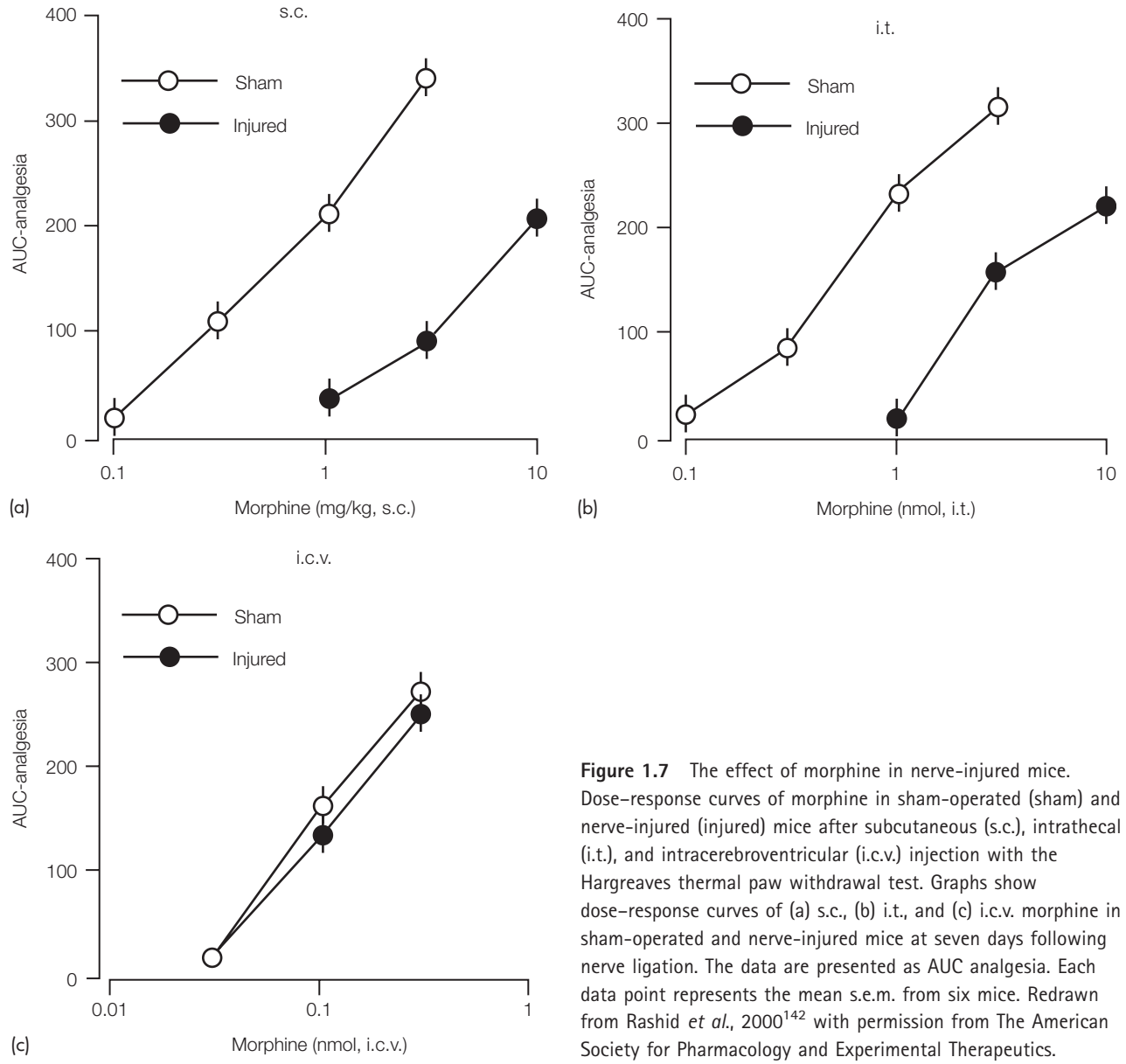

Figure 1.7 The effect of morphine in nerve-injured mice. Dose–response curves of morphine in sham-operated (sham) and nerve-injured (injured) mice after subcutaneous (s.c.), intrathecal (i.t.), and intracerebroventricular (i.c.v.) injection with the Hargreaves thermal paw withdrawal test. Graphs show dose–response curves of (a) s.c., (b) i.t., and (c) i.c.v. morphine in sham-operated and nerve-injured mice at seven days following nerve ligation. The data are presented as AUC analgesia. Each data point represents the mean s.e.m. from six mice. Redrawn from Rashid *et al.*, 2000[142] with permission from The American Society for Pharmacology and Experimental Therapeutics.

It is not clear what factors activate spinal microglia in peripheral neuropathic pain states. Several molecules have been implicated, including macrophage colony-stimulating factor (MCSF),[161] IL-6,[162] substance P, ATP, and the chemokines, fracktalkine,[163] and CCL2.[164] Activated microglia express various molecules allowing them to respond to such stimuli, including the ATP gated ligand-gated cation channels, P2 × 4,[165] and P2 × 7,[166] and the chemotactic cytokine receptor 2 (CCR2), a receptor for CCL2/MCP-1. Recent evidence suggests that ATP-stimulated microglia signal to lamina I neurons via their release of BDNF, causing a depolarizing shift in the neuronal anion reversal potential inverting the polarity of currents activated by GABA. This means that GABA now results in excitation of the cell as opposed to inhibition.[158] Evidence for a role of CCR2 in nerve injury-induced hypersensitivity[95] comes from mutant mice lacking the receptor. However, as CCR2 is also up-regulated in the peripheral nerve, at the site of the nerve injury and in the DRG, it is unclear whether spinal microglia expressed CCR2 is responsible. The cannabinoid receptor subtype CB_2 may also be expressed by spinal microglia after nerve injury and therefore cannabinoids may play a role as modulators of neuropathic pain via actions on microglia.[167] Accordingly, systemically administered CB_2 agonists can inhibit nerve injury-evoked pain behaviors.[95, 168] However, CB_2 agonists might act in the periphery and therefore the role of microglial CB_2 receptors is, at present, unclear.[169, 170]

The recruitment of microglia is commonly associated with the activation (phosphorylation) of p38 MAP (MAP) kinase and MAP kinase ERK (extracellular signal-regulated kinase) in the spinal cord. Phosphorylation of p38 is probably a key intracellular signal in the microglial response in neuropathic pain[157, 171] and the sequential

activation of ERK in neurons, then microglia, and finally astrocytes in a neuropathic pain model[172] suggests that microgial activation might be the first step in a cascade of immune responses in the CNS.[86, 94] The aforementioned molecules expressed by activated microglia in neuropathic pain states, or associated intracellular signaling cascades may be potential analgesic targets.

Supraspinal mechanisms

DESCENDING MODULATION

In addition to the peripheral and spinal mechanisms discussed, supraspinal mechanisms are thought to play an important role in neuropathic pain.[173, 174] The periaqueductal gray (PAG) is the most characterized part of a CNS circuit that controls nociceptive transmission at the level of the spinal cord.[175] The PAG integrates inputs from areas such as the limbic forebrain, diencephalon, amygdala, and hippocampus with ascending nociceptive input from the dorsal horn[176] and is therefore associated with the affective and autonomic responses to pain.

The PAG is closely associated with the brainstem including the rostral ventromedial medulla (RVM), and is critical in the descending modulation of spinal activity through monoaminergic and other pathways.[177] Likely via anatomically distinct pathways, the PAG and RVM can exert both facilitatory and inhibitory influences on the spinal cord.[178] The balance of these two supraspinal pathways and primary afferent input, ultimately determines the excitability of spinal neurons.[174] Under pathological conditions, enhancement of descending facilitatory controls to the spinal cord are likely to allow excitatory influences to predominate to maintain spinal central sensitization (**Figure 1.8**).

Facilitatory cells within the RVM are classed as ON cells, whereas cells that have inhibitory influences on the spinal cord are termed OFF cells.[179] Following nerve injury, there is enhanced descending excitatory drive from the RVM[180] which may represent a central compensatory mechanism for the loss of normal sensory input following peripheral nerve damage.[174] The brainstem areas involved are also implicated in autonomic responses, emotions, and sleep. Therefore, these same pathways likely underpin the well-established links between these states and pain, and may provide a basis for an affective component of pain.[181]

Various transmitter pathways are implicated in descending control mechanisms. For example, CCK, an antianalgesic peptide, may contribute to RVM neuron excitability.[182] Intra-RVM CCK produces reversible thermal and tactile hypersensitivity in naive rats[141] and prevents both the activation of OFF cells and the antinociception produced by systemic morphine.[183] Additionally, although thought mainly to play an inhibitory role in supraspinal systems,[184] supraspinal serotonergic inputs to the spinal cord originating in the RVM may play a role in facilitatory influences following peripheral nerve injury.[185] The 5HT3 receptor, localized to a novel group of small diameter afferents, and a larger

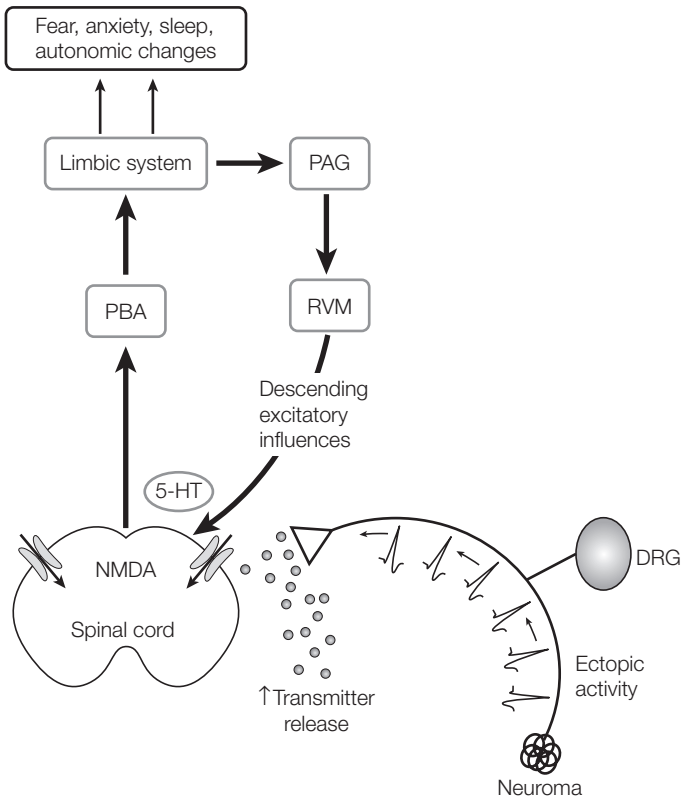

Figure 1.8 Overview of supraspinal involvement in neuropathic pain. Peripheral nerve injury induces spontaneous ectopic activity at the site of injury and the dorsal root ganglion (DRG) resulting in increased release of glutamate and neuropeptides (such as substance P) to the spinal cord, thereby promoting sensory transmission in the spinal cord. Centrally, there is increased function of the *N*-methyl-D-aspartic acid (NMDA) receptor and enhanced descending activity from the rostral ventromedial medulla (RVM) serotonergic excitatory pathways. All these mechanisms can contribute to the development of abnormal pain accompanying nerve injury. Plasticity is seen in the expression and function of ion channels (e.g. Na^+ channels) and neurotransmitters (e.g. substance P). Sprouting of sympathetic nerve fibers in the DRG act to sensitize peripheral afferents. Adapted from Suzuki and Dickenson, 2005,[174] by permission of S Karger AG, Basel.

number of presumed A-delta afferent fibers,[186] has been implicated as the target receptor of this system. Ondansetron, a $5HT_3$ antagonist exerts influences particularly on punctate mechanical responses after nerve injury.[187] Additionally, a preliminary clinical study suggests that block of $5HT_3$ receptors has clinical utility in the treatment of pain.[188]

Finally, evidence suggests that cannabinoids produce their antinociceptive effect at least in part by recruiting the PAG–RVM modulatory system.[189] CB_1 receptors are densely expressed in the PAG, and microinjection of CB_1 agonists into the PAG or RVM produces antinociception.[190] CB_1 receptors are also known to be expressed on rostrocaudally directed fibers in the dorsolateral funiculus, a major tract for descending control systems.[169, 170]

IMAGING OF THE BRAIN IN NEUROPATHIC PAIN

Recent advances in human brain imaging techniques offer an exciting opportunity to examine brain processes in experimental and clinical pain conditions. This has allowed insights into neural correlates of pain and led to a much greater understanding of the pain matrix,[191, 192] which includes brain structures, such as the anterior cingulate cortex (ACC), insula, frontal cortices, S1, second somatosensory cortex (S2), and amygdala.[193]

Neural correlates of allodynia have been examined in various conditions, including patients with neuropathic pain, central pain, or experimentally provoked allodynia. However, the existing data are controversial with some suggesting that allodynia is processed differently than nociceptive pain and others suggesting they share a common neural basis. Areas shown to be involved in allodynia include the parietal association cortex,[194] medial thalamus, putamen, and prefrontal cortex.[195] The ACC, which is almost always activated during acute pain in normal subjects and is involved in the affective (cognitive–evaluative) component of pain, has been differentially associated with processing of allodynia.[196, 197, 198, 199] This suggests that A-β-mediated pain may have a unique cortical representation in some situations which may aid further understanding of the phenomenon that is tactile allodynia. The amygdala, which plays an important role in fear-conditioning and affective disorders, such as anxiety and depression,[200] is activated by a diverse range of persistent nociceptive stimuli in the rat.[201, 202] Evidence suggests a role for the amygdala in the affective–emotional pain response in a rodent model of neuropathy involving GABAergic systems.[203] The amygdala has also been linked to spontaneous pain in humans suffering from postherpetic neuralgia.[204] Such studies highlight the involvement of a number of brain areas in pain responses in neuropathic pain conditions. However, further work using brain imaging techniques is required before our understanding of such systems is complete.

CONCLUSIONS

This brief overview of mechanisms of neuropathic pain outlines the complex nature of the response of the nervous system to a peripheral nerve injury. There is little doubt that a combination of mechanisms, involving peripheral, spinal, and supraspinal mediated events, contribute to the manifestation of neuropathic pain in any one individual. Eventually, it may be possible to improve the ethos of clinical management protocols so that they will move away from disease-based treatment towards symptom or, ultimately, mechanism-based therapies.[34] However, this will require a better understanding of mechanisms involved in neuropathic pain and reliable convenient tools for their assessment in the clinic.[33] It must be emphasized that the majority of preclinical studies employ animal models of nerve injury and measure associated hypersensitivity, which is only evident in a subset of patients with neuropathic pain. Therefore, improvement of animal models and behavioral tests will possibly unravel more therapeutically relevant mechanisms. Advances in technology have led to new approaches for the identification of novel targets involved in neuropathic pain. For example, microarray technology generates data regarding a large number of genes which can lead to the investigation of promising novel targets in neuropathic pain.[205] Additionally, our understanding of genetics may uncover genetic variation in the susceptibility of individuals to develop neuropathic pain,[206] which can also aid our understanding of specific mechanistic alterations and "genetically tailor" analgesics based on an individual's pharmacogenetic profile.

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