Behavioral Models of Pain States Evoked by Physical Injury to the Peripheral Nerve

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Summary: Physical injury or compression of the root, dorsal root ganglion, or peripheral sensory axon leads to well-defined changes in biology and function. Behaviorally, humans report ongoing painful dysesthesias and aberrations in function, such that an otherwise innocuous stimulus will yield a pain report. These behavioral reports are believed to reflect the underlying changes in nerve function after injury, wherein increased spontaneous activity arises from the neuroma and dorsal root ganglion and spinal changes increase the response of spinal projection neurons. These pain states are distinct from those associated with tissue injury and pose particular problems in management. To provide for developing an understanding of the underlying mechanisms of these pain states and to promote development of therapeutic agents, preclinical models involving section, compression, and constriction of the peripheral nerve or compression of the dorsal root ganglion have been developed. These models give rise to behaviors, which parallel those observed in the human after nerve injury. The present review considers these models and their application. **Key Words:** Tactile allodynia, spontaneous pain, dorsal root ganglion, nerve compression, autotomy.

INTRODUCTION

Classic observations in humans emphasize that nerve section can lead to sensory experiences that reflect the neural organization that originally subserved the body region innervated by the sectioned nerve. Frequently this "phantom" is reported as painful.[1] Incomplete injury to a nerve trunk, as generated by blunt trauma or chronic compression, will lead to well characterized ongoing sensations (dysesthesias) and exaggerated sensitivity to otherwise innocuous stimuli (e.g., allodynia).[2] Current thinking suggests that mechanical allodynia represents activity in low threshold afferents.[3] The functional mechanisms underlying these pain states are presumed to result from post-injury changes. At a systems level, nerve injury results in increases in ectopic activity from the nerve at the site of injury (e.g., the neuroma) and/or at the dorsal root ganglion (DRG) of the injured axons.[4] Injury produces alterations in dorsal horn excitability, leading to lowered thresholds in dorsal horn neurons and increases in their receptive field size.[5] Several mechanisms have been identified that are believed to underlie these changes.

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Three points should be made: 1) Although understanding the biology of nerve injury can be approached through morphological and biochemical assessments, the role played by those mechanisms in the nociceptor, produced by nerve injury, requires a behavioral correlate reflecting the "pain" state of the organism; 2) when a mechanism is proposed that is believed to underlie neuropathic pain, drugs targeting that mechanism must have corollary effects on the behavior of the animal; and 3) meaningful validation of the preclinical model depends on demonstration of a parallel pharmacology (when possible) with that observed in the human condition. A variety of drug classes have indeed been shown to have efficacy. These include certain anticonvulsants (such as gabapentin),[6] sodium channel blockers (such as lidocaine),[7] and various amine uptake inhibitors, notably those which block norepinephrine and serotonin transporters (such as amitriptilline).[8] Opiates are also used and have reported efficacy.[9,10] In the past several years, many other targets/agents have been implicated, but assertions of their efficacy must be considered, dependent on the still evolving data sets.

The importance of behavioral paradigms in devising targets and specific drugs to act on them in neuropathic pain regulation has led to an increased implementation of behavioral models. In general, the types of nerve injury models can be broadly divided into those that produce a complete or partial physical injury to a component of the

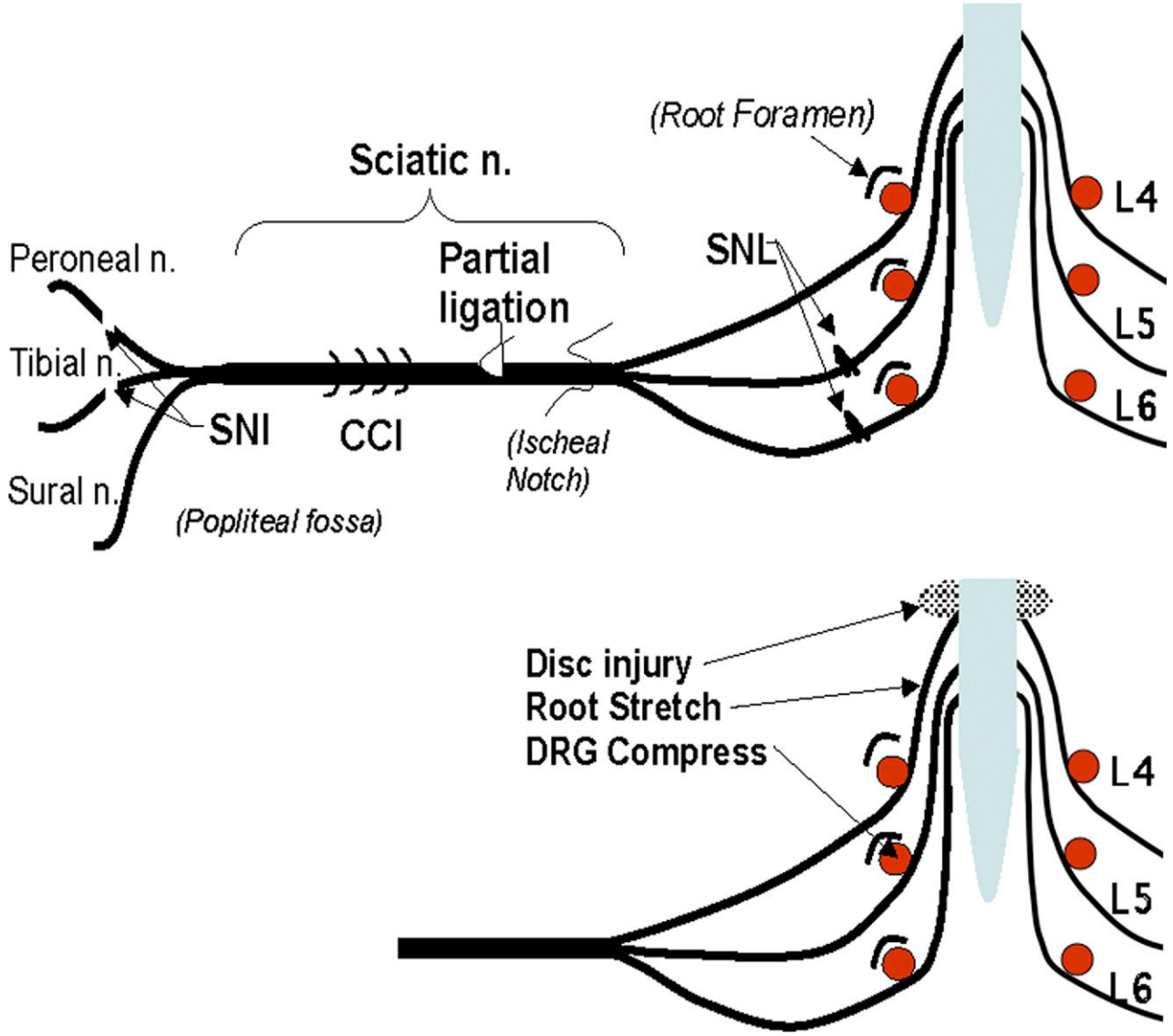

FIG. 1. Schematic summary of several surgical injuries to the peripheral nerve (above) and injuries to the dorsal root ganglion (DRG) and dorsal root (below), which resulted in pathological pain states. CCI = chronic constriction injury; Peroneal n. = peroneal nerves; Sciatic n. = sciatic nerve; SNI = spared nerve injury; Sural n. = sural nerve; SNL = sciatic nerve ligation; Tibial n. = tibial nerve.

peripheral sensory nerve DRG or root. The injury may be induced by mechanical (i.e., section, crush, or compression), chemical, metabolic, or immunological insult directed at some or all of the aforementioned anatomic elements. Because of the breadth of the material, we have limited our focus to those injuries that are generally considered to be peripheral to the spinal cord. It should also be noted that the aim of the present commentary is to consider those reports that seek to establish the treatment as a model. Thus, many interventions have been reported, but at the least, for such a treatment to be considered a model, there should be effort to characterize time course, and, where relevant, elements that impact the expression of the behavioral phenotype. Unfortunately, this is not always appreciated. The impact of a variety of animal (genetic, gender), environmental (stressors, housing, diurnal cyclicity, or presence of investigator), and treatment (diet) variables on the expression of a neuropathic pain phenotype have been extensively reviewed elsewhere.[11–13] In the following sections, we review representative injuries specifically generated by physical trauma to the peripheral nerve. A summary of these interventions is presented in FIG. 1.

NERVE SECTION

In the course of studying regenerating nerves, it was observed that complete lesion of the sciatic nerve during a period of days to weeks would lead to self-injury to the digits and distal extremities, formerly innervated by the

sectioned nerve. Such autotomy has been observed after complete sciatic section,[14] crush,[15] or cryolesions (transient freezing).[16] Trunk lesions have been observed to produce such autotomy in several species. This model was proposed by Wall et al.[14] to be a model of anesthesia dolorosa in man. Complete trunk lesions have been reported to yield other aberrant behaviors targeted at the denervated limb in several species, including the mouse, rat, rabbit, and primate.[17] Importantly, lesions limited to nerve trunk branches, such as the saphenous[18] or the tibial/common peroneal[19,20] fail to produce autotomy. The principle concern from the outset has been the controversy as to whether this self-mutilation is an index of a painful experience or an abnormal sensation (or even a lack of sensation). Although controversial, considerable evidence supports the conclusion that deafferentation yields behaviors that are an index of the degree of dysesthesia that results from limb deafferentation, as reported in humans.[21,22]

Several variables have been shown to influence autotomy after nerve section, including gender (incidence of autotomy is greater in males than in females),[23] strain[24] (autotomy is a single-gene recessive trait[25]), and method of section. Systematic comparison revealed that the lowest incidence of autotomy after sciatic neurectomy was noted after injury with a CO_2 laser, tight ligation, or severance with scissors; comparatively, cryoneurolysis and electrocautery yielded higher autotomy scores.[26]

NERVE LIGATIONS

Currently, the most intensely investigated of the traumatic animal neuropathic pain models are those involving a surgical trauma/ligation of the sciatic, spinal, or peripheral nerves. Axotomy and nerve crush were first used to investigate effects of denervation and neuroma development, but have been gradually superceded by injuries, which only partially denervate the tissue and involve the sympathetic nervous system to some extent. The following sections will discuss the ligation models. An interesting article to be considered is one by Dowdall et al[27] who undertake a concurrent assessment in the same laboratory of several of the models discussed below using a variety of end points.

Chronic loose ligation

The Bennett or chronic constriction injury (CCI) model was the first of these models.[28] Surgical preparation involves placement of loose ligatures located 1 mm apart on the mid-sciatic nerve. Ligatures are tied such that flow through superficial epineural vasculature is reduced, but not eliminated. This procedure results in sciatic nerve swelling, a substantial loss of axons distal to the ligatures and neuroma formation at the level of the ligatures. Nerve swelling and pain behavior are enhanced if the ligatures are chromic gut, as they contribute to the immune component of the neuropathy.[29] There is a major loss of myelinated fibers followed by unmyelinated fibers.[30–32] Loss of myelinated fibers is usually reported to outnumber that of unmyelinated fibers, although both inspection of histology and examination of conduction velocity may have confused demyelinated A fibers with C fibers and thus, inflated their number. Growth cones are present at the level of the ligatures and signs of remyelination and fiber regeneration distal to the ligatures have been reported. In all cases, macrophage infiltration[33] is believed to play a major role in the etiology of the nociception. Variations of the procedure are performed on branches of the trigeminal nerve.[34–36] Pain behavior and electrophysiological changes resulting from CCI have been reported in rats, mice,[37] and subhuman primates.[38]

Thermal hyperalgesia is the predominant presentation of pain behavior, although both mechanical hyperalgesia and cold allodynia are frequent. Bilateral CCI has been used to model cold hyperalgesia.[39] Pain behaviors last between 2 weeks to 3 months, depending on the laboratory,[28,40,41] and was first reported to be exclusively ipsilateral.[42] However, there are now reports of bilateral pathological pain after CCI,[43,44] although initial reports indicated only ipsilateral thermal hyperalgesia. Motor deficits parallel loss of peripheral axons,[45] and motor disturbances and damage to motor axons may extend to the contralateral "noninjured" nerve.[46] CCI clearly interrupts local vasculature and blood flow is reduced between the ligatures; thus, CCI also has an ischemic component.[47] Nerve fiber abnormalities due to ischemia are present within 8.5 h.[48] Femoral artery ligation or stripping of the epineural vasculature alone also results in thermal hyperalgesia.[47]

Several days after ligature placement, sympathetic efferent fibers grow into the DRG,[49] and their terminals surround some neuronal somata in a basket-like structure.[50] This occurs prior to development of pain behavior.[49] Wallerian degeneration and macrophage infiltration are necessary for sympathetic in-growth; manipulations that either block or delay degeneration also reduce both sympathetic sprouting and pain behavior,[51] although this has some modality specificity. Guanethidine treatment reduced cold allodynia and thermal sensitivity, and, to a much smaller extent, mechanical hyperalgesia.[52,53] Pain behavior was first reported to not be influenced by gender,[28] but others have seen evidence of longer lasting thermal, but not mechanical, hyperalgesia in females and castrated males than in intact males rats.[54]

After CCI, there is an early ipsilateral increase in μ-opioid binding in laminae I to II of the dorsal horn and a bilateral increase in laminae V and X. All changes are resolved within 10 days postinjury except for the increase in lamina X. Delta and κ-opioid binding show a

progressive bilateral postinjury decrease compared to basal.[55] Backonja et al.[56] reported that systemic morphine dose dependently reversed thermal hyperalgesia in this model for a 7-day period. This anti-hyperalgesic effect of systemic morphine has been confirmed for cold responses[40] and paw pressure.[57] Systemic administration of μ, δ, and κ opiates is associated with reduction of mechanical hyperalgesia.[57] Interestingly, both μ and κ opiates exert a significant amount of their effects through the peripheral tissue, as injection of receptor specific antagonists into the paw reversed the antihyperalgesia.[58] Notably, touch-evoked allodynia is insensitive to intravenously administered morphine.[59] In parallel, intravenously administered morphine does not reduce light touch-evoked Fos, but does reduce heat activated Fos in the dorsal horn in CCI rats.[59] Intrathecal administration of morphine and oxycodone (κ2b) produce a reversal of tactile allodynia.[60] Intrathecal morphine and DPDPE ([$_{D}$-Pen^{2}, $_{D}$-Pen^{5}]-Enkephalin, a δ opiate agonist), and to a lesser extent U-50 (κ agonist), reversed both thermal hyperalgesia and mechanical allodynia.[61,62]

Pre-emptive treatment of the nerve with lidocaine to block the early injury induced discharge reduces both the duration and magnitude of thermal hyperalgesia.[63,64] Depot placement of bupivacaine around the sciatic nerve prior to injury, such that development of ectopic activity is blocked for several days, totally prevented the development of the pain behavior.[65] Low-dose systemic lidocaine, which achieves plasma levels too low to block nerve conduction, reduces ectopic discharge from peripheral neuroma, DRG, and dorsal horn neurons after CCI.[66,67] Systemic lidocaine effectively reduces cold allodynia and thermal hyperalgesia after CCI, as does its quaternary metabolite, CX-314.[40,68,69] Systemic administration of amiodarone, a longer acting sodium channel blocker, was also effective in blocking mechanical, thermal, and cold allodynia.[70] Spinal lidocaine, at doses that work in a variety of other pain models, has been reported to be without effect.[71] However, Tian et al.[72] have demonstrated efficacy with higher doses, and thermal sensitivity was more sensitive to lidocaine reversal than was mechanical allodynia. In addition to changes in sodium channel sensitivity, the injured nerve develops a P2-receptor mediated sensitivity to ATP.[73]

After CCI in mice, descending noradrenergic innervation of the spinal cord increases.[74] Systemic clonidine is highly efficacious in blocking cold allodynia in this model.[40] Intrathecal tizanidine and other α2 adrenergic agonists[75] are effective in reversing cold and mechanical hyperalgesia[76] and thermal hyperalgesia.[62] Pre-emptive systemic clonidine blocks development of mechanical hyperalgesia,[77] and post-treatment reverses thermal hyperalgesia.[78]

Pre- and post-treatment with systemic nonsedating doses of the dual norpinepherine/serotonin uptake inhibitor venlafaxine respectively blocks or reverses the development of thermal hyperalgesia.[79] Intrathecal milnacipran, a newer reuptake inhibitor, was anti-allodynic.[80] Comparatively high doses of amitriptyline block mechanical hyperalgesia.[81] Intrathecal administration of a chi-conopeptide, Xen2174, reversed mechanoallodynia through a related mechanism as it blocked the norepinephrine transporter.[82] The maximum effect was better than that achieved with morphine.

Partial sciatic ligation

The Seltzer or partial sciatic nerve ligation model of neuropathic pain is achieved by tight ligation of approximately one third to one half of the sciatic nerve at the level of the upper thigh, proximal to the sciatic notch.[83] Variations involving branches of the trigeminal nerve have been successfully developed,[84,85] and the traditional sciatic version is frequently used in mice.[86] The plantar surface of the ipsilateral foot develops guarding behavior, whereas bilaterally there is an increased response to repeated Von Frey hair stimulation, heat, and pin prick, suggesting mirror image pain and a strong sympathetic component. Pain behavior is more intense on the side ipsilateral to the injury,[87] and is said to last for months.[88] Levels of thermal hyperalgesia are quite variable across different strains of rats (e.g., Lewis rats develop disturbances only in mechanical sensitivity,[89] whereas Fischer 344 rats develop only thermal allodynia and hyperalgesia[90]). Large myelinated fibers are believed to mediate mechanical sensitivity, whereas C fibers mediate the thermal component.[91] Accordingly, both extracellular signal-related kinase and Jun N-terminal kinase MAP kinase phosphorylation in astrocytes has been demonstrated in the terminal projection areas of both of these fiber types (i.e., spinal dorsal horn and gracile nucleus).[92] Gender differences play a large role in this model, and female rats have a significantly higher probability of developing pain behavior than males; this propensity is reversed with ovariectomy.[93] The location at which estrogen interacts to cause this enhancement is unknown.

Sympathetic fiber sprouting occurs in both the DRG and, to a greater extent, in the gracile nucleus. In the DRG, basket-like structures encircle neurons with both injured and uninjured axons.[94] Chemical sympathectomy eliminates the mechanical hyperalgesia and α2 antagonists relieve it.[95]

Pre-emptive treatment of the ligation site with lidocaine is ineffective in blocking development of the thermal hyperalgesia.[63] Systemic lidocaine has no effect,[96] but equivalent doses of spinal lidocaine are reported to be effective and greatly outlast effects in the sciatic nerve ligation (SNL) model by days.[96] Intrathecal clonidine is highly effective both as a pre- and post-treatment in relieving tactile hypersensitivity; interestingly, sub-ef-

fective doses of clonidine are combined with spinal cord stimulation to achieve anti-allodynia with a better side effect profile.[97] Perineural clonidine at the nerve injury site prevents upregulation of cytokines, particularly tumor necrosis factor along the length of the neuraxis, and mitigates the mechanical allodynia.[98,99] Tricyclic antidepressants (imiprimine and reuptake inhibitors [paroxetine and milnacipran]) reduce both thermal and mechanical hyperalgesia.[86,100] Amitriptyline is also effective as a post-treatment against thermal hyperalgesia.[101]

Sciatic nerve ligation

The third surgical model of neuropathic pain is the SNL model.[102] The L5 and L6 spinal nerves are tightly ligated just distal to their respective ganglia. Common variations include ligation of only L5, and combining ligation with transection distal to the ligature. All variations are frequently referred to as SNL. The model was first described as having an ipsilateral thermal hyperalgesia lasting more than 1 month and a much longer lasting mechanical allodynia. Guarding behavior develops, which may be indicative of spontaneous pain. Others have described an ipsilateral cold allodynia. More recent articles document a contralateral mechanical and cold allodynia that are delayed and of lesser magnitude than that seen on the ipsilateral side.[103] Ligation of the spinal nerves is more effective in producing allodynia and guarding behavior in young rats than in old or mature animals.[104] Transection of the spinal nerves, in addition to ligation, increases the pain behavior in the older animals.[105] Mechanisms responsible for generation of the causalgia have been debated. One school of thought is that the pain is caused by the intermingling of the injured L5 and L6 fibers, with the intact fibers of the L4 spinal nerve within the sciatic nerve.[106,107] The idea is that macrophage infiltration and local Schwann cell activation release injury factors that are transported retrogradely to the cell bodies of the L4 ganglia. Certainly, the SNL injury results in MAP kinase activation in the L4 DRG, and chemical sensitization and ectopic activation of L4 neurons.[108–110] Transection of the L5 ventral root, which results in Wallerian degeneration of large myelinated axons within the sciatic nerve, also causes allodynia of several weeks duration.[111,112]

Pain behavior resulting from SNL is reported to be sympathetically maintained as surgical sympathectomy permanently and sympathetic block by adrenergic antagonists reversibly causes a cessation of mechanical and cold allodynia.[113,114] In addition, SNL induces sympathetic sprouting into the dorsal root ganglia.[115] However, the sympathetic component of the model has been disputed,[116] and the belief now is that the sympathetic component is influenced by not only the strain, but also, perhaps, by the vendor-dependent substrain.[117] Variables affecting ligation-evoked changes in pain thresholds have included gender. In this respect, autotomy differs from partial nerve ligation-induced neuropathy, because the incidence of allodynia after spinal nerve ligation is higher in female than male rats.[118] However, this observation may be influenced by strain, because female Sprague-Dawley but not Holtzman rats are reported to develop greater mechanical allodynia than their male counterparts.[119]

Systemic, but not local, lidocaine works effectively to reverse tactile allodynia arising from SNL.[120] Systemic administration of fluphenazine, an anti-psychotic that also blocks Na+ channels, reduces ectopic activity in afferent fibers and reverses mechanical allodynia.[121] Strichartz reports that intravenously administered lidocaine produces a partial but permanent reversal (plasma levels, 2.1 ug/mL plasma) of ipsilateral allodynia, whereas lower plasma levels resulted in a temporary reversal only. Contralateral allodynia, in this model, is reversed only acutely by intravenously administered lidocaine at even the highest plasma levels.[87] In contrast to the lack of efficacy of spinal lidocaine on SNL-induced allodynia, reported by Chaplan, spinal mexiletene reduces Aδ and C fiber and von Frey hair-evoked responses in SNL, but not sham animals,[122] and anti-allodynia of spinal lidocaine is reported by others.[96] Interestingly, continuous systemic lidocaine started before the lesion reduces sympathetic sprouting into the L5 DRG.[123] This effect lasted more than a week after cessation of treatment.

Systemic (intraperitoneal) and intracerebroventricular morphine completely reverse mechanical allodynia generated by SNL.[124,125] This has been shown to be specific for the static component of allodynia (maintained application of von Frey filaments) and not for withdrawal evoked by a more dynamic stimulus (stroking with a cotton applicator).[126] In contrast, Kontinen et al.[127] has reported no effect of systemic morphine, administered either pre-emptively or as a continuous post-treatment, on either mechanical or cold allodynia. Intrathecal administration of μ, δ, and κ agonists are reported to be without effect on mechanoallodynia.[125] However, in electrophysiological studies, systemic morphine was less effective than morphine administered via direct spinal application in the inhibition of C-fiber, heat, and mechanical stimulation-evoked activity in dorsal horn neurons[128] and intrathecal administration of morphine has been shown to be effective in reversing mechanical allodynia.[129]

Intrathecal α2 agonists reverse SNL-induced mechanical allodynia.[130] This is substantiated by recent work indicating that intrathecal α2 agonists exacerbate thermal hyperalgesia after SNL.[131] Chronic treatment with the tricyclic antidepressants (desipramine and milnacipran) attenuate mechanical and thermal allodynia.[132,133] Acute treatment with milnacipran is effective in reversing ther-

mal, but not mechanical sensitization.[133] Spinal administration of Xen2174 produces similar results to CCI.

The spared nerve injury[19] model is a lesion of the tibial and common peroneal nerves, but spares the sural nerve. This permits testing of skin containing no injured or degenerating fibers. Thus, it does not result in close proximity of injured and degenerating fibers with intact axons in the periphery, although mixing does occur more proximally in the sciatic nerve. The spared nerve injury model produces an increased ipsilateral response to mechanical (both low- and high-threshold) and thermal (hot and cold) stimuli within the sural distribution, and to a lesser extent within the saphenous veins, which lasts more than 6 months.[19] The mechanical allodynia is more prominent in hairy skin.[129] Strain differences influence the extent of the pain behavior (Lewis rats are least affected), but all strains exhibit mechanical sensitivity.[134] Late sprouting of sympathetic fibers into the DRG is documented at 8 weeks post-injury, resulting in basket structures around the neuronal stomata.[94,135] Surgical sympathectomy has no effect on either mechanical allodynia or hyperalgesia,[135,136] but greatly attenuates the cold allodynia.[136]

Systemic morphine dose dependently reduces mechanical allodynia and hyperalgesia, as well as cold allodynia.[129,134,137] Spinal morphine is also effective in blocking mechanical allodynia.[129,134] However, Decosterd et al.[138] found that systemic morphine, amitriptyline, and carbamazepine produced only modest reversal of mechanical and cold allodynia.

Early and sustained blockade of peripheral nerve activity with bupivacaine for 1 week or more does not block development of spared nerve injury; this points to an initiating mechanism other than an afferent barrage of neural activity.[139] In rats, systemic administration of lidocaine and lamotrigine, as well as moderate doses of tocainide (50 mg/kg), has no effect of mechanical or cold allodynia or mechanical hyperalgesia; however, higher doses of tocainide (75 mg/kg) and mexiletine (37.5 mg/kg) successfully reverse sensitivity to both mechanical and cold allodynia.[140,141] Lamotrigine (30 and 60 mg/kg) and tocainide (50 and 75 mg/kg) are both able to reverse mechanical hyperalgesia.[141] Systemic fluphenazine attenuates tactile allodynia and blocks ectopic discharge in primary afferent fibers, presumably through its ability to block Na^+ channels.[121]

PLEXUS AVULSION

Plexus avulsions are surprisingly common after upper torso injuries and typically result in severe pain states.[142] Unilateral avulsion of the brachial plexus in male Wistar rats produced a long-lasting (through 90 days) bilateral cold and mechanical allodynia with no change in locomotor activity.[143] In subsequent work, this group reported that systemic morphine, clonidine, ketamine, or gabapentin reduced both mechanical and cold allodynia. Celecoxib blocked mechanical allodynia, but not cold allodynia, whereas lidocaine attenuated only cold allodynia. Diclofenac, dexamethasone, or imipramine had no effect.[143]

Nerve ischemia models

There are several models of nerve ischemia generally performed on the sciatic nerve. Wiesenfeld-Hallin and colleagues developed an interesting version of photochemically induced ischemia on the rat[144–146] and mouse[147] that involves intravenous injection of erythrosine B, a photosensitizing dye, followed by exposure of a length of the sciatic nerve and irradiating it with an argon ion laser for a proscribed period of time. This results in long-lasting (up to 28 days for some modalities) bilateral mechanical and cold allodynia and unilateral thermal hyperalgesia. In general, ipsilateral pathological pain behavior was of greater magnitude than contralateral, and the onset was faster. Approximately 95% of the animals develop pathological pain. Rats, but not mice, display signs of spontaneous pain.[146,147] Damage to myelinated axons and Wallerian degeneration in ipsilateral nerve is extensive, accompanied by macrophage infiltration and phagocytosis of Schwann cells. Normal Remak bundles of unmyelinated axons are disturbed with only isolated axons remaining. The contralateral nerve displays no axonal injury or immune cell infiltrate. Despite the fact that the extent of sciatic nerve damage is the same after focal ischemia in several strains of rat, genetic strain greatly affects development of pain behavior.[148] Extent of nerve injury and behavioral abnormalities are dependent on the duration of exposure to the laser.[146] After resolution of pain behavior, all fiber types regenerate.[149] Spinal morphine dose dependently inhibits mechanical and cold allodynia, and spinal clonidine reverses hypersensitivity to cold but not mechanical stimulation.[145]

A major variation of sciatic nerve ischemia is hindpaw ischemia and reperfusion. This induces long-lasting bilateral mechanical allodynia and hyperalgesia, as well as sensitivity to cold.[150] Mechanical allodynia in this model within a few days of the injury can be reversed by systemic administration of sympathetic antagonists, such as guanethidine, phentolamine, clonidine, and prazosin.[151] These treatments become ineffective several days after the insult.

INJURY TO THE DRG

In humans, herniated discs or spinal stenoses, which compress the adjacent root and DRG, can evoke paresthesias and leg pain.[152] Mechanisms underlying this pain state are complex, but reflect the mechanical and chemical sensitivity of the DRG. Thus, the DRG, unlike the

peripheral axon, has the ability to respond in a graded fashion to mechanical distortion and to display persistent activation secondary to the local release or application of a variety of pro-inflammatory chemicals, such as prostaglandins, kinins, amines and cytokines. Compression injury of the DRG leads to ongoing ectopic activity.[153–155] Similarly, avulsion of the disc can lead to the local release of disc products from the injured disc. Application of nucleus pulposus products will initiate discharge in the DRG. Furthermore, studies specifically examining delivery of a pro-inflammatory product to the previously compressed DRG yield an enhanced electrophysiological response in DRG neurons.[156]

Compression of the DRG/root

Metal rods placed into the intervertebral foramen at L4 and/or L5 produced a thermal hyperalgesia and cold and tactile allodynia during an extended 35-day postoperative period. The tactile allodynia corresponds with the ability of a cotton wisp to evoke a reflex withdrawal of the hind paw. Sham surgeries were without persisting effects.[157,158] Both unilateral and bilateral effects have been reported. An alternate method is to use an epidural catheter and a nylon rod.[159] The spontaneous activity of injured DRG cells is blocked by gabapentin without interrupting spike transmission.

LAMINECTORY

After laminectomy, pain of the lower back along with sciatica is frequently noted. In rats, a lumbar laminectomy resulted in 8 weeks of paraspinous muscle spasm, tail contracture, pain behavior, and tactile allodynia. These observations correlated with epidural and nerve root scarring, and nerve root adherence to the associated disc and adjacent pedicle.[160]

DISC INJURY

Annular tears in an intervertebral disc have been found to correlate with low back pain in human patients.[161,162] The mechanism of this pain state is not certain. Annular injury may reflect activation of local sensory receptors in the annulus or the sprouting of sensory axons into the disc. Puncture of the L4 to L5 discs resulted in increases in defined pain behaviors, including "grooming" and "wet-dog shakes."[163,164] Consistent with the role of active factors arising from the ruptured disc, a behavioral model has been developed wherein autologous nucleus pulposus is placed onto the L5 DRG exposed by unilateral facetectomy. This treatment resulted in marked ambulatory asymmetry and a preference to bear weight on the contralateral limb at extended intervals after treatment.[165]

CONCLUSION

In the past 30 years, it has become increasingly appreciated that mechanisms underlying pain states associated with nerve injury (e.g., painful neuropathies) may well mediate a variety of pain states arising from a wide variety of stimulus/treatment conditions. Thus, it is appreciated that frank nerve injury will lead to a variety of changes in the biology of the dorsal root ganglion cells of the injured axon, such as, for example, an increase in the expression of DRG activation transcription factor-3.[166] In this regard, changes in DRG activation transcription factor-3 expression have been observed not only after nerve section and compression, but after chemical stimuli (paclitaxel[135]), in diabetes,[167] and even in some peripheral chronic inflammatory syndromes as diverse as equine laminitis.[168] It is thus reasonable to expect that many of these chronic states may lead to changes in nerve function that lead to the encoding of a nociceptive signal.

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