

Common animal models for spasticity and pain

Mary Eaton, PhD

Veterans Affairs Rehabilitation Research and Development Center of Excellence in Functional Recovery in Chronic Spinal Cord Injury, Veterans Affairs Medical Center, Miami, FL; The Miami Project to Cure Paralysis, University of Miami School of Medicine, Miami, FL

Abstract—Animal models of spasticity and pain have allowed for the elucidation of possible mechanisms and the evaluation of potential therapeutic interventions for these serious clinical problems. Each model mirrors the clinical appearance of many features of the syndrome, but few reproduce the myriad patient reports of either intensity or relevant contributing factors, especially in models of chronic neuropathic pain. Often these models have been used to predict the potency and efficacy of pharmacologic agents that work in human pain states. Pain models have relied on measurements of the shifts in behavioral hypersensitivity to tactile and thermal stimuli, tests that are not used quantitatively in human patients. Even with the multiple peripheral and central models of spasticity and pain used in animals, only a few actually test human conditions: namely, diabetic neuropathy, chemotherapy, and immunotherapy for tumors. However, all these models have allowed for the comparison of certain behavioral, cellular, biochemical, and molecular mechanisms with human patient populations. Here we review the few extant models of spasticity, nerve injury, and central injury models of pain, and describe their features and use.

Key words: allodynia, cell therapy, hyperalgesia, partial nerve injury, sacral transection.

INTRODUCTION

Despite improvements [1–3] in surgical management, physical therapy, and the availability of pharmacological agents with a variety of delivery systems, many patients [4–6], following peripheral and central neural

injuries, continue to suffer from intractable chronic pain and spasticity [7,8]. Although opioids are the most commonly used agent for the control of pain, only about 32 percent of patients receive any significant relief with long-term use [9]; moreover, long-term use often leads to untoward effects associated with tolerance, tolerability,

Abbreviations: CCI = chronic construction injury, CNS = central nervous system, EMG = electromyographic, GD2 = gangliocide, GABA = gamma-aminobutyric acid, IASP = International Association for the Study of Pain, MC = Medical Center, NMDA = N-methyl-D-aspartate, NO = nitric oxide, NSAID = nonsteroid anti-inflammatory drug, PNS = peripheral nervous system, QUIS = quisqualic acid, rCBF = regional cerebral blood flow, RR&D = Rehabilitation Research and Development, SCI = spinal cord injury, SP = substance P, STZ = streptozotocin, VA = Veterans Affairs, WDR = wide dynamic range.

This material was based on work supported partially by the Center of Excellence in Functional Recovery in Chronic Spinal Cord Injury, Veterans Affairs Medical Center, Miami, FL; the Veterans Affairs Rehabilitation Research and Development Merit Review; The Miami Project to Cure Paralysis, University of Miami School of Medicine, Miami, FL; the Spinal Cord Research Foundation; and the American Syringomyelia Alliance Foundation.

Address all correspondence and requests for reprints to Mary J. Eaton, PhD; Veterans Affairs Rehabilitation Research and Development Center of Excellence in Functional Recovery in Chronic Spinal Cord Injury, Veterans Affairs Medical Center, 1201 NW 16th Street, Miami, FL 33125; 305-243-7136; fax: 305-243-3923; email: meaton@miami.edu.

drug diversion, and other side effects [10], including opioid-induced neurotoxicity. Nonopioid medications can attenuate some types of neuropathic pain, but seldom remove the painful sensation completely [11]. The recent attempts at classification of neuropathic, nociceptive, and other pain, aided by an International Association for the Study of Pain (IASP) taskforce [12,13], have been of help to understand mechanisms and to improve and devise better treatments for chronic pain. Similar descriptions of the etiology and management of spasticity [14–16] have allowed for reasonable predictions of possible mechanisms and research directions [17] for basic and clinical studies. But without adequate or successful clinical trials to advance treatment options for these problems, especially for chronic neuropathic pain [11], the development and use of animal models, and the need to translate interventions to clinical trials, is driving new interest in more sophisticated techniques for these problems [18–27]. Some of these new interventions include *ex vivo* and *in vivo* genetic and viral enhancement of the damaged peripheral nervous system (PNS) and central nervous system (CNS), as well as techniques for gene knockout in mouse lines [28,29].

ANIMAL MODELS FOR SPASTICITY

Following spinal cord injury (SCI), spasticity is a common problem in both the nonveteran [30] and veteran [31] populations, but robust spasticity has been difficult to reproduce in animal models, such as the SCI cat [32–34] or rat [35–37]. Without complete spinal transections, animals recover most motor function, a situation not seen in humans, where even partial spinal lesions often lead to chronic spasticity [38]. However, complete transection results in an animal that requires at least daily bowel and bladder expression, and often results in myriad postsurgical complications and morbidity, such as autonomic dysreflexia, cystitis, skin and gastric lesions, and autotomy [39–42]. Studies with the rat as the model animal have usually involved hemisections, partial transections [36], or contusion injuries [37], all injuries similar to those used in studies of spasticity in the cat [32–34, 43].

Only complete spinal transection in animal models would duplicate completely and permanently what is seen in humans after SCI, but bowel and bladder dysfunction, as well as gait abnormalities, are difficult to manage long-term. The earliest use of complete transection of the

spinal cord as a model of spasticity that resulted in intact bowel and bladder function and hindlimb gait and reflexes has been used in the sacrocaudal transection in the cat [44]. After Ca1 spinal transection, tail muscle function is diminished, and the tail becomes ventroflexed in a midline position and exhibits spasticity (i.e., hypertonia, hyperreflexia, and clonus) that remained permanent for at least three years in most animals. Also following transection is exaggerated flexion reflex to cutaneous stimulation of the tail. Although it offers many advantages for the health and well-being of a large animal and the potential to develop a quantitative measurement to test reparative strategies, this cat model does not allow any investigation of spinal control of limb movements, an important correlate of paralysis in humans. However, this model is a significant improvement over spasticity hemisection studies from the same laboratory [43], in which electrophysiologic measurements were significantly linked with behavioral observations of spasticity.

More recently, a similar sacral transection for the development of spasticity was developed in a rat model [45]. Again, this S2 spinal transection affected only the tail musculature, and otherwise was minimally disruptive to normal functions, not interfering with bowel, bladder, or hindlimb locomotor function. After spinal transection, initially the tail musculature was paralyzed for two weeks, followed by increasing hypertonia, hyperreflexia, and clonus that developed over weeks and remains permanent in tail function (easily assessed in the awake rat). Muscle stretch or cutaneous stimulation of the tail produced muscle spasms and marked increases in muscle tone, measured with force or electromyographic (EMG) recordings. Spontaneous or reflex-induced flexor and extensor spasms are readily seen in the unconstrained tail. The tail and surrounding area, including the skin and hair, develop thermal hyperalgesia and tactile allodynia, suggesting a variety of sensory disturbances, features that often accompany spasticity in at- or below-level spinal injury in humans [13], including the development of chronic pain. Such behaviors are only now being quantified in this model.

Such a preparation has also been used to examine the nature of the change in intrinsic excitability in motoneurons with sustained tail motor unit firing in unanesthetized, chronically spastic rats, examined *in vitro* [46] and *in vivo* [47]. In the absence of descending monoaminergic brainstem facilitation and inhibition in this complete transection, these sacrocaudal motoneurons develop

prolonged, often spontaneous, responses that contribute to exaggerated long-lasting reflexes and spastic behaviors, without the normal inhibitory control to turn off sustained firing. Such studies, with an easily handled, surviving animal that develops permanent spasticity, will provide considerable insight on the nature of the differences in inhibitory, as well as excitatory, control of motoneurons in intact versus spinal states.

ANIMAL MODELS FOR PAIN

Treatment of sensory neuropathies that result in chronic pain, whether inherited [48] or caused by trauma [49] or the progress of diabetic [50] or other disease states [51,52], is one of the most difficult problems in modern clinical practice. Its prevalence has been conservatively estimated at 0.6 percent of the U.S. population [53]. To the extent that low-back pain is sometimes neuropathic, the actual figure might be far higher. Neuropathic pain might realistically affect 1.5 percent of the total population nationwide, and current treatments often prove ineffective, or at least must be administered at impractical dose levels, such as those seen with morphine or its analogues [54]. Neuropathic pain, the most common chronic pain with SCI, results from the abnormal processing of sensory input due to damage to the nervous system. Of the greater than 250,000 SCIs in the United States, at least 22 percent of these are veterans. Review of clinical data suggests that greater than 65 percent of SCI persons develop intractable pain, adding a significant patient care burden to VA and other medical centers.

The neuropathic syndrome has a multitude of possible causes [55], making both diagnosis and eventual treatment difficult with such a heterogeneous patient population. Clinical classification schemes [51] that group the asymmetrical and symmetrical types, such as diabetic or post-traumatic and metabolic or immune-mediated types, depend on presumed etiology for classification. However, it has been difficult to (1) identify a common cause of pain among the different conditions and (2) explain why symptoms within an etiologically defined population of patients can be extremely diverse. Therefore, another classification can be made to identify distinct symptoms and tailor treatments based on the assumption that each sensory abnormality is related to pathophysiological changes in the PNS or CNS [56].

Current and developing treatment strategies for neuropathic pain are based on principles elucidated in recent research, especially concerning “central spinal sensitization” after nerve injury, and the spinal mechanisms that are thought to be the origin and ongoing cause of persistent pain [57], even when the injury is peripheral in location [58]. For example, persistent, small afferent input, as generated by tissue or nerve damage, results in a hyperalgesia at the site of injury and a tactile allodynia in areas adjacent to the site. Hyperalgesia is the result of sensitization of the peripheral terminal and a central, or spinal, facilitation evoked by persistent, small afferent input. The allodynia reflects a central sensitization, with excitatory neurotransmitter (e.g., glutamate and substance P) release initiating a cascade of downstream events, such as release of nitric oxide (NO) and various cyclooxygenase (COX) products, and activation of several key kinase enzymes. Specific receptors mediate the initial events, namely through the N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors and neurokinin 1 substance P (SP) receptors. Specific activation of these receptors enhances prostaglandin E₂ release, which in turn facilitates further release of spinal amino acids and peptides. Activation of specific receptors (μ/δ opioid, α^2 adrenergic, neuropeptide Y) on spinal C fiber terminals prevents the release of primary afferent peptides and spinal amino acids and blocks acute and facilitated pain states. On the other hand, glutamate receptor antagonists and COX-2 and NO-synthase inhibitors only act to diminish hyperalgesia. Spinal delivery of some of these agents diminishes pain in injured humans [59,60], suggesting that such preclinical mechanisms may reflect the induction of some types of neuropathic pain [61].

Animal models have been used extensively in basic pain research based on the premise that these models can serve as surrogate assays that can reliably predict the potency and efficacy of the pharmacologic action of, and, in some cases, the molecular response to, agents that work in human pain states [62]. But in contrast to the polymorphic nature of pain that is described as a sensation in humans, pain in animals can best be estimated only by examining their reactions to various chemical, thermal, and mechanical stimuli, with the latency or nature of response altered in the “pain” state. In an early review, Beecher cited 60 original publications in 1957 [63] that related to the description, development, and application of experimental tests of pain in animals. By 1999 [64], more than 425 reports were published. If the

tests are divided into acute, tissue injury, nerve injury, and central injury models, the reports published up to 1999 represent only the acute and tissue injury models; of these, the tail-flick and hot-plate tests remain the most commonly used. There has been a progressive increase in publications since 1970 on the use of the formalin model and the various tests that involve withdrawal of the paws from mechanical stimuli, or tactile allodynia [64]. This certainly reflects the heightened interest in understanding the mechanisms of pain and the need to have reliable methods to test interventions preclinically in rat models.

One easy way to describe and delineate the great variety of animal models for pain would be to separate them by differences in the stimulus required, the time course of development of the injury or response, and identification of the afferent nociceptive fibers or spinal or supra spinal systems involved (if known) [62,64,65].

Short-Duration Stimuli Tests (Acute Phasic Pain)

Acute tests, such as hot-plate, tail-flick, and paw-pressure tests, require a high-intensity stimulus (such as thermal, mechanical, or chemical) and do not test a preinjured animal. The response measured (1) is immediate (or within seconds), (2) uses the A δ and C-fiber input, and (3) is known to activate the spinal dorsal horn, the cells of which are nociceptive-specific and/or wide dynamic range (WDR) neurons. In addition, the response is proportional to the frequency of stimulus and the fiber class of afferent input.

Some of these acute tests are based on the use of thermal stimuli, such as the tail-flick test, which uses a radiant heat source and an automated timer to determine the withdrawal time of the tail [66]. A variation of this test increases the area of stimulation and, rather than aiming a hot stimulus at the base of the tail, requires a complete immersion of the animal's tail in hot water [67]. Such thermal tail-flick tests are most widely and reliably used for revealing the potency of opioid analgesics, useful for predicting analgesic effects in humans [68]. Another acute pain test that uses a thermal stimulus is the hot-plate test, in which a rat or mouse is placed in an open-ended cylindrical space with a floor capable of being precisely heated [69]. The plate floor, heated to a constant temperature, produces two responses, measured in terms of their reaction times: paw licking and jumping/lifting. Both are considered supraspinally integrated responses. Such "chaotic defensive movements" are complex in the rat (compared with the mouse), making

observation and identification difficult. Thus, this can be a very inconsistent test to use.

The paw-pressure, or mechanical hyperalgesia, test uses a pressure of increasing intensity applied to a punctiform area on the hindpaw or, far less commonly, on the tail. In practice, the paw or tail is placed between a plane surface and a blunt, plastic-coated point mounted on top of a system of cogwheels, with a cursor that can be displaced along the length of a graduated beam [70] for an automated readout. The application of increasing pressure is interrupted when the animal removes its tail, an action that is read out as force in grams for the threshold of response. However, the intensity is difficult to measure reproducibly, and is more often used when the paw is injured beforehand, by inflammation or nerve injury; then the threshold is compared to the noninjured paw [71].

Long-Duration Stimuli Tests (Tonic Pain)

These tests use an irritant, foreign chemical agent as the nociceptive stimulus. They differ from most other pain tests in that (1) they do not measure a threshold response; (2) they quantitatively measure the resulting behavior after the stimulus, which varies in potency with time; and (3) they are not models of chronic pain, since the duration of the behaviors is short, usually minutes or tens of minutes. Hence, long-duration stimuli tests are considered models of tonic pain. They are usually based on intradermal or intraperitoneal injections of the agent.

Closely related are the weeks-long, chronic inflammatory pain models that use the intracapsular administration of urate crystals, Freund's adjuvant, capsaicin, or carrageenin [72–74]. Such long-term tonic pain in rats has been used to model human arthritis and to examine the safety and efficacy of various nonsteroid anti-inflammatory drugs (NSAIDs) [75], including the COX-1 and COX-2 inhibitors commonly used by patients for inflammatory pain [76].

Intradermal Injections

Formalin, a 37 percent solution of formaldehyde, is the most commonly used agent for intradermal paw injection (the formalin test) [77]. Other agents less commonly used are hypertonic saline [78], Freund's adjuvant [79], ethylene diamine tetra-acetic acid [80], capsaicin [81], or bee sting [82].

A 0.5 to 15 percent solution of formalin (usually about 3.5%) injected into the dorsal or plantar surface of the rat fore- or hindpaw produces a biphasic painful

response of increasing and decreasing intensity for about 60 min after the injection. Typical responses include the paw being lifted, licked, nibbled, or shaken [82]; these responses are considered nociceptive, since formalin predominantly evokes activity in C fibers, and not in A δ afferents [77]. The initial phase of the response, which lasts 3 to 5 min, is probably due to direct chemical stimulation of nociceptors [83]; this is followed by 10 to 15 min during which animals display little behavior suggestive of nociception. The second phase of this response starts about 15 to 20 min after the formalin injection and lasts 20 to 40 min, initially rising with both number and frequency of nociceptive behaviors, reaching a peak, then falling off. The intensities of these nociceptive behaviors are dependent on the concentration of formalin used, and the second phase involves a period of sensitization during which inflammatory phenomena occur. These inflammatory phenomena are possibly a result of central processes triggered by the neuronal activation during the first phase, since glutamate NMDA receptor antagonists significantly and dose-dependently reduce nociceptive activity during the second phase of the formalin test when they are given before the formalin [84].

A few approaches have been used to compute a composite pain score that is weighted according to the time spent in each behavioral category—for example, per 5 min interval over 60 min after injection [85]. This method and its modifications are all based on the concept that the different behaviors express degrees of a single nociceptive experience, and can be expressed as a single number, or pain score. In rats, other behaviors, such as flinching or jerking of the injected paws, have also been quantified; but scoring these common behavioral responses becomes more difficult in mice, due to rapid movements in these animals. Again, scoring of the time spent licking, or licking and biting, the injected paw is the most common method of behavioral assessment in mice [86].

Opioid analgesics provide analgesia for both phases of the behavioral response (but the second, delayed phase is more sensitive), while agents such as NSAIDs only suppress the second phase [87]. Thus, the formalin test is best used to examine opioid mimetics.

Intraperitoneal Injections of Irritants (“Writhing Test”)

Intraperitoneal injection of agents (originally phenylbenzoquinone) that are irritating to serous membranes provokes a stereotypical behavior in rodents that is

characterized by abdominal contractions, whole body movements, contortions of the abdominal muscles, and reduced motor activity and incoordination. In this test, commonly called the “writhing test,” the behaviors are considered reflexive, and are evidence of peritoneovisceral or visceral pain associated with visceral chemoreceptors [88]. Unfortunately, the frequency of cramps decreases spontaneously with time to such an extent, and with such variability, that is difficult to evaluate the effect of an analgesic on the behaviors of any single animal [89]. Even with multiple modifications in the nature of the chemical irritant used, the concentration, temperature, and volume of the injectant, and other modifications to simplify the test and measurements of behaviors, the test lacks specificity, because these tests work so well for all major and minor analgesics [89], as well as nonanalgesic substances such as muscle relaxants. Even with poor specificity of action, the writhing test can predict effective analgesic doses for agents that can be used in humans [90].

Peripheral Nerve Injury Tests

A variety of pain models have been developed that use an injury to a peripheral nerve, such as the sciatic nerve, to produce temporary or permanent behavioral hypersensitivity, such as tactile allodynia or thermal hyperalgesia. This hypersensitivity develops over several days after the injury and can lead to chronic pain [91]. Injuries include partial constriction [92–95] or complete transection [96] of the nerve, freezing [97], and metabolic (streptozotocin (STZ)-induced diabetes [98]), chemical (vinca alkaloid [99]) or immune (anti-ganglioside (GD2) antibody [100]) insults. Allodynia is the abnormal response, and change in threshold, to nonnoxious stimuli, such as tactile stimulation with von Frey hairs. Hyperalgesia is a decrease in the latency of response to normally noxious stimuli, such as radiant heat delivered with an automated Hargreaves device [101]. When the injury is to the sciatic nerve, the animal’s hindpaw is used for these behavioral tests. Often contralateral paws are tested as the control for unilateral injury, but the inherent assumption for this approach is that spinal or supraspinal mechanisms are not globally affected by a unilateral injury, which is often not based experimentally.

Partial nerve injuries, such as unilateral loose ligation or chronic constriction injury (CCI) of the sciatic nerve, result in the animal persistently holding the ipsilateral hindpaw in a guarded position. Depending on the tightness

of ligation, the allodynia and hyperalgesia can resolve in about 8 weeks [92], or it may persist for many months. Bennett originally reported [92] that this model likely involved the presence of spontaneous pain, since appetite was suppressed and spontaneous nocifensive behaviors frequently occurred, but such nonevoked behaviors are neither common nor easily measured. This model has been used for a great number (>300) and variety of studies since its first description, to examine both the development of spinal and supraspinal sensitization following CCI [102–105] and its genetic basis [106–109], as well as to examine a number of potential therapeutic interventions [19,110,111] for the partial nerve-injury-related pain.

Similar to the CCI model are the Seltzer [94] and Chung [93] models of tight ligation of parts of the sciatic nerve closer to the dorsal root or the L5 root alone, respectively. Each model produces reproducible tactile allodynia and thermal hyperalgesia, usually with early onset of symptoms and long-lasting behavioral hypersensitivity to tactile stimulation (>10 weeks). In addition, unilateral tight ligation of about half of the sciatic nerve in rats (Seltzer model) rapidly produces sympathetically dependent neuropathic pain that lasts many months and resembles causalgia in humans. When sympathectomy is performed, by removing the sympathetic chain bilaterally from the L2 to L6 levels after nerve injury in the Chung model [112], it relieved both tactile allodynia and thermal hyperalgesia, suggesting that these sciatic ligation models of nerve injury are sympathetically maintained.

Complete transection of a peripheral nerve, such as the sciatic, invariably leads to tactile allodynia and thermal hyperalgesia, as well as autotomy, excessive self-grooming that leads to bite wounds and self-amputation of digits [96]. Even with some controversy, which questions whether autotomy behavior is a sign of pain, excessive grooming and autotomy following a nerve lesion are now considered to reflect neuropathic pain following a nerve lesion [113]. Both autotomy and vocalization behaviors are considered signs of severe pain following nerve deafferentation and have been used commonly in the earliest studies of these injuries [92,96,114–116]. More recently, vocalization response to noxious stimulation and various nerve injuries has been used to index the response of the animal to analgesics, such as morphine [117,118] and other agents [104,119,120].

Sciatic cryoneurolysis [97] results in behavioral outcomes unique to this injury: namely, long-lasting expression (>10 weeks) of tactile allodynia, the complete absence

of thermal hyperalgesia, increased frequency of severe autotomy, and pale eye syndrome or loss of retinal color, associated with heightened sympathetic efferent activity [121]. The development of thermal hyperalgesia requires partial freeze lesions, with some surviving nerve fibers [122]; tactile allodynia behaviors are not sympathetically mediated [123]; and, autotomy severity is greater in male animals [124].

Three recent nerve injury models reproduce the development of certain types of neuropathic pain in humans: diabetic neuropathy (STZ-induced diabetes [98]), chemotherapy-induced neuropathy (vinca alkaloid [99]), and oncology-related immunotherapy (anti-GD2 antibody [100]). STZ can induce diabetes mellitus in experimental animals through its toxic effects on pancreatic beta cells, where a single dose (50 mg/kg, i.p.) leads to the development of allodynia within 10 days [125]. Mechanical hyperalgesia (paw pressure) is the most commonly reported outcome to STZ injections, and this model for painful diabetic neuropathy has been used to examine the effectiveness of analgesics such as morphine [98], as well as to elucidate the cellular mechanisms involved [102].

Another clinically relevant peripheral nerve model of pain follows the injection of the chemotherapeutic agent vincristine [99]. A daily dose of 100 μ g/kg given for two weeks results in potent tactile allodynia and thermal hyperalgesia that begins after the second day. Morphine is ineffective for controlling this type of pain. The recovery from symptoms is often incomplete, and a long period of regeneration is required to restore function. No medication is available to reliably prevent or cure chemotherapy-induced neuropathy [126]. The management of pediatric neuroblastoma has used systemic infusion of a human/mouse chimeric anti-GD2 antibody, which unfortunately causes severe pain, often controlled with high doses of morphine. Monoclonal antibody treatment is represented in a similar animal model [100], where GD2 antibody infusion leads to quantifiable allodynia, with no thermal hyperalgesia. It is likely that the antibody reacts with an antigen on a peripheral nerve and/or myelin to initiate its effect [127]. Both lidocaine and gabapentin, tested in this model, may also be useful to treat this type of pain [128,129].

Central Pain Models

The clinical presentation of chronic pain, particularly after SCI, is common but underreported, especially among

SCI persons; and chronic central neuropathic pain has proven difficult to treat. Neuropathic pain is the most common type of chronic pain with SCI [130,131], with 30 to 70 percent of patients developing at least moderate central pain. Such pain results from the abnormal processing of sensory input due to damage to the CNS. Nociceptive pain associated with SCI is (1) either musculoskeletal or visceral and located in those associated structures; (2) usually described as dull, aching, movement-related, and eased by rest; and (3) often relieved by opioids or NSAIDs [14]. A specific stimulus or cause of neuropathic pain is often difficult to identify, and this type of pain is notoriously unresponsive to conventional methods of pain treatment. SCI pain (also called central, dysesthetic, or diffuse pain) is neuropathic pain at or below the level of injury and is often diffuse and poorly localized. At-level neuropathic pain is referred to dermatomes near the spinal injury site and is usually present from the time of injury or soon thereafter. Below-level pain gradually develops after SCI and is referred to dermatomes below the level of injury. In animal models of central pain that depend on evoked nociception after SCI, allodynia and hyperalgesia are dependent on direct observation and measurement of nocifensive behaviors, such as withdrawal of a stimulated limb or tail. However, in humans, especially those with below-level pain after complete spinal transection, there can be a dissociation between reported chronic pain and elicited nociception [132], so animal models that use limb withdrawal to tactile or thermal stimuli must be interpreted with caution [133].

At-Level Models of Central Pain

As reported in humans after SCI, abnormal sensations and dysesthesias are common features of pain [134], and in animal models of central pain, overgrooming and/or autotomy reflects the presence of abnormal sensations and is regarded as an indication of dysesthesia/pain [133,135].

One of the earliest spinal models of central cord damage that produces neuropathic pain behaviors is the ischemic model. This model uses focal laser lesions of spinal vessels, where there is an acute period of hypersensitivity and tactile allodynia, associated with reduced gamma-aminobutyric acid (GABA) inhibition (a decrease in GABA synthesis in the dorsal horn [136]), which is insensitive to intrathecal morphine [137].

More recent and commonly evaluated regeneration models of SCI—namely, weight-drop contusion and

complete transection—are relatively difficult to use for the study of behavioral hypersensitivity, such as allodynia and hyperalgesia, given the variability in outcomes. However, contusion injury and central cord lesions have demonstrated lowered thresholds for nocifensive behavior with stimulation of at-level dermatomes and tactile allodynia in skin responses [138,139], and in a few cases, use of paw withdrawal responses or vocalization to paw pressure in a moderate contusion [139–141]. Both contusion and transection have better used biochemical and electrophysiologic methods to assess markers of at-level neuropathic pain [41, 142–145]. In addition, changes in supraspinally mediated behaviors, such as activity levels and exploratory behaviors, have been linked with moderate contusion spinal injury [146] and are relevant to similar reports of decreased activity with pain after human SCI [147]. In an unusual animal model that combines both moderate contusion and complete spinal transection [41], electrophysiologic recording of dorsal neurons immediately rostral to the injury demonstrated that the SCI caused abnormal discharge frequency with mechanical stimulation, in addition and related to autotomy and excessive grooming, the onset of which was delayed.

A useful model of neuropathic pain following SCI is the recently described focal chemical lesion of the cord following injection of a glutamate receptor agonist [131,148,149]. This model not only allows for quantitative assessment of behavioral hypersensitivity after injury but, with focused spinal microinjections of the excitotoxic agent, also permits an investigation of the cellular mechanisms in the cord that might be associated with the onset of that pain. As well, this excitotoxic SCI pain model has been used to evaluate the effects of cell transplantation of primary adrenal chromaffin tissue to reverse the chronic behavioral allodynia and hyperalgesia [150] that chemical lesioning of the dorsal horn pain processing centers produces. The model makes use of intraspinal injection of the glutamate receptor agonist, quisqualic acid (QUIS), just above the lumbar segments that control sensory function in the hindlimbs, which leads to a predictable and quantifiable temporal profile of pain behaviors, without the complications of a loss in motor systems, paralysis, or loss of bowel and bladder function [148]. Typical with this model is tactile allodynia and thermal hyperalgesia, with the development of progressive, severe grooming behaviors in the dermatomes associated with the QUIS injection. Most

animals require euthanasia within 30 days of the lesion. However, as with this model, the spread of secondary injury over time to spinal segments rostral and caudal to the injury site is critical to the nature and distribution of SCI pain [151]. With the addition of kaolin to QUIS injections, this is also a reproducible model for progressive syringomyelia and pain after SCI [152], where arachnoiditis is also a feature.

Below-Level Models of Central Pain

Lesions of the anterolateral column in monkeys and rats result in overgrooming and autotomy caudal to the lesion [153,154], with deafferentation of rostral targets and interruption of the spinothalamic tract, important to the development of below-level neuropathic pain in humans [132]. Transection of a single antero-lateral quadrant reliably results in contralateral hypoalgesia, but some patients develop contralateral and ipsilateral dysesthesias and pain or allodynia and hyperalgesia [155]. In a similar animal model, with T13 unilateral spinal hemisection, rats develop bilateral tactile allodynia in both fore- and hindlimbs [156], with evidence of bilateral spinal reorganization [157] following injury. Dorsal column interruption may also contribute to below-level pain that develops after SCI in humans [158], with allodynia and hyperalgesia seen after stimulation caudal and ipsilateral to dorsolateral column lesions in monkeys [159].

Additional Studies Using Animal Models of Pain

Complete SCI and tetraplegia can result in central pain, likely a result of supraspinal plasticity [160] following the loss of normal somatosensory ascending input to thalamic pain-processing regions, that develops with deafferentation and SCI [161,162]. Regional cerebral blood flow (rCBF) in multiple forebrain structures, including thalamic pain processing areas, has been used in the formalin model [163], the CCI model [164], and, more recently, the QUIS SCI pain model [165], to demonstrate significantly altered rCBF associated with the processing of somatosensory information and chronic pain. All these studies suggest significant injury-induced reorganization of thalamic and cortical receptive fields, as is seen in humans with spinal transection [166] and nonhuman primates with spinal cord or peripheral nerve damage [167]. Certainly, deafferentation supersensitivity resulting from the loss of or abnormal spinal inputs to supraspinal sites could lead to the development of abnormal "pain" generators in the spinal cord and supraspinal

structures. Further studies are necessary to understand the supraspinal changes that contribute to the establishment and maintenance of chronic pain states.

CONCLUSION

In summary, animal models have contributed much to the understanding of the mechanisms of pain and spasticity in humans, and current clinical treatments are based, in part, on those studies. But the future of effective strategies that go beyond palliative care will also use these models to screen novel, safe, and useful approaches in a preclinical setting. Much resource effort and expense can be conserved by testing novel methodologies in multiple animal models—not relying on a single animal model, strain, or species—before clinical testing begins.

REFERENCES

1. Argoff CE. Pharmacologic management of chronic pain. *J Am Osteopath Assoc* 2002;102:S21-7.
2. Goldstein EM. Spasticity management: an overview. *J Child Neurol* 2001;16:16-23.
3. MacPherson RD. New directions in pain management. *Drugs Today* 2002;38:135-45.
4. Devulder J, Crombez E, Mortier E. Central pain: an overview. *Acta Neurol Belg* 2002;102:97-103.
5. Dworkin RH. An overview of neuropathic pain: syndromes, symptoms, signs, and several mechanisms. *Clin J Pain* 2002;18:343-9.
6. Schwartzman RJ, Grothusen J, Kiefer TR, Rohr P. Neuropathic central pain: epidemiology, etiology, and treatment options. *Arch Neurol* 2002;58:1547-50.
7. Dietz V. Proprioception and locomotor disorders. *Nat Rev Neurosci* 2002;3:781-90.
8. Lazorthes Y, Sol JC, Sallerin B, Verdier JC. The surgical management of spasticity. *Eur J Neurol* 2002;9:35-41.
9. Turk DC, Okifuji A. Treatment of chronic pain patients: clinical outcome, cost effectiveness, and cost benefits. *Crit Rev Phys Med Rehabil Med* 1998;10:181-208.
10. Breivik H. Opioids in cancer and chronic noncancer pain therapy: indications and controversies. *Acta Anesthesiol Scand* 2001;45:1059-66.
11. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet* 1999;353:1959-64.
12. Siddall PJ, Taylor DA, Cousins MJ. Classification of pain following spinal cord injury. *Spinal Cord* 1997;35:69-75.

13. Siddall PJ, Yeziarski RP, Loeser J. Pain following spinal cord injury: clinical features, prevalence, and taxonomy. *IASP Newsletter* 2000;3:3–7.
14. Burchiel KJ, Hsu FP. Pain and spasticity after spinal cord injury: mechanisms and treatment. *Spine* 2001;26:S146–60.
15. Meythaler JM. Spastic hypertonia [appendix]. *Phy Med Rehabil Clin N Am* 2001;12:953–6.
16. Sanger TD, Delgado MR, Gaebler-Spira D, Hallet M. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics* 2003;111:e89–97.
17. Schalow G, Zach GA. Reorganization of the human central nervous system. *Gen Physiol Biophys* 2000;19 Suppl 1: 11–24.
18. Carter GT, Galer BS. Advances in the management of neuropathic pain. *Phys Med Rehabil Clin N Am* 2001; 12:447–59.
19. Eaton MJ. Emerging cell and molecular strategies for the study and treatment of painful peripheral neuropathies. *J Peripher Nerv Sys* 2000;5:59–74.
20. Eaton MJ, Herman JP, Jullien N, Lopez T. Immortalized chromaffin cells disimmortalized with Cre/lox site-directed recombination for use in cell therapy for pain. *Exp Neurol* 2002;175:49–60.
21. Hottinger AF, Aebischer P. Treatment of diseases of the central nervous system using encapsulated cells. *Adv Tech Stand Neurosurg* 1999;25:3–20.
22. Joung I, Kim HS, Hong JS, Kwon H. Effective gene transfer into regenerating sciatic nerves by adenoviral vectors: potentials for gene therapy of peripheral nerve injury. *Mol Cells* 2000;10:540–5.
23. Latchman DS. Gene therapy with herpes simplex virus vectors: progress and prospects for clinical neuroscience. *Neuroscientist* 2001;7:528–37.
24. Lazorthes Y, Sallerin B, Verdie JC, Sol JC. Management of intractable cancer pain: from intrathecal morphine to cell allograft. *Neurochirurgie* 2000;46:454–65.
25. Martino G, Furlan R, Comi G, Adorini L. The ependymal route to the CNS: an emerging gene-therapy approach for MS. *Trends Immunol* 2001;22:483–90.
26. Surges R, Feuerstein TJ. Mode of action of gabapentin in chronic neuropathic pain syndromes: a short review about its cellular mechanisms in nociceptive neurotransmission. *Arz Forsch* 2002;52:583–6.
27. Wilson SP, Yeomans DC. Genetic therapy for pain management. *Curr Rev Pain* 2000;4:445–50.
28. Lariviere WR, Chesler EJ, Mogil JS. Transgenic studies of pain and analgesia: mutation or background genotype? *J Pharmacol Exp Ther* 2001;297:467–73.
29. Wilson SG, Mogil JS. Measuring pain in the (knockout) mouse: big challenges in a small mammal. *Behav Brain Res* 2001;125:65–73.
30. Maynard FM, Karunas RS, Waring WP. Epidemiology of spasticity following traumatic spinal cord injury. *Arch Phys Med Rehabil* 1990;71:566–9.
31. Walter JS, Sacks J, Othman R, Rankin AZ. A database of self-reported secondary medical problems among VA spinal cord injury patients: its role in clinical care and management. *J Rehabil Res Dev* 2002;39:53–61.
32. Hultborn H, Malmsten J. Changes in segmental reflexes following chronic spinal cord hemisection in the cat. I. Increased monosynaptic and polysynaptic ventral root discharges. *Acta Physiol Scand* 1983;119:405–22.
33. Powers RK, Rymer WZ. Effects of acute dorsal spinal hemisection on motoneuron discharge in the medial gastrocnemius of the decerebrate cat. *J Neurophysiology* 1988;59:1540–56.
34. Taylor JS, Friedman RF, Munson JB, Vierck CJ. Stretch hyperreflexia of triceps surae muscles in the conscious cat after dorsolateral spinal lesions. *J Neurosci* 1997;17: 5004–15.
35. Bertman LJ, Advokat C. Comparison of the antinociceptive and antispastic action of (-)baclofen after systemic and intrathecal administration in intact, acute and chronic spinal rats. *Brain Res* 1995;684:8–18.
36. Chen XY, Feng-Chen KC, Chen L, Stark DM. Short-term and medium-term effects of spinal cord tract transections on soleus H-reflex in freely moving rats. *J Neurotrauma* 2001;18:313–27.
37. Thompson FJ, Parmer R, Reier PJ. Alteration in rate modulation of reflexes to lumbar motoneurons after midthoracic spinal cord injury in the rat. I. Contusion injury. *J Neurotrauma* 1998;15:495–508.
38. Skold C, Levi R, Seiger A. Spasticity after traumatic spinal cord injury: nature, severity, and location. *Arch Phys Med Rehabil* 1999;80:1548–57.
39. Gondim FA, Rodrigues CL, da Gracaq JR, Camurca FD. Neural mechanisms involved in the delay of gastric emptying and gastrointestinal transit of liquid after thoracic spinal cord transection in awake rats. *Auton Neurosci* 2001;87:52–8.
40. Krassioukov AV, Weaver LC. Episodic hypertension due to autonomic dysreflexia in acute and chronic spinal cord-injured rats. *Am J Physiol* 1995;268:H2077–83.
41. Scheifer C, Hoheisel U, Trudrung P, Unger T. Rats with chronic spinal cord transection as a possible model for the at-level pain of paraplegic patients. *Neurosci Lett* 2002; 323:117–20.
42. Waldrop RD, Rubin NH, MacLellan DEG, Rayford PL. Daily variations in the formation of gastric ulcers caused by cervical cord transection in the rat. *Gastroenterology* 1988;94:1080–2.
43. Carter RL, Ritz LA, Shank CP, Scott EW. Correlative electrophysiological and behavioral evaluation following

- L5 lesions in the cat: a model of spasticity. *Exp Neurol* 1991;114:206–15.
44. Ritz LA, Friedman RM, Rhoton EL, Sparkes ML. Lesions of cat sacrocaudal spinal cord: a minimally disruptive model of injury. *J Neurotrauma* 1992;9:219–30.
45. Bennett DJ, Gorassini M, Fouad K, Sanelli L. Spasticity in rats with sacral spinal cord injury. *J Neurotrauma* 1999;16:69–84.
46. Bennett DJ, Li Y, Siu M. Plateau potentials in sacrocaudal motoneurons of chronic spinal rats, recorded in vitro. *J Neurophysiology* 2001;86:1955–71.
47. Bennett DJ, Li Y, Harvey PJ, Gorassini M. Evidence for plateau potentials in tail motoneurons of awake chronic rats with spasticity. *J Neurophysiology* 2001;86:1972–82.
48. Keller MP, Chance PF. Inherited neuropathies: from gene to disease. *Brain Pathol* 1999;9:327–41.
49. Schwartzman RJ, Maleki J. Postinjury neuropathic pain syndromes. *Med Clin North Am* 1999;83:597–626.
50. Benbow SJ, Cossins L, MacFarlane IA. Painful diabetic neuropathy. *Diabet Med* 1999;16:632–44.
51. Koltzenburg M. Painful neuropathies. *Curr Opin Neurol* 1998;11:515–21.
52. Wokke JH, van Dijk GW. Sensory neuropathies including painful and toxic neuropathies. *J Neurol* 1997;244:209–21.
53. Bennett GJ. Neuropathic pain: new insights, new interventions. *Hosp Prac* 1998;33:95–114.
54. Bowsher D. Pain syndromes and their treatment. *Curr Opin Neurol Neurosurg* 1993;6:257–63.
55. McLeod JG. Investigation of peripheral neuropathy. *J Neurol Neurosurg Psych* 1995;58:274–83.
56. Koltzenberg M. Afferent mechanisms mediating pain and hyperalgesia in neuralgia. In: Janig W, Stanton-Hicks M, editors. *Reflex sympathetic dystrophy: a reappraisal*. Seattle: IASP Press; 1996. p. 123–50.
57. Siddall P, Cousins MJ. Spine update: Spinal pain mechanisms. *Spine* 1997;22:98–100.
58. Yaksh TL, Hua XY, Kalcheva I, Nozaki-Taguchi N. The spinal biology in humans and animals of pain states generated by persistent small afferent input. *Proc Nat Acad Sci, USA* 1999;96:7680–6.
59. Ebert B, Thorikildsen C, Andersens S, Christrup LL. Opioid analgesics as noncompetitive N-methyl-D-aspartate (NMDA) antagonists. *Biochem Pharmacol* 1998;56:553–9.
60. Power I, Barratt S. Analgesic agents for the postoperative period. *Nonopioids*. *Surg Clin North Am* 1999;79:275–95.
61. Millan MJ. The induction of pain: an integrative review. *Prog Neurobiol* 1999;57:1–164.
62. Yaksh TL. Spinal systems and pain processing: development of novel analgesic drugs with mechanistically defined models. *TIPS* 1999;20:329–37.
63. Beecher HK. The measurement of pain: prototype for the quantitative study of subjective responses. *Pharmacol Rev* 1957;9:159–209.
64. Le Bars D, Gozariu M, Cadden SW. Animal models of nociception. *Pharmacol Rev* 2001;53:597–652.
65. Yeziarski RP. Pathophysiology and animal models of spinal cord injury pain. In: Yeziarski RP, Burchiel KJ, editors. *Spinal cord injury pain: assessment, mechanisms, management*. Seattle: IASP Press; 2002. p. 117–36.
66. Bass WB, Vanderbrook MJ. A note on an improved method of analgesic evaluation. *J Am Pharm Assoc Sci Ed* 1952;41:569–70.
67. Ben-Bassat J, Peretz E, Sulman FG. Analgesimetry and ranking of analgesic drugs by the receptacle method. *Arch Int Pharmacodyn Ther* 1959;122:434–47.
68. Grumbach L. The prediction of analgesic activity in man by animal testing. In: Knighton RS, Dumke PR, editors. *Pain, 15th International Symposium, Detroit, 1964*. Boston: Little Brown; 1966. p. 163–82.
69. O'Callaghan JP, Holzman SG. Quantification of the analgesic activity of narcotic antagonists by a modified hot plate procedure. *J Pharmacol Exp Ther* 1975;192:497–505.
70. Green AF, Young PA, Godfrey EI. A comparison of heat and pressure analgesimetric methods in rats. *Br J Pharmacol* 1951;6:572–85.
71. Randall L, Selitto J. A method for measurement of analgesic activity on inflamed tissue. *Arch Int Pharmacodyn* 1957;4:409–19.
72. Coderre TJ, Wall PD. Ankle joint urate arthritis (AJUA) in rats: an alternative animal model of arthritis to that produced by Freund's adjuvant. *Pain* 1987;28:379–93.
73. Otsuki T, Nakahama I, Niizuma H, Suzuki J. Evaluation of the analgesic effects of capsaicin using a new rat model for tonic pain. *Brain Res* 1986;365:235–40.
74. Tonussi CR, Ferreira SH. Rat knee-joint carrageenin incapacitation test: an objective screen for central and peripheral analgesics. *Pain* 1992;48:421–7.
75. Fiorucci S, Antonelli E, Burgaud, JL Morelli A. Nitric oxide-releasing NSAIDs: a review of their current status. *Drug Safety* 2001;24:801–11.
76. Giuliano F, Warner TD. Origins of prostaglandins E2: involvements of cyclooxygenase (COX)-1 and COX-2 in human and rat systems. *J Pharmacol Exp Ther* 2002;303:1001–6.
77. Heapy CG, Jamieson A, Russell NJW. Afferent C-fibre and A-delta activity in models of inflammation. *Br J Pharmacol* 1987;90:164P.
78. Hwang AS, Wilcox GL. Intradermal hypertonic saline-induced behavior as a nociceptive test in mice. *Life Sci* 1986;38:2389–96.

79. Teiger DG. A test for antinociceptive activity of narcotic and narcotic antagonist analgesics in the guinea pig. *J Pharmacol Exp Ther* 1976;197:311–6.
80. Iadarola MJ, Brady LS, Draisci G, Dubner R. Enhancement of dynorphin gene expression in spinal cord following experimental inflammation: stimulus specificity, behavioral parameters and opioid receptor binding. *Pain* 1988;35:313–26.
81. Sakurada T, Katsumata K, Tan-No K, Sakurada S. The capsaicin test in mice for evaluating tachykinin antagonists in the spinal cord. *Neuropharm* 1992;31:1279–85.
82. Lariviere WR, Melzack R. The bee venom test: a new tonic-pain test. *Pain* 1996;66:271–7.
83. Humnskarr S, Fasmer OB, Hole K. Formalin test in mice, a useful technique for evaluating mild analgesics. *J Neurosci Methods* 1985;14:69–76.
84. Berrino L, Oliva P, Massimo F, Aurilio C, Maione S, Grella, et al. Antinociceptive effect in mice of intraperitoneal N-methyl-D-aspartate receptor antagonists in the formalin test. *Eur J Pain* 2003;7:131–7.
85. Watson GS, Sufka KJ, Coderre TJ. Optimal scoring strategies and weights for the formalin test in rats. *Pain* 1997;70:53–8.
86. Calvino B, Couraud JY, Maillet S, Pradelles P. Increased reactivity to chemical but not to heat noxious stimuli in mice producing anti-idiotypic antibodies for substance P. *Brain Res* 1988;460:389–93.
87. McCormack K, Prather P, Chapleo C. Some new insights into the effects of opioids in phasic and tonic nociceptive tests. *Pain* 1998;78:79–98.
88. Hammond DL. Inference of pain and its modulation from simple behaviors. In: Chapman CR, Loeser JD, editors. *Issues in pain management: advances in pain research and therapy*. New York: Raven Press; 1989. p. 69–91.
89. Loux JJ, Smith S, Salem H. Comparative analgesic testing of various compounds in mice using writhing techniques. *Arzneim Forsch* 1978;28:1644–7.
90. Dubinsky B, Gebre-Mariam S, Capetola RJ, Rosenthale ME. The antalgic drugs: human therapeutic correlates of their potency in laboratory animal models of hyperalgesia. *Agents Actions* 1987;20:50–60.
91. Zimmerman M. Pathobiology of neuropathic pain. *Eur J Pharmacol* 2001;429:23–37.
92. Bennett GJ, Xie Y-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* 1988;33:87–107.
93. Kim SH, Chung JM. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. *Pain* 1992;50:355–63.
94. Seltzer Z, Dubner R, Shir Y. A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury. *Pain* 1990;43:205–18.
95. Shir Y, Seltzer Z. A-fibers mediate mechanical hyperesthesia and allodynia and C-fibers mediate thermal hyperalgesia in a new model of causalgiform pain disorders in rats. *Neurosci Lett* 1990;115:62–7.
96. Wall PD, Devor M, Inbal R, Scadding JW. Autotomy following peripheral nerve lesions: experimental anesthesia dolorosa. *Pain* 1979;7:103–11.
97. DeLeo J, Coombs D, Willenbring S, Colburn RW. Characterization of a neuropathic pain model: sciatic cryoneurolysis in the rat. *Pain* 1994;56:9–16.
98. Courteix C, Bardin M, Chantelauze C, Lavarenne J. Study of the sensitivity of the diabetes-induced pain model in rats to a range of analgesics. *Pain* 1994;57:153–60.
99. Aley KO, Reichling DB, Levine JD. Vincristine hyperalgesia in the rat: a model of painful vincristine neuropathy in humans. *Neurosci* 1996;73:259–65.
100. Slart R, Yu AL, Yaksh TL, Sorkin LS. An animal model of pain produced by systemic administration of an immunotherapeutic anti-ganglioside antibody. *Pain* 1997;69:119–25.
101. Hargreaves K, Dubner R, Brown F, Flores C. A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. *Pain* 1988;32:77–88.
102. Aley KO, Levine JD. Different peripheral mechanisms mediate enhanced nociception in metabolic/toxic and traumatic painful peripheral neuropathies in the rat. *Neurosci* 2002;111:389–97.
103. Danziger N, Gautron M, Le Bars D, Bouhassira D. Activation of diffuse noxious inhibitory controls (DNIC) in rats with an experimental peripheral mononeuropathy. *Pain* 2001;91:287–96.
104. Kontinen VK, Meert TF. Vocalization responses after intrathecal administration of ionotropic glutamate receptor agonists in rats. *Anesth Analges* 2002;95:997–1001.
105. Novakovic SD, Tzoumaka E, McGivern JG, Haraguchi M. Distribution of the tetrodotoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic conditions. *J Neurosci* 1998;18:2174–87.
106. Dai Y, Iwata K, Kondo E, Morimoto T. A selective increase in Fos expression in spinal dorsal horn neurons following graded thermal stimulation in rats with experimental mononeuropathy. *Pain* 2001;90:287–96.
107. Draisci G, Kajander KC, Dubner R, Bennett GJ. Up-regulation of opioid gene expression in spinal cord evoked by experimental nerve injuries and inflammation. *Brain Res* 1991;560:186–92.
108. Kim DS, Choi Jo, Rim HD, Cho HJ. Downregulation of voltage-gated potassium channel alpha gene expression in dorsal root ganglia following chronic constriction injury of the rat sciatic nerve. *Brain Res Mol Brain Res* 2002;105:146–52.
109. Kim DS, Lee SJ, Park SY, Yoo HJ. Differentially

- expressed genes in rat dorsal root ganglia following peripheral nerve injury. *Neuroreport* 2001;12:3401–5.
110. Cejas PJ, Martinez M, Karmally S, McKillop M. Lumbar transplant of neurons genetically modified to secrete brain-derived neurotrophic factor attenuate allodynia and hyperalgesia after sciatic nerve constriction. *Pain* 2000; 86:195–210.
 111. Eaton MJ, Blits B, Ruitenbergh MJ, Verhaagen J. Amelioration of chronic neuropathic pain by adeno-associated viral (AAV) vector-mediated overexpression of BDNF in the rat spinal cord. *Gene Ther* 2002;9:1387–95.
 112. Kim SH, Na HS, Sheen K, Chung JM. Effects of sympathectomy on a rat model of peripheral neuropathy. *Pain* 1993;55:85–92.
 113. Kauppila T. Correlation between autotomy-behavior and current theories of neuropathic pain. *Neurosci Biobehav Rev* 1998;23:111–29.
 114. Pircio AW, Fedele CT, Bierwagen ME. A new method for the evaluation of analgesic activity using adjuvant-induced arthritis in the rat. *Eur J Pharm* 1975;31:207–15.
 115. Wall PD, Scadding JW, Tomkiewicz MM. The production and prevention of experimental anesthesia dolorosa. *Pain* 1979;6:175–82.
 116. Wiesenfeld Z, Lindblom U. Behavioral and electrophysiological effects of various types of peripheral nerve lesions in the rat: a comparison of possible models for chronic pain. *Pain* 1980;8:285–98.
 117. Christensen D, Kayser V. The development of pain-related behaviour and opioid tolerance after neuropathy-inducing surgery and sham surgery. *Pain* 2000;88:231–8.
 118. Walker J, Catheline G, Guilbaud G, Kayser V. Lack of cross-tolerance between the antinociceptive effects of systemic morphine and asimadolone, a peripherally-selective kappa-opioid agonist, in CCI-neuropathic rats. *Pain* 1999;83:509–16.
 119. Kayser V, Aubel B, Hamon M, Bourgoin S. The antimigraine 5-HT_{1B/1D} receptor agonists, sumatriptan, zolmitriptan and dihydroergotamine, attenuate pain-related behavior in a rat model of trigeminal neuropathic pain. *Br J Pharmacol* 2002;137:1287–97.
 120. Martinez V, Christensen D, Kayser V. The glycine/NMDA receptor antagonist (+)-HA966 enhances the peripheral effect of morphine in neuropathic rats. *Pain* 2002;99:537–45.
 121. Willenbring S, DeLeo J, Coombs D. Differential behavioral outcomes in the sciatic cryoneurolysis model of neuropathic pain in rats. *Pain* 1994;58:135–40.
 122. Myers R, Heckman HM, Powell HC. Axonal viability and the persistence of thermal hyperalgesia after partial freeze lesions of nerve. *J Neurol Sci* 1996;139:28–38.
 123. Willenbring S, Beauprie IG, DeLeo J. Sciatic cryoneurolysis in rats: a model of sympathetically independent pain. Part 1: effects of sympathectomy. *Anesth Analges* 1995;81:544–8.
 124. Wagner R, DeLeo J, Coombs D, Myers R. Gender differences in autotomy following sciatic cryoneurolysis in the rat. *Physiol Behav* 1995;58:37–41.
 125. Field MJ, McCleary S, Hughes J, Singh L. Gabapentin and pregabalin, but not morphine and amitriptyline, block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat. *Pain* 1999; 80:391–8.
 126. Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. *J Neurol* 2002;249:9–17.
 127. Sorkin LS, Yu AL, Junger H, Doom CM. Antibody directed against GD (2) produces mechanical allodynia, but not thermal hyperalgesia when administered systemically or intrathecally despite its dependence on capsaicin sensitive afferents. *Brain Res* 2002;930:67–74.
 128. Gillin S, Sorkin LS. Gabapentin reverses the allodynia produced by the administration of anti-GD2 ganglioside, an immunotherapeutic drug. *Anesth Analges* 1998;86:111–6.
 129. Wallace MS, Lee J, Sorkin LS, Dunn JS. Intravenous lidocaine: effects on controlling pain after anti-GD2 antibody therapy in children with neuroblastoma—a report of a series. *Anesth Analges* 1997;85:794–6.
 130. Bonica JJ. Introduction: semantic, epidemiologic, and educational issues. In: Casey KL, editor. *Pain and central nervous system disease*. New York: Raven Press; 1991. p. 13–29.
 131. Yeziarski RP. Pain following spinal cord injury: the clinical problem and experimental studies. *Pain* 1996;68: 185–94.
 132. Bowsher D. Central pain: clinical and physiological characteristics. *J Neurol Neurosurg Psychiatry* 1996;61: 62–9.
 133. Vierck CJ, Siddall P, Yeziarski RP. Pain following spinal cord injury: animal models and mechanistic studies. *Pain* 2000;89:1–5.
 134. Putke JD, Richards JS, Hicken BL, Ness TJ. Pain classification following spinal cord injury: the utility of verbal descriptors. *Spinal Cord* 2002;40:118–27.
 135. Widerstrom-Noga E. Chronic pain and nonpainful sensations after spinal cord injury: is there a relation? *Clin J Pain* 2003;19:39–47.
 136. Wiesenfeld-Hallin Z, Aldskogius H, Grant G, Hao J. Central inhibitory dysfunctions: mechanisms and clinical implications. *Behav Brain Sci* 1997;20:420–5.
 137. Yu W, Hao J-X, Xu X-J, Hokefelt T. Spinal cord ischemia reduces mu-opioid receptors in rats: correlation with morphine sensitivity. *Neuro Report* 1999;10:87–91.
 138. Hubscher CH, Johnson RD. Changes in neuronal receptive field characteristics in caudal brain stem following chronic spinal cord injury. *J Neurotrauma* 1999;16:533–41.

139. Lindsey AE, LoVerso RL, Tovar CA, Hill CE. An analysis of changes in sensory thresholds to mild tactile and cold stimuli after experimental spinal cord injury in the rat. *Neurorehabil Neural Repair* 2000;14:287–300.
140. Hulsebosch CE, Xu GY, Perez-Polo JR, Westlund KN. Rodent model of chronic central pain after spinal cord contusion injury and effects of gabapentin. *J Neurotrauma* 2000;17:1205–17.
141. Siddall P, Xu CL, Cousins M. Allodynia following traumatic spinal cord injury in the rat. *Neuro Report* 1995;6:1241–4.
142. Hains BC, Yucra JA, Hulsebosch CE. Reduction of pathological and behavioral deficits following spinal contusion injury with selective cyclooxygenase-2 inhibitor. *J Neurotrauma* 2001;18:409–23.
143. Mills CD, Hulsebosch CE. Increased expression of metabotropic glutamate receptor subtype 1 on spinothalamic tract neurons following spinal cord injury in the rat. *Neurosci Lett* 2002;319:59–62.
144. Mills CD, Johnson KM, Hulsebosch CE. Role of group II and group III metabotropic glutamate receptors in spinal cord injury. *Exp Neurol* 2002;173:153–67.
145. Qiu J, Nesic O, Ye Z, Rea H. Bcl-xL expression after contusion to the rat spinal cord. *J Neurotrauma* 2001;18:1267–78.
146. Mills CD, Grady JJ, Hulsebosch CE. Changes in exploratory behavior as a measure of chronic central pain following spinal cord injury. *J Neurotrauma* 2001;18:1091–105.
147. Widerstrom-Noga EG, Duncan R, Felipe-Cuervo E, Turk DC. Assessment of the impact of pain and impairments associated with spinal cord injuries. *Arch Phys Med Rehabil* 2002;83:395–404.
148. Yeziarski RP, Liu S, Ruenes GL, Kajander KJ. Excitotoxic spinal cord injury: behavioral and morphological characteristics of a central pain model. *Pain* 1998;75:141–55.
149. Yeziarski RP, Santana M, Park SH, Madsen PW. Neuronal degeneration and spinal cavitation following intraspinal injections of quisqualic acid in the rat. *J Neurotrauma* 1993;10:445–56.
150. Brewer KL, Yeziarski RP. Effects of adrenal medullary transplants on pain-related behaviors following excitotoxic spinal cord injury. *Pain* 1998;79:83–92.
151. Yeziarski RP. Pain following spinal cord injury: pathophysiology and central mechanisms. *Prog Brain Res* 2000;129:429–48.
152. Yang L, Jones NR, Stoodley MA, Blumbergs PC. Excitotoxic model of post-traumatic syringomyelia in the rat. *Spine* 2001;26:1842–9.
153. Levitt M, Levitt J. The deafferentation syndrome in monkeys: dyesthesias of spinal origin. *Pain* 1981;10:129–47.
154. Ovelmen-Levitt J, Gorecki J, Nguyen K, Iskandar B. Spontaneous and evoked dyesthesias observed in the rat after spinal cordotomies. *Stereo Func Neurosurg* 1995;65:157–60.
155. Vierck CJ, Light AR. Allodynia and hyperalgesia within dermatomes caudal to a spinal cord injury in primates and rodents. In: Sandkuhler J, Bromm B, Gebhart GF, editors. *Nervous system plasticity and chronic pain*. Amsterdam: Elsevier; 2000. p. 411–28.
156. Christensen MD, Hulsebosch CE. Chronic central pain after spinal cord injury. *J Neurotrauma* 1997;14:517–37.
157. Christensen MD, Hulsebosch CE. Spinal cord injury and anti-NGF treatment results in changes in CGRP density and distribution in the dorsal horn in the rat. *Exp Neurol* 1997;147:463–75.
158. Nathan PW, Smith MC, Cook AW. Sensory effects in man of lesions of the posterior columns and of some other afferent pathways. *Brain* 1986;109:1003–41.
159. Vierck CJ, Greenspan JD, Ritz LA, Yeomans DC. The spinal pathways contributing to the ascending conduction and the descending modulations of pain sensations and reactions. In: Yaksh T, editor. *Spinal systems of afferent processing*. New York: Plenum; 1986. p. 275–329.
160. Lenz FA, Tasker RR, Dostrovsky JO, Kwan HC. Abnormal single-unit activity recorded in the somatosensory thalamus of a quadriplegic patient with central pain. *Pain* 1987;31:225–36.
161. Hirayama T, Dostrovsky JO, Gorecky J, Tasker RR. Recording of abnormal activity in patients with deafferentation and central pain. *Stereo Func Neurosurg* 1989;52:120–6.
162. Pattany PM, Yeziarski RP, Widerstrom-Noga EG, Bowen BC. Proton magnetic resonance spectroscopy of the thalamus in patients with chronic neuropathic pain after spinal cord injury. *Am J Neuroradiol* 2002;23:901–5.
163. Morrow TJ, Paulson PE, Danneman PJ, Casey KL. Regional changes in forebrain activation during the early and late phase of formalin nociception: analysis using cerebral blood flow in the rat. *Pain* 1998;75:355–65.
164. Paulson PE, Morrow TJ, Casey KL. Bilateral behavioral and regional cerebral blood flow changes during painful peripheral mononeuropathy in the rat. *Pain* 2000;84:233–45.
165. Morrow TJ, Paulson PE, Brewer KL, Yeziarski RP. Chronic, selective forebrain responses to excitotoxic dorsal horn injury. *Exp Neurol* 2000;161:220–6.
166. Lenz FA, Kwan HC, Martin R, Tasker RR. Characteristics of somatotopic organization and spontaneous neuronal activity in the region of the thalamic principal sensory nucleus in patients with spinal cord transection. *J Neurophysiol* 1994;72:1570–87.
167. Jain N, Florencde SL, Kaas JH. Reorganization of somatosensory cortex after nerve and spinal cord injury. *News Physiol Sci* 1998;13:143–9.